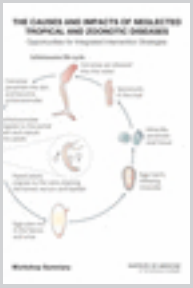

The Causes and Impacts of Neglected Tropical and Zoonotic Diseases: Opportunities for Integrated Intervention Strategies: Workshop Summary

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THE CAUSES AND IMPACTS OF NEGLECTED TROPICAL AND ZOONOTIC DISEASES

Opportunities for Integrated Intervention Strategies

Eileen R. Choffnes and David A. Relman, *Rapporteurs*

Forum on Microbial Threats
Board on Global Health

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

Cover image: The life cycles of hookworms and schistosomes. Reprinted with the permission of *Nature Reviews: Microbiology*.

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"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

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[2] Board member since December 2010.

[3] Board member since September 2010.

Reviewers

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the process. We wish to thank the following individuals for their review of this report:

Enriqueta Bond, Consultant
Richard L. Guerrant, Division of Infectious Diseases and International Health, School of Medicine, University of Virginia
Carole A. Heilman, National Institute of Allergy and Infectious Diseases, National Institutes of Health
David Heymann, Health Protection Agency
Regina Rabinovich, Infectious Disease and Global Health Program, Bill & Melinda Gates Foundation

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the final draft of the report before its release. The review of this report was overseen by **Dr. Melvin Worth.** Appointed by the Institute of Medicine, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Acknowledgments

The Forum on Emerging Infections was created by the Institute of Medicine (IOM) in 1996 in response to a request from the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH). The purpose of the Forum is to provide structured opportunities for leaders from government, academia, and industry to regularly meet and examine issues of shared concern regarding research, prevention, detection, and management of emerging, reemerging, and novel infectious diseases in humans, plants, and animals. In pursuing this task, the Forum provides a venue to foster the exchange of information and ideas, identify areas in need of greater attention, clarify policy issues by enhancing knowledge and identifying points of agreement, and inform decision makers about science and policy issues. The Forum seeks to illuminate issues rather than resolve them. For this reason, it does not provide advice or recommendations on any specific policy initiative pending before any agency or organization. Its value derives instead from the diversity of its membership and from the contributions that individual members make throughout the activities of the Forum. In September 2003, the Forum changed its name to the Forum on Microbial Threats.

The Forum on Microbial Threats and the IOM wish to express their warmest appreciation to the individuals and organizations who gave their valuable time to provide information and advice to the Forum through their participation in the planning and execution of this workshop. A full list of presenters, and their biographical information, may be found in Appendixes B and F, respectively. We would also like to express our deepest appreciation and gratitude to those that helped to identify or provided images illustrating the diseases of interest found in Text Box WO-6, including Doris Bravo (National Veterinary Services

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[1] Sponsor as of October 1, 2010.

Contents

Tables, Figures, and Boxes

TABLES

FIGURES

BOXES

Workshop Overview

THE CAUSES AND IMPACTS OF NEGLECTED TROPICAL AND ZOONOTIC DISEASES: OPPORTUNITIES FOR INTEGRATED INTERVENTION STRATEGIES

Neglected tropical diseases[1] (NTDs) have afflicted humanity since time immemorial and in their long histories have acquired notoriety as chronically disabling and deforming diseases. There is no single consensus definition for this group of diseases. Different organizations such as the World Health Organization, the U.S. Centers for Disease Control and Prevention, the U.S. Agency for International Development, and the Bill & Melinda Gates Foundation to name a few define the suite of these diseases differently. Be that as it may, these diseases, however they are defined, afflict more than 1.4 billion people, many of whom live on less than $1.25 per day. In the past, their serious impact on health and productivity led to considerable knowledge about the diseases, and effective control tools were developed for many. As living conditions improved in many parts of the world, opportunities for transmission were drastically reduced. As a result, these diseases are now rarely seen in populations that enjoy good access to health services and a reasonable standard of living.

[1] The 13 parasitic and bacterial infections known as the neglected tropical diseases include three soil-transmitted helminth infections (ascariasis, hookworm infection, and trichuriasis), lymphatic filariasis, onchocerciasis, dracunculiasis, schistosomiasis, Chagas disease, human African trypanosomiasis, leishmaniasis, Buruli ulcer, leprosy, and trachoma.These diseases afflict more than 1.4 billion people, most of whom live on less than $1.25 per day (WHO, 2006). On October 14, 2010, the World Health Organization released a major report on this topic with an expanded list of NTDs that includes the following diseases: dengue, rabies, endemic treponematoses, cysticercosis, echinococcosis, and food-borne trematode infections (WHO, 2010b).

NTDs today are a symptom of poverty and disadvantage. Those most affected are the poorest populations often living in remote, rural areas, in urban slums, or in conflict zones. With little political voice, NTDs have a low profile and status in public health priorities. Lack of reliable statistics coupled with the often unpronounceable names of these diseases have all held back efforts to bring them out of the shadows. Although medically diverse, NTDs share features that allow them to persist in conditions of poverty, where they cluster and frequently overlap. Approximately 1.4 billion people—one-sixth of the world's population[2]—suffer from one or more NTDs. Conflict situations or natural disasters aggravate conditions that are conducive to the spread of these diseases. Around half of the world's population is at risk of contracting these infections. The human NTDs are diseases of poverty, trapping the world's poorest in a cycle of poverty. The global burden of the NTDs is equivalent to at least half of the combined global burden of HIV/AIDS, tuberculosis (TB), and malaria.

Several NTDs are zoonoses—infections that can be transmitted between animal and human hosts. Such infections can be transmitted directly; others are transmitted indirectly either through food and water or by means of a vector. One of the parasites that causes African trypanosomiasis, or sleeping sickness, can infect livestock and wild animals as well as humans and is transmitted by the bite of a tsetse fly. Additional neglected zoonotic diseases (NZDs) such as brucellosis, bovine tuberculosis, and rabies, which are not typically included among the NTDs, profoundly affect impoverished people not only through their direct effects on human health but also by sickening and killing the livestock upon which their livelihoods depend (WHO, 2006).

NTDs and NZDs not only share features that allow them to persist in conditions of poverty, where they cluster and frequently overlap, but they also present common opportunities for effective, integrated, intervention and control strategies. Significant (though imperfect) control measures—including drugs and vaccines, improvements in water and sanitation, and vector control measures, employed singly or in combination—have been developed for most NTDs and NZDs (Hotez and Pecoul, 2010; Spiegel et al., 2010). Policy makers and funding agencies have begun to acknowledge the public health and economic importance of the NTDs and NZDs, leading to increased support for the use of existing tools (such as the mass administration of drugs to combat several NTDs simultaneously) and the development of more effective integrated programs to control, and in some cases eradicate, these neglected diseases of poverty.

The Institute of Medicine's (IOM's) Forum on Microbial Threats hosted a two-day public workshop on September 21 and 22, 2010, in Washington, DC, to explore the scientific and policy dimensions of NTDs and NZDs. Through presentations and discussions, workshop participants discussed the origins and impacts of these diseases, both individually and as a collective phenomenon.

[2] A group sometimes referred to as the "bottom billion."

They reviewed the influence of NTDs and NZDs on human and animal health and on economic productivity, discussed prospects for disease control and mitigation, and considered opportunities for medical diplomacy and global engagement to reduce the profound, yet long-hidden, consequences of neglected diseases.

Organization of the Workshop Summary

This workshop summary was prepared for the Forum membership by the rapporteurs and includes a collection of individually authored papers and commentary. Sections of the workshop summary not specifically attributed to an individual reflect the views of the rapporteurs and not those of the Forum on Microbial Threats, its sponsors, or the IOM. The contents of the unattributed sections are based on the presentations and discussions at the workshop.

The workshop summary is organized into sections as a topic-by-topic synthesis of the presentations and discussions that took place at the workshop. Its purpose is to present lessons from relevant experience, to delineate a range of pivotal issues and their respective problems, and to offer potential responses as discussed and described by the workshop participants. Manuscripts and reprinted articles, submitted by some but not all of the workshop's participants, may be found in alphabetical order in Appendix A.

Although this workshop summary provides an account of the individual presentations, it also reflects an important facet of the Forum's philosophy. The workshop functions as a dialogue among representatives from different sectors and allows them to present *their* beliefs and viewpoints about which areas may merit further attention. This report only summarizes the statements of participants at the workshop. It is not intended to be an exhaustive exploration of the subject matter nor does it represent the findings, conclusions, or recommendations of a consensus committee process.

Defining the NTDs

Workshop presentations and discussions reflected the dual nature of NTDs[3] as both a public health phenomenon and a medically diverse group of diseases. This section examines common attributes of NTDs and, in particular, their inextricable association with poverty and conflict. The next section profiles individual diseases, their origins and effects on individuals and populations, and prospects for prevention and treatment. Brief descriptions of NTDs and NZDs described in this overview are presented in Box WO-6 (which appears on pages 86–107).

[3] General statements regarding NTDs in this overview frequently apply to NZDs as well.

Burden of the "Bottom Billion"

NTDs[4] comprise some of the most common infections of poverty and some of the leading causes of chronic disability in low- and middle-income countries (Hotez and Pecoul, 2010). As illustrated in Figure WO-1 and discussed further by Hotez in this volume, NTDs represent a group of more than a dozen major chronic, mostly parasitic, infectious diseases, with high endemicity in the developing countries of Africa, Asia, and the Americas (Hotez, 2010a; Musgrove and Hotez, 2009). It has been estimated that every person among the world's poorest—the destitute "bottom billion"—suffers from co-infections by one or more NTD (Hotez et al., 2009b). The greatest health and economic burden of NTDs is borne by people whose existence is often overlooked: subsistence farmers and their families living in remote rural areas, and the teeming poor of urban slums and shantytowns (WHO, 2010b).

NTDs are not exclusively restricted to impoverished tropical regions of the world. Several of these diseases were once endemic in the United States and remain highly prevalent among the nation's poorest residents (Hotez, 2008b, 2009a; Hotez and Wilkins, 2009). In the relatively poor south of Europe and in Turkey, ascariasis, trichuriasis, and a host of zoonotic helminth infections are associated with intestinal, neurological, and respiratory problems. Dogs in that region also serve as a reservoir for visceral leishmaniasis (Hotez, 2009a). Even impoverished Arctic natives contract helminth and protozoan infections through the consumption of undercooked wild animal meat and from contact with infected livestock such as reindeer and elk (Hotez, 2010b).

NTDs have plagued life on Earth for millennia. As noted in Box WO-1, accurate descriptions of these often painful and disfiguring parasitic infections appear in ancient texts including the Bible, Talmud, and Vedas; in the works of Hippocrates; and in Egyptian papyri (Cox, 2002; Hotez, 2010a).

In a presentation discussing NTDs in the United States, Peter Hotez, of the George Washington University and the Sabin Vaccine Institute, noted that most NTDs in the Americas—with the possible exceptions of Chagas disease and trachoma—were the living legacies of slavery and the slave trade. (Dr. Hotez's contribution to the workshop summary report can be found in Appendix A, pages 221–293.) As illustrated in Figure WO-2, these parasites traveled to the Americas in the bodies of West African slaves, who worked in the sugar plantations of Latin America and the Carribbean and, to a lesser extent, in the cotton and sugar plantations of the American South (Hotez, 2009a). NTDs introduced into the United States by slavery, such as hookworm, schistosomiasis, and lymphatic filariasis (LF), became endemic in the New World (Hotez, 2009a).

The burden of hookworm disease in the American South inspired one of the

[4] The concept of the "NTDs" was formulated in response to the Millennium Declaration and its eight Millennium Development Goals (MDGs) for sustainable poverty reduction (Hotez, 2006, 2008a; Hotez et al., 2006, 2007b; Molyneux et al., 2005).

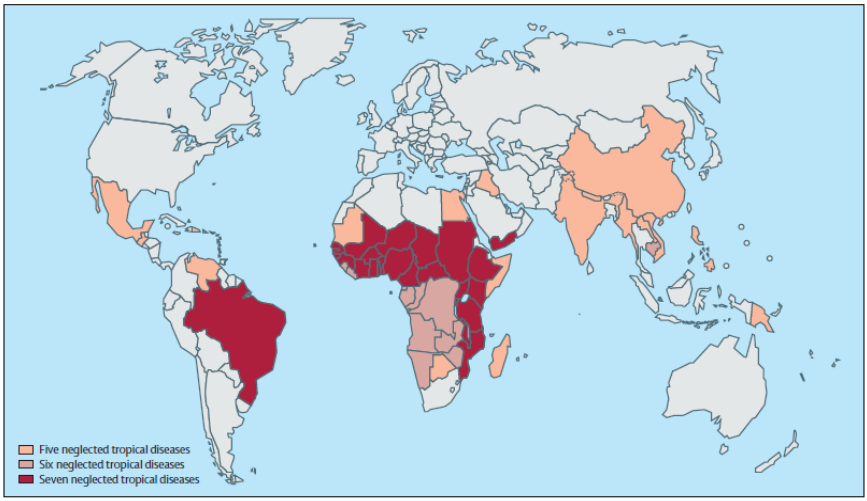


FIGURE WO-1 Geographical overlap and distribution of the seven most common neglected tropical diseases: ascariasis, hookworm infection, trichuriasis, schistosomiasis, lymphatic filariasis, onchocerciasis, and trachoma.
SOURCE: Hotez et al. (2009b). Reprinted from The Lancet, Vol. 373, Hotez PJ, Fenwick A, Savioli L, and Molyneux DH, Rescuing the bottom billion through control of neglected tropical diseases, pp. 1570–1575, Copyright (2009), with permission from Elsevier.

first large-scale, integrated attempts to combat the diseases now known as NTDs, which was launched by the philanthropist John D. Rockefeller in the first decade of the 20th century (CDC, 1993; Ettling, 2000; Humphreys, 2009). Viewing hookworm as a disease that stunted economic development as well as the lives of individuals and communities in the American South, the Rockefeller Sanitary Commission for the Eradication of Hookworm set out in 1909 to achieve the goal of hookworm eradication through the mass treatment of affected populations with anti-helminthic therapy. Although this effort reduced the severity of disease in infected individuals, it failed to eliminate the source of infection and re-infection occurred following the termination of therapy.

Hookworm remained endemic to the American South until profound economic development and urbanization occurred in the years prior to the beginning of World War II (Humphreys, 2009). The same can be said for three additional diseases of poverty that plagued the American South during the 19th and early 20th centuries: yellow fever, malaria, and pellagra. Humphreys (2009) observed that "the southern liberation from disease paralleled the end of sharecropping and the rise of prosperity in the South. It also occurred in decades that saw a vast migration from the countryside to the city and from the South to the North." Similar transformations are now taking place in China, Hotez added. Over the

BOX WO-1
Ancient Scourges, New Names

The illnesses we now call neglected tropical diseases have been plaguing humanity since the beginning of recorded history. Indeed, public health experts sometimes refer to NTDs as the "biblical diseases" because of their long history of causing human suffering (Hotez, 2006). Descriptions of parasitic worm and skin infections can be found in Egyptian papyri and the Vedas dating back to 1500 BC. These conditions are also described numerous times in the Bible, in the Talmud, and in the writings of ancient scholars such as Hippocrates (Cox, 2002; Hotez, 2010a).

Early Descriptions of Parasitic Worm Infections

Ancient Egyptian papyri represent some of the earliest written descriptions of parasitic worms infecting and causing disease in humans. For instance, the Ebers Papyrus, which dates back to 1500 BC, includes instructions for how to use pomegranate root to treat roundworm infections (Grove, 1990).

Detailed descriptions of worm infections and ancient treatments for them can also be found in the writings of Hippocrates. In his *Treatise on Diseases IV*, Hippocrates outlines his theories on the origins of both flat and round worms, describing the courses of infection for each. For example, he writes, "When it [the worm] matches the gut in size, it keeps growing; and the parts which exceed the length of the gut separate off at the anus along with the feces, and what is expelled is like a cucumber seed, or often even larger" (Lonie,1981).

The Bible also contains passages that scholars believe refer to parasitic worm infections. In Numbers, there is a passage that describes how God sent "fiery serpents" to attack the Israelites who had spoken out against him. Once the Israelites repent for their sins, God instructs Moses to "Make a fiery serpent and set it on a pole, and everyone who is bitten, when he sees it, shall live" (Numbers 21:8). Many historians believe that this passage is a reference to Guinea worm (Kristoff, 2010). Indeed, wrapping the worm around a stick and slowly pulling it from the body remains the standard method for removing the worms today.

Early Descriptions of Skin Infections

The Bible, the Talmud, and the Vedas all contain numerous references to skin diseases, which are often described as punishments for those who do not follow religious laws. For example, the Bible mentions "leprosy" (which religious scholars now believe refers to a number of different skin diseases including what we now consider leprosy) in Leviticus, Numbers, Samuel, Kings, Chronicles, Matthew, Mark, and Luke.

Leviticus contains a detailed passage describing what to do when a person has a case of "leprosy." In the passage, God explains to Moses and Aaron, "When a man is afflicted with a leprous disease, he shall be brought to the priest, and the priest shall look. And if there is a white swelling in the skin that has turned the hair white, and there is raw flesh in the swelling, it is a chronic leprous disease in the skin of his body, and the priest shall pronounce him unclean" (Leviticus 13:9–11). Similarly, Treatise XV of the Talmud discusses the signs and proper ways to handle skin diseases at length and includes detailed instructions on how they should be identified, inspected, and properly treated according to religious law (Barclay, 1878).

FIGURE WO-2 Depiction of the classical model of the Triangular trade. The use of African slaves was fundamental to growing colonial cash crops, which were then exported to Europe. European goods, in turn, were used to purchase African slaves, which were then brought on the sea lane west from Africa to the Americas, the so-called middle passage. SOURCE: Triangular trade. http://en.wikipedia.org/wiki/Triangular_Trade (accessed November 12, 2010).

past decade, as the number of its people who live on less than a dollar a day has declined from 60 percent to 16 percent, there have been equally dramatic decreases in the prevalence of neglected infections of poverty, he stated.

Nevertheless, NTDs remain endemic to many less fortunate places left behind by socioeconomic progress. Collectively, these diseases cause an estimated 530,000 deaths per year and annual disability equivalent to 57 million life-years (Hotez et al., 2006, 2007b; Sachs and Hotez, 2006) (see Table WO-1). The heavy burden of disability associated with NTDs—which exceeds that of malaria and TB (Hotez at al., 2006)—reflects the chronic nature of these infections, coupled with the lack of health care delivery available to the vast majority of people who suffer from them.

As several speakers observed throughout the meeting, NTDs frequently present as co-infections with each other, as well as with malaria, TB, or HIV/AIDS (Brooker et al., 2006, 2007). Hotez noted that the geographic ranges of

TABLE WO-1 High-Prevalence and Other Vector-Borne Neglected Tropical Diseases

	Disability-Adjusted Life-Years	Deaths	Approximate Global Prevalence	Approaches to Control
High-prevalence diseases	14.9–52.1 million	24,000–415,000	1.0–1.2 billion	MDA with rapid effect package
Hookworm Infection	1.8–22.1 million	3,000–65,000	600 million	MDA with rapid effect package or albendazole
Ascariasis	1.2–10.5 million	3,000–60,000	800 million	MDA with rapid effect package or albendazole or mebendazole
Trichuriasis	1.6–6.4 million	3,000–10,000	600 million	MDA with rapid effect package or albendazole or mebendazole
Lymphatic filariasis	5.8 million	<500	120 million	MDA with rapid effect package or diethylcarbamazine+ albendazole or ivermectin+albendazole
Schistosomiasis	1.7–4.5 million	15,000–280,000	200 million	MDA with rapid effect package or praziquantiel
Trachoma	2.3 million	<500	84 million	SAFE strategy with azithromycin
Onchocerciasis	0.7 million	<500	37 million	MDA with rapid effect package or ivermectin
Vector-borne protozoan and viral diseases	5.0 million	132,000	70 million	Integrated vector management or case detection and management or both
Dengue fever	0.7 million	19,000	50 million	Integrated vector management
Leishmaniasis	2.1 million	51,000	12 million	Case detection and management and integrated vector management
Chagas disease	0.7 million	14,000	8–9 million	Integrated vector management
Human African trypanosomiasis	1.5 million	48,000	<0.1 million	Case detection and management, and tsetse control

NOTE: MDA, mass drug administration.
SOURCE: Hotez et al. (2009b).

hookworm and schistosomiasis frequently overlap, as do schistosomiasis and HIV/AIDS, especially in rural areas. The additive effects of such multiple infections include profound anemia, complications of pregnancy, and physical and mental stunting in children, he said. Subsequent descriptions of the disability and disfigurement caused by individual diseases (collected in Box WO-6 and discussed in the next section of this overview), and of their magnified effects on women, children, and people living in conflict (below), further illustrate the broad and insidious public health impact of NTDs.

NTDs and Poverty

Poverty is by far the greatest risk factor for NTD infections, Hotez observed; and, he asserted, it is equally true that NTDs promote poverty and interfere with economic development. He and several other speakers featured poverty among their lists of common attributes of countries or regions afflicted with NTDs; workshop participants frequently connected the control of NTDs with the Millennium Development Goals (MDGs) (UNDP, 2010), a set of important benchmarks for poverty reduction, global health, and political equity.[5] A major report on NTDs from WHO, released in the weeks following the workshop (WHO, 2010b), stated that "working to overcome the impact of NTDs represents a largely untapped development opportunity to alleviate the poverty of many populations and thereby make a direct impact on the achievement of the Millennium Development Goals (MDGs)."

NTDs and poverty are linked in numerous ways. Lack of access to clean water, sanitation, hygiene, housing, and health care leaves the poor vulnerable to a host of infections, including NTDs (Spiegel et al., 2010). Previous Forum workshops have examined how water, sanitation, and hygiene coupled with additional environmental factors—including climate change, extreme weather events, land use patterns, and ecosystem disruption—contribute to the persistence and geographic expansion of the NTDs, within the broader context of infectious disease emergence (IOM, 2008a,b, 2009). Water is an important common denominator in many of the NTDs. Water may serve as a medium through which parasites such as helminths are transmitted; as a breeding ground for vector species such as mosquitoes and tsetse flies; or as the habitat for intermediate hosts, such as snails that transmit schistosomiasis (see Table WO-2) and, therefore, represents an important route to NTD control.

Each of the three workshop presentations summarized below discussed additional important links between NTDs and poverty: the disproportionate burden of NTDs borne by women and children, the persistent effects of NTDs on cognitive

[5] Among the eight MDGs, the sixth goal—"to combat HIV/AIDS, malaria and other diseases"—is now widely interpreted to include NTDs (Hotez and Pecoul, 2010; WHO, 2010b).

TABLE WO-2 Environmental Classification of Water- and Excreta-Related Infections

Category	Examples	Control Strategies
A. Fecal-oral (Potentially water-borne or water-washed)	Viral Hepatitis A, E, and F Poliomyelitis Viral diarrhoeas Bacterial Campylobacteriosis Cholera Pathogenic *E. coli* Salmonellosis Typhoid, paratyphoid Protozoal Amoebiasis Cryptosporidiosis Giardiasis	Improve water quality (to prevent water-borne transmission), improve water availability, hygiene promotion (to prevent water-washed transmission)
B. Purely water-washed	Skin and eye infections Scabies Conjunctivitis Trachoma Louse-borne infections Relapsing fever	Improve water availability, hygiene promotion
C. Soil-transmitted helminths	Ascariasis Trichuriasis Hookworm infection Strongyloidiasis	Sanitation, hygiene promotion, treatment of excreta before re-use
D. Food-borne diseases	Bacterial Cholera Campylobacter Salmonellosis and Shigellosis Viral infections Hepatitis A and E Norovirus Helminth infections Trichinellosis Food-borne trematode infections Clonorchiasis Opisthorchiasis Paragonimiasisis Tapeworms Diphyllobothrium infection *Taenia solium* infection *Taenia saginata* infection	As C above, plus meat inspection and cooking

TABLE WO-2 Continued

E. Water-based diseases	Bacterial Cholera Legionellosis Leptospirosis Helminthic Schistosomiasis Clonorchiasis, and, Dracunculiasis	Reduce contact with/ consumption of infected water, sanitation, treatment of excreta before re-use
F. Insect vector diseases	Water-related Dengue Yellow fever Malaria West African trypanosomiasis Excreta-related Bancroftian filariasis Trachoma Fly- and cockroach-borne excreted infections[a]	Reduce number of potential breeding sites and need to pass near them, improve surface water drainage, use repellent/insecticide where appropriate
G. Rodent-borne diseases	Rodent-borne excreted infections Leptospirosis Tularaemia	Rodent control, hygiene promotion, reduce contact with infected water

[a]Excreted infections comprise all those in categories A, C, and D plus helminthic diseases in category E.
SOURCE: Adapted from Bartram and Cairncross (2010).

development, and the role of conflict in making people more vulnerable to NTD infection and its consequences.

Impact on women's and children's health Speaker Marian McDonald, of the Centers for Disease Control and Prevention (CDC), examined the NTDs in terms of the MDGs and also of the "convergence model," a framework for examining risk factors for disease emergence proposed in a seminal IOM report (IOM, 2003) that has informed much of the Forum's work. (Dr. McDonald's contribution to the workshop summary report can be found in Appendix A, pages 357–388.) As seen in Figure WO-3, the model consists of four sets of intersecting factors.

In the case of NTDs, these factors influence the burden of disease for women and children, as follows:

- *Genetic and biological factors.* Women are biologically "at risk" for acquiring NTDs during pregnancy and birth, McDonald said. These vulnerabilities in turn affect children's development. For example, she noted, soil-transmitted helminths (STHs) contribute to anemia in pregnant women, jeopardizing the health of both mother and fetus. Hotez noted

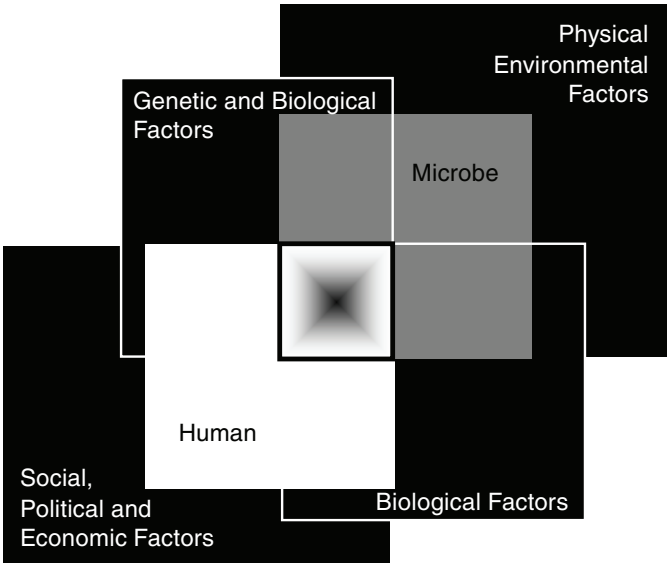


FIGURE WO-3 The convergence model. At the center of the model is a box representing the convergence of factors leading to the emergence of an infectious disease. The interior of the box is a gradient flowing from white to black; the white outer edges represent what is known about the factors in emergence, and the black center represents the unknown (similar to the theoretical construct of the "black box" with its unknown constituents and means of operation). Interlocking with the center box are the two focal players in a microbial threat to health—the human and the microbe. The microbe–host interaction is influenced by the interlocking domains of the determinants of the emergence of infection: genetic and biological factors; physical environmental factors; ecological factors; and social, political, and economic factors.
SOURCE: IOM (2003).

that up to one-third of pregnant women in sub-Saharan Africa are infected with hookworms.

- *Physical and environmental factors.* While not unique to women and children, environmental and infrastructural conditions—such as substandard housing and inadequate sanitation—strongly affect NTDs, as described above.
- *Ecological factors.* While not unique to women and children, ecological factors that influence NTDs—such as access to freshwater, and poultry and small livestock caretaking responsibilities—may have different consequences that result from women's societal roles, McDonald observed. For example, she said, women account for 64 percent of all water collec-

tion, and men for 25 percent (the remainder is done by children, with girls twice as likely to carry water as boys); this task exposes the collector to parasites, infectious disease vectors, and, in regions where conflict is rife, violence as well, all of which raise the risk for NTDs.

- *Social, political, and economic factors.* These have the greatest influence on NTD impact for women and children, according to McDonald. They include disproportionate rates of poverty and illiteracy, lack of education and land ownership, lack of political power, gender inequality, conflict, and war.

NTDs such as female genital schistosomiasis (FGS) and trichomoniasis shape women's reproductive, sexual, social, and economic health, McDonald stated; they cause sexual dysfunction, increase risk for sexually transmitted infections, decrease fertility, and threaten pregnancy outcome. Stigma and exclusion experienced by people with disfiguring NTDs such as lymphatic filariasis (LF) are especially acute for women and can have severe economic consequences by preventing marriage or childbearing, she added. Caring for young children can also increase a woman's risk of infection with an NTD; for example, she said, women frequently contract trachoma while caring for an infected child, and they are three times more likely than men to be permanently blinded by the disease. She also noted that FGS is associated with increased risk of acquiring HIV in women, as well as with ectopic pregnancy, which can be fatal.

Unfortunately, McDonald observed, one of the most effective strategies for prevention and control of NTDs, mass drug administration (MDA), can be problematic during pregnancy. STHs can be treated safely, and treatment of pregnant women with schistosomiasis was recommended by WHO in 2002. The lack of pregnancy safety trials for the drug praziquantel has restricted its use for that purpose, she said. LF cannot be safely treated in pregnant women, leaving them as a potential disease reservoir and at risk for infection, she added.

McDonald stated that NTDs are a scourge on children's health globally, damaging children's health and development in a number of ways. They also take children's lives. NTDs are often considered diseases that make people sick but don't kill them. That is not the case with children, as NTDs contribute to global child mortality (Black et al., 2010; Global Network, 2010; WHO, 2008f). She noted that many NTDs impair children's growth and cognitive development, which—along with another frequent symptom, anemia—stunts their educational and economic prospects as well. The effects of stigma and social isolation associated with a disfiguring NTD are similarly devastating for children. In addition, she said that NTDs may increase the risk that a child will acquire HIV or malaria. Thus, the profound effects of NTDs on the lives of impoverished children not only increase their vulnerability to a range of chronic diseases and disabilities but also contribute to their being trapped in a cycle of poverty.

Parasite prevalence and the worldwide distribution of cognitive ability As McDonald noted, chronic NTD infections have been shown to not only inhibit children's growth and development but also impair cognition and memory (Hotez et al., 2009b). It is therefore not surprising that these parasitic infections are associated with reduced educational performance and school attendance. Moreover, as speaker Christopher Eppig of the University of New Mexico suggested, this effect may influence average national intelligence, as measured by intelligence quotient (IQ) (Eppig et al., 2010). (Dr. Eppig's contribution to the workshop summary report can be found in Appendix A, pages 155–172.)

"The topic of the worldwide variation of intelligence has been of interest to scientists for quite some time," Eppig observed, "but it wasn't until recently when Richard Lynn and Tatu Vanhanen published empirical data on average IQ by nation that formal studies were possible" (Lynn and Vanhanen, 2001, 2002, 2006). Eppig described a series of studies that followed this work, attempting to explain global patterns of intelligence distribution (as determined by Lynn and Vanhanen[6]) by such factors as education and employment prospects (Barber, 2005); climate (Templer and Arikawa, 2006); evolutionary novelty of environment, approximated as distance from Central Africa, where the human species is presumed to have originated (Kanazawa, 2008); and inbreeding depression studies (Saadat, 2008; Woodley, 2009). The study Eppig and coworkers conducted found the most robust association of them all: a strong inverse correlation between infectious disease burden (measured in disability-adjusted life-years, or DALYs) and IQ at the national level (Eppig et al., 2010).

The high metabolic demands of brain development and early childhood provide a plausible explanation for this effect, according to Eppig and coauthors (2010), who speculated that "a developing human will have difficulty building a brain and fighting off infectious diseases at the same time, as both are very metabolically costly tasks."[7] Moreover, Eppig said, "if our hypothesis is correct, that infectious disease is the primary driver of the worldwide distribution of human intelligence, then [this correlation should hold] . . . on other geographical scales, such as across the U.S. states." To test this theory, they compared a measure of average state IQ, determined from scores on a commonly used standardized test, with a measure of infectious diseases–related stress based on statewide CDC data.

[6] The approach taken by Lynn and Vanhanen has aroused considerable criticism. For example, Morse (2006) argued "that while there is nothing mathematically incorrect with their calculations, there are concerns over the data they employ. Even more fundamentally it is argued that statistically significant correlations between the various components of the HDI [Human Development Index, as calculated by the United Nations Development Program; http://hdr.undp.org/en/statistics/] and national IQ can occur via a host of cause–effect pathways."

[7] On this point, Hotez observed that several studies conducted in the 1920s found that the more hookworms infecting a person, the greater the loss in his/her IQ. "In that case it probably operates through iron-deficiency anemia," he added, because iron is required for the biosynthesis of dopaminergic neurons.

In the comparator group, they used three measures of wealth (median household income, income per capita, and gross state product) and two measures of education (expenditure per student and percentage of teachers ranked as "highly qualified" by the U.S. Department of Education). In this comparison too, infectious disease proved a far more important variable than education or wealth in predicting statewide IQ, Eppig stated, although education and wealth were found to be more significant to IQ than in their cross-national analysis.

Eppig maintained that a key interpretation of this finding is that efforts to increase the average IQ of an area should be focused on reducing infectious disease, especially those infectious diseases like the NTDs that affect brain development during early childhood. He also noted that considerable work still remained to test the relationship between IQ and infectious disease, including longitudinal studies tracking both variables among a cohort of individuals and continued exploration of possible mechanisms to explain their findings.

Eppig's work points to additional types of studies that could be conducted with regard to NTDs that occur in the United States, Hotez observed (see discussion of these NTDs and their impact in next section). For example, he said, one could look at *Toxocara* infections as a risk factor in existing large asthma cohort studies, or examine the impact of cytomegalovirus infection on intellectual delays in African-American communities. "There are a number of important studies now that you could include in some large analyses that might already be being supported by the NIH and other agencies," he advised.

Forum member Michael Osterholm, of the University of Minnesota, cautioned that the data Eppig and colleagues used to make their analyses were unreliable. "Even the data for across the states has [*sic*] to be very carefully looked at," he said. "We have had many a Forum meeting here looking at disease surveillance, understanding how absolutely soft, erratic, and, in some cases, absolutely impossible to predict [*sic*] surveillance data are."

"We fully admit that there are going to be sampling-error issues," Eppig replied, adding that their hypothesis was far from proven. "Only by continuing to get finer and finer with the scale of our analyses we can say this is solved," he added, but he also contended that the association between IQ and infectious disease burden had been supported on two very different geographical scales.

NTDs and conflict In a presentation titled, "Neglected Diseases, Civil Conflicts, and the Right to Health," Chris Beyrer of the Johns Hopkins University discussed multiple mechanisms through which conflicts specifically increase vulnerability to NTDs, and how conflict situations contribute to an overall increase in neglect. (Dr. Beyrer's contribution to the workshop summary report can be found in Appendix A, pages 132–155.) He also demonstrated that although interventions to address NTDs in conflict settings are challenging they can, nevertheless, have measurable impacts.

"NTDs are diseases of neglected peoples; conflicts fuel neglect," Beyrer

stated. Conflicts cause displacement and overcrowding in camps and settlements and prevent access to adequate water, hygiene, food, and health care, he observed. These factors, in turn, increase exposures to and transmission of NTDs, and result in treatment gaps or delays. Conflicts and terror regimes further contribute to the neglect by obstructing or preventing disease surveillance and research, disabling health care systems, and, most directly, through the removal of health care providers, who either flee or are caught up in—and potentially harmed by—conflicts, he said. "The worst of these associations [occur during] . . . civil conflicts," he added. "It's really within country settings, and less about militaries fighting than it is about militaries contending in civilian spaces."[8]

Several of these factors were in evidence during a civil conflict that erupted in Côte d'Ivoire in 2002, Beyrer recalled. While as much as one-half of the adult population became displaced from some areas during this period, 98 percent of the doctors and 86 percent of nurses fled some places (Betsi et al., 2006). The effects of conflict on health research are apparent in the numbers of HIV/AIDS and malaria studies conducted in the Democratic Republic of Congo (DRC). Beyrer observed that during the Mobutu regime, as political terror increased, those numbers rapidly declined to zero and have only recently begun to increase (Beyrer, 2007).

Similarly, he reported that cases of human African trypanosomiasis (HAT; sleeping sickness) in the DRC—which peaked in the 1930s, then declined as a result of control measures to about 1,000 cases per year and remained steady until the country gained independence from Belgium in 1960—rose as the Mobutu government began its violent regime. Between 1991 and 1994, cases of HAT reached their highest levels in the 20th century, more than 34,000 per year, coincident with the height of social and political chaos (Ekwanzala et al., 1996). The numbers of HAT infections, transmission rates, and the cost and toxicity of treatment in the DRC increased during this period, Beyrer observed. A contemporaneous "big-picture" analysis of HAT outbreaks in Central Africa found that nearly every outbreak has occurred in an area of conflict and that outbreak severity and conflict severity were strongly correlated across space and time (Berrang-Ford et al., 2010).

Since 1993, Beyrer has been working to address NTD infections and other critical health problems among people living inside conflict zones in eastern Burma (Myanmar). He described a successful intervention deployed across the Thai–Burma border called the Mobile Obstetric Medics program (Mullany et al., 2010). This program trains Burmese community health workers in a safe environment in Thailand. Upon completion of their training, these health care workers then return to Burma to provide basic health services, including mass de-

[8] On this point, Osterholm noted that similar risks of infectious disease occur wherever conflicts arise due to the increased transmission of diseases formerly controlled by the public health infrastructure.

worming, to people living in conflict zones in eastern Burma. "These internally displaced populations are not reachable from the government sector and they are certainly not reachable from international organizations working in Burma," Beyrer observed. In his formal remarks, Beyrer provided a range of evidence suggesting that the community health workers were able to deliver a basic set of services to significant numbers of displaced people.

That this program trained and empowered local health care workers was crucial to its success, Beyrer emphasized. The trainees, who represented each of four major ethnic groups in eastern Burma, were "the only people who can deliver those kinds of services in these conflict settings—people who can get into areas that none of us can and that international organizations really can't," he said. "Hopefully, we have been able, with this work and with the evaluation of it, to demonstrate, in an exceptionally challenging environment, interventions that might be useful and scalable in less challenging environments," he concluded.

Why Are NTDs Neglected?

Despite their significant contribution to the global burden of disease, several workshop participants offered their opinions as to why the NTDs as a group are neglected, as well as the opportunity they present for poverty reduction and global development. Clearly, NTDs contribute to a cycle of poverty and disease in which each condition exacerbates and perpetuates the other. Many speakers emphasized that the lack of political voice among those most afflicted by NTDs is a primary reason for their neglect, as Beyrer expressed when he called them "neglected diseases of neglected people."

The epidemiological characteristics of NTDs may also contribute to their neglect, several participants observed. Keynote speaker Ezekiel Emanuel of the White House Office of Management and Budget, among others, remarked that because these diseases cause high morbidity—which is often difficult to measure—and fewer deaths than HIV/AIDS and malaria, the health effects of NTDs are less apparent. Forum member Lonnie King, of the Ohio State University, noted that NTDs rarely cause explosive outbreaks, which tend to draw attention to infectious diseases. (Dr. Lonnie King's contribution to the workshop summary report can be found in Appendix A, pages 342–346.) Speaker Lorenzo Savioli of WHO observed that, although NTDs are communicable, they are not easily or often exported to developed countries and are therefore not perceived as threats. (Dr. Savioli's contribution to the workshop summary report can be found in Appendix A, pages 481–489.)

As both Emanuel and Savioli observed, another strike against the NTDs is their weakness as a "brand" if taken individually. Most diseases that comprise the NTDs have complex, hard-to-pronounce names, Emanuel observed. Exactly which diseases are NTDs is another unresolved question—a range of lists were presented at the workshop, from the "7 most common and/or most treatable

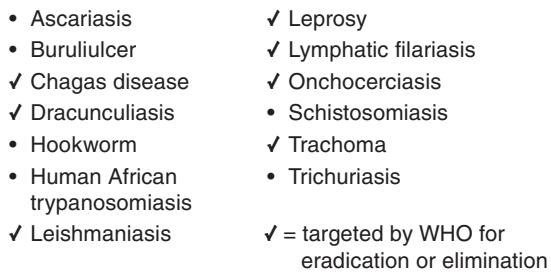


FIGURE WO-4 WHO list of neglected tropical diseases.
SOURCES: Hopkins (2010); Carter Center.

diseases" to a list of 30 "neglected diseases of poverty." There was considerable controversy as to whether or not dengue is an NTD. Some argued that dengue is an acute emerging febrile illness, rather than a chronic, debilitating disease, and therefore does not fit the NTD model; others contended that dengue and other intermittent, acute diseases—which also include chikungunya and Japanese encephalitis—result in lifetime disability that is indeed neglected.

Keynote speaker Donald Hopkins, of the Carter Center, suggested that the field would benefit if a single list of diseases, such as WHO's list of 13 NTDs,[9] presented in Figure WO-4, served as a standard and guide for prioritizing research. (Dr. Hopkins' contribution to the workshop summary report can be found in Appendix A, pages 208–221.) Pursue the diseases on this list as a cohort for a set period, he advised, and focus on eliminating or controlling this limited number of disease targets for the foreseeable future. "Adding and subtracting diseases in these different lists is unnecessarily confusing and defeats our objective," he concluded.

Profiles of Neglected Diseases

Although NTDs have much in common, each disease has its own history, and each presents certain unique challenges and intervention opportunities. As speaker Eric Ottesen, of the Task Force for Global Health, observed, "we know that we are going to deal with these diseases in an integrated fashion . . . but it's also important that we focus on the progress within each of the diseases. (Dr. Ottesen's contribution to the workshop summary report can be found in Appendix A, pages 414–480.) Certainly we can integrate the implementation [of interventions], but we have to make sure that each of the diseases is being

[9] However, as previously noted, that list was increased to 17 diseases shortly after the workshop in October 2010.

addressed successfully." The workshop presentations summarized in this section focused on individual NTDs and their specific health and socioeconomic effects, as well as prospects for reducing these burdens.

Diseases Targeted for Eradication and Elimination

Hopkins began his workshop presentation by defining the terms "elimination," "eradication," and "control," as they apply to infectious diseases (see Box WO-2). "Eradication means reducing the incidence of a disease to zero worldwide, such that further control measures are unnecessary," he said. "It means total interruption of transmission." After a specified period when no cases of the disease are reported, WHO can certify that it is eradicated. "Eradication will always be a rare phenomenon," he added.

Hopkins defined elimination as the cessation of transmission of a disease in a limited geographic area, where control measures may continue in order to combat or prevent reintroduction. He also noted that this term is frequently misused to describe control of a disease that persists in lesser amounts and that, therefore, poses an ongoing threat of transmission. "I believe such imprecise use of the word 'elimination' devalues the term, risks credibility, and confuses the public," he observed (Hopkins, 2009). WHO is the only international organization that can legally declare a disease eradicated or eliminated, Hopkins stated; its governing body, the World Health Assembly, or one of its regional committees, can officially sanction targeting of any disease for eradication or elimination. Of the seven NTDs that have been targeted in this way (see Box WO-3), Hopkins focused his remarks on four diseases—dracunculiasis, onchocerciasis, trachoma, and LF—and the progress being made against them. LF was also the topic of a workshop presentation by Eric Ottesen, director of the Lymphatic Filariasis Support Center at the Task Force for Global Health, discussed below.

BOX WO-2
Definitions of Elimination, Eradication, and Control

Elimination: cessation of transmission in a country, continent, or other limited geographic area; complete prevention of a clinical manifestation.

Eradication: deliberate reduction of global incidence to zero, no further control measures necessary.

Control: reduced incidence or prevalence, control measures still necessary.

SOURCE: Hopkins (2010).

BOX WO-3
NTDs Targeted by WHO for Elimination or Eradication

Dracunculiasis: global *eradication* (WHA57.9) 2004

Onchocerciasis: regional *elimination* (*interrupting transmission of the parasite*) (PAHO CD48.R12) 2008

Lymphatic filariasis: global *elimination as a public health problem* (WHA50.29) 1997

Trachoma: global *elimination of blinding trachoma* (WHA51.11) 1998

Leprosy: global *elimination* (*reduction of cases to less than 1 per 10,000 population*) (WHA44.9) 1991; *elimination as a public health problem* (WHA51.15) 1998

Chagas disease: regional *elimination of transmission "as technically feasible"* (WHA51.14) 1998; *"control and elimination"* (WHA63.20) 2010

Visceral leishmaniasis: regional *elimination* (WHA60.13) 2007

SOURCE: Hopkins (2010).

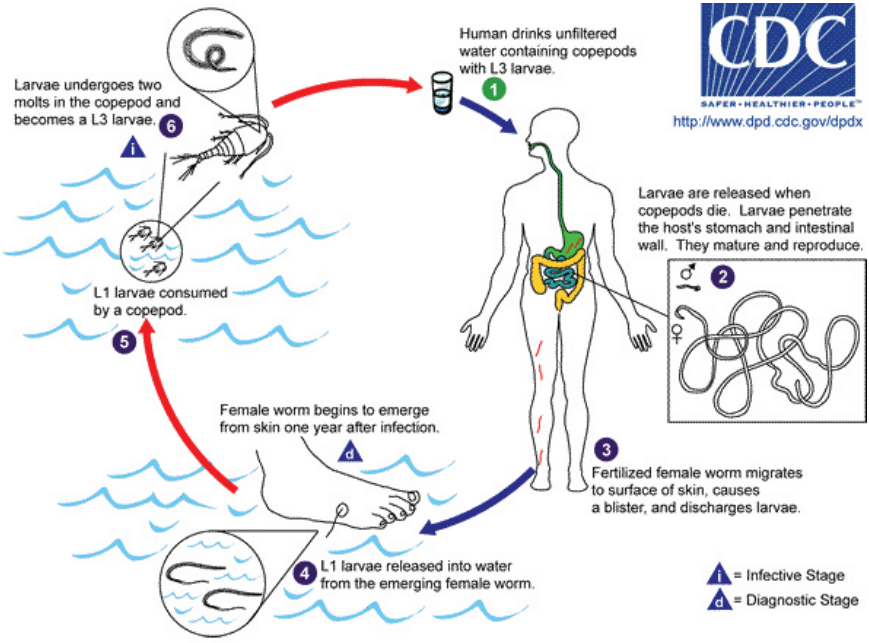


FIGURE WO-5 Life cycle for dracunculiasis.
SOURCE: Centers for Disease Control and Prevention.

Dracunculiasis Also known as Guinea worm disease, dracunculiasis was the first (and to date, the only) NTD targeted by WHO for eradication, Hopkins said. It is a painful infection caused by the roundworm *Dracunculus medinensis,* which is transmitted through contaminated drinking water (see Box WO-6). Two- to 3-foot-long worms, each of which is capable of depositing hundreds of thousands of larvae, emerge directly through the skin approximately one year after infection, he explained. People with dracunculiasis endure weeks of pain and disability, preventing them from doing physical labor or from attending school. Figure WO-5 provides a schematic of the life cycle of dracunculiasis.

There is no pharmacological cure or vaccine for dracunculiasis, Hopkins observed, nor are recovered patients immune to future infections. Today, the only therapy for dracunculiasis is to physically extract the worm from the lower extremities or elsewhere. Humans, however, are the sole host for the parasite. Therefore, he said, dracunculiasis can be prevented through several relatively simple routes:

- filtering drinking water;
- keeping infected people from bathing or entering into drinking water sources;
- applying larvicide to infected water sources; and
- providing clean, safe water from wells.

Since 1986, the Carter Center has led efforts to eradicate dracunculiasis, in collaboration with the endemic countries, CDC, the United Nations Children's Fund (UNICEF), and WHO, Hopkins said. Donors to this initiative have included manufacturers of water filtration fabric and larvicide, charitable foundations, the U.S. Agency for International Development (USAID), among many donors, as well as service volunteers from many countries. "Tens of thousands of grassroots village volunteers are the bedrock of the Guinea worm eradication program," he observed. "They were the first to show the utility of village volunteers in Africa as the basis for a surveillance network that provides reliable village-based reports of a disease," he continued, and he noted that village volunteers also educate their neighbors about disease prevention and distribute water filters. The dracunculiasis eradication program has also benefited from the strong political participation by several African heads of state and the leadership and engagement of former President Jimmy Carter.

In 2009, there were fewer than 3,200 cases of dracunculiasis reported in 645 endemic villages, compared with an estimated 3.5 million cases in more than 23,000 villages in 1986, Dr. Hopkins stated. Once prevalent in 20 nations in Africa and Asia, by 2009, only 4 countries in Africa reported cases. As of August 2010, 97 percent of all cases were reported from Sudan—especially from war-torn southern Sudan. According to Hopkins, the remaining cases are being reported from Ethiopia, Mali, and Ghana. Since 2005, when a peace agreement

was signed ending the most recent phase of the Sudanese civil war, significant progress has been made against dracunculiasis in southern Sudan, Hopkins observed. This occurred "despite pitiful infrastructure, low literacy, and sporadic insecurity that disrupted program operations 32 times in different places in 2009," he added. "We are now aiming to stop transmission in southern Sudan by the end of 2012, political conditions permitting," he stated.

Hopkins described five key benchmarks that have charted the dracunculiasis eradication program over the past 30 years:

- a clear, quantitative goal, defined from the program's outset;
- identification of all endemic countries;
- establishment of effective village-based active surveillance;
- extension of interventions throughout endemic areas; and
- monitoring of cases and status of interventions, followed by response, on a monthly basis.

"When the Guinea worm eradication program succeeds, it will set a precedent as the first parasitic disease of humans to be eradicated and as the first disease to be eradicated without a vaccine or curative treatment," Hopkins observed. "Its legacy in endemic areas will include improved health, more productive agriculture, and better school attendance, as well as experienced health workers and village volunteers, and changed attitudes."

Onchocerciasis Also known as river blindness, onchocerciasis is a potentially blinding parasitic infection that is spread by the bite of black flies that breed in fast-flowing rivers, rapids, or dams. In Africa, suitable habitat for these flies has expanded with increased dam construction, Hopkins noted. Of an estimated 123 million people at risk for onchocerciasis in 37 mostly African countries, about 37 million are actually infected, he reported. Approximately half a million people are at risk in six countries in the Americas, and a few thousand in Yemen.

The infection can be treated or prevented by annual doses of ivermectin, a product of Merck & Co., Inc., but because the drug only affects the immature microfilariae, not the adult worms, annual treatments must continue for at least a decade, until the adult worms die out, he explained. In 1987, Merck made the precedent-setting announcement that it would provide unlimited amounts of its then-novel drug to treat people with onchocerciasis in poor countries free of charge, and for as long as necessary.

The Pan-American Health Organization (PAHO), WHO's regional body in the Americas, targeted this disease in 1991 for interruption of transmission by 2012, Hopkins said. In the Americas, efforts to combat onchocerciasis among people living in 13 disease foci in the six affected countries (see Figure WO-6) have involved mass treatment with ivermectin at least twice per year, Hopkins stated, with a minimum coverage of 85 percent of the eligible population.

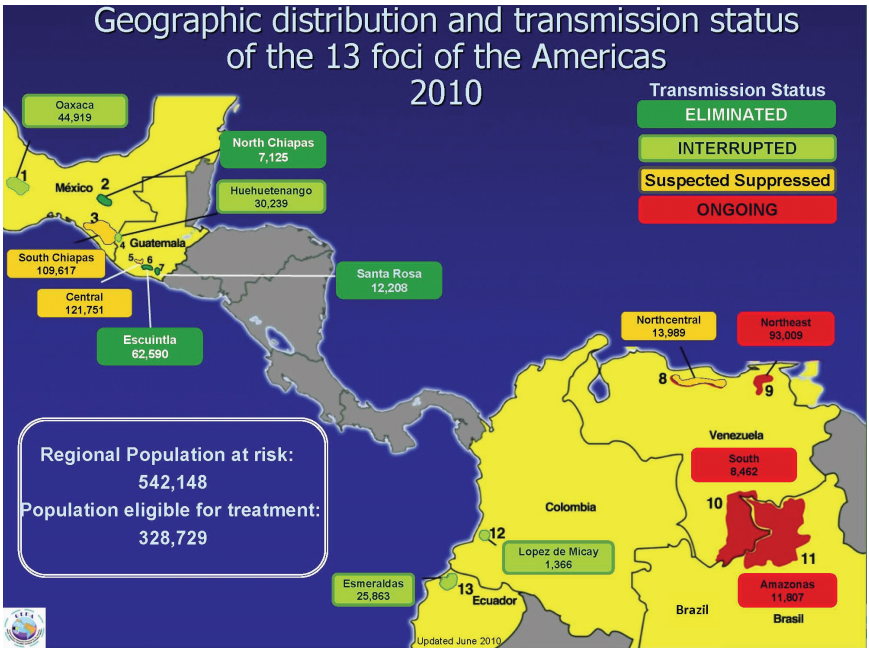


FIGURE WO-6 Geographic distribution and transmission status of the 13 onchocerciasis foci of the Americas (2010).
SOURCE: Hopkins (2010).

Some of the highly endemic communities in Mexico have been treated four times per year. At present, Hopkins stated, 10 of those foci have either been eliminated (that is, they have stopped semiannual treatments for at least three years, maintained surveillance, and have had no resurgence of disease), are believed to have suppressed transmission, or they are in post-treatment surveillance, having interrupted transmission and stopped semiannual treatments, but have not yet gone for three years without new cases. The remaining active foci are located in Venezuela and Brazil.

Most black fly species that carry onchocerciasis in the Americas do not transmit the disease as efficiently as do their African counterparts, Hopkins observed. That, in part, explains why onchocerciasis elimination is more feasible in the Americas than in Africa. The first African onchocerciasis control program—sponsored by WHO, the World Bank, and others—involved 11 West African countries from 1994 to 2002. By combining vector control—spraying rivers with insecticides to prevent breeding of black flies—with annual mass administration of ivermectin, transmission of onchocerciasis was completely eliminated across a vast area of Africa. He described that approach as effective but expensive and said

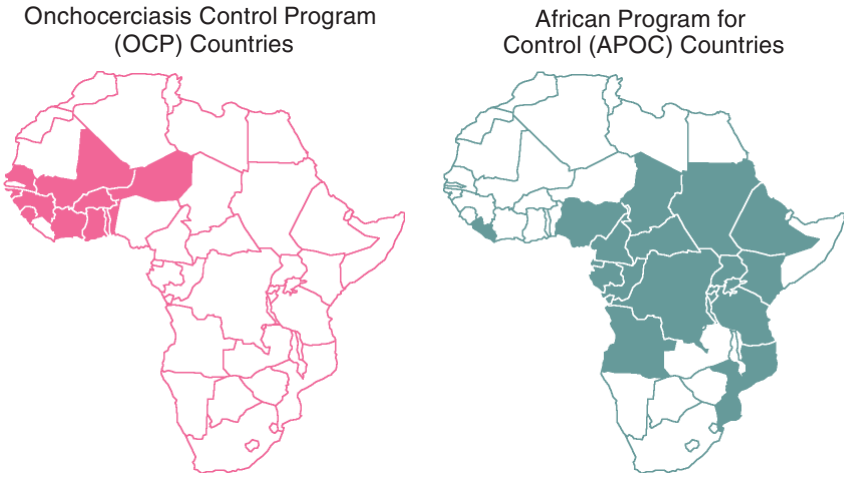


FIGURE WO-7 Onchocerciasis control programs in Africa.
SOURCES: Hopkins (2010); WHO/APOC.

that it would not be feasible in the other forested endemic areas of Africa. Fortunately, he added, ivermectin has been widely used in such areas under the African Program for Onchocerciasis Control (APOC). As illustrated in Figure WO-7, APOC reaches endemic regions of 19 African countries, and pioneered the use of volunteers selected by their own communities to distribute the drug.

Under APOC's leadership, onchocerciasis prevalence was reduced from 47 percent in 1995 to 29 percent in 2008, Hopkins reported. However, studies conducted by the Carter Center in Cameroon and Nigeria have shown that transmission has persisted after 11 years of MDA in some areas, he continued, as well as in some untreated hypoendemic areas that were ineligible for APOC intervention. Hopkins went on to observe that these results suggested that, without continued external support, some endemic countries would be unable to sustain annual MDA with ivermectin. Indeed, in 2002, at a conference on the eradicability of onchocerciasis co-hosted by WHO and the Carter Center, participants concluded that the disease could not be eliminated throughout Africa without the development of a macrofilaricide to kill the adult worms. On the other hand, participants at this same meeting concluded that the disease *could* be eliminated with current tools in the Americas and in certain vulnerable foci in Africa and Yemen. Hopkins noted considerable progress toward these goals, including:

- the elimination of onchocerciasis transmission in some hyperendemic foci in Mali and Senegal;

- an effort to eliminate onchocerciasis in an isolated focus of the disease on the Sudanese island of Abu Hamad, in the Nile;
- the launching of a nationwide onchocerciasis elimination program in Uganda; and
- a 90 percent coverage rate of endemic areas in the Americas with ivermectin administration.

Hopkins noted that the presence of the *Loa loa* parasite presents a barrier to ivermectin use in 10 of the 30 endemic African countries, because people infected with *Loa loa* can develop potentially fatal neurological complications when treated with ivermectin, or with albendazole, a drug used to treat LF (see below). Rather than risk these consequences of MDA in *Loa loa*–endemic areas, he said, ivermectin must be administered only in non-endemic communities, and perhaps even on a patient-by-patient basis; however, he observed, more creative solutions will be needed if the parasite is to be eliminated in Africa. "There really is a tangible risk of inadvertently killing people," he observed, and the reaction to such a blunder could cause ivermectin to be withheld from people who could benefit from it.

Trachoma Trachoma is a blinding bacterial infection spread by contaminated hands, cloths, and flies. An estimated 120 million people are at risk for the disease, Hopkins reported; 84 million people in 57 countries are infected.

The World Health Assembly established a target to eliminate blinding trachoma (but not all infections) by 2020, using a strategy known by the acronym SAFE:

- **S**urgery to prevent progression to blindness;
- **A**ntibiotic administration to treat active infections and prevent spread;
- **F**acial cleanliness; and
- **E**nvironmental improvements (e.g., building latrines to suppress breeding of vector flies, which favor human feces deposited on the ground).

He said that it has yet to be determined how best to measure the quantifiable goals of this effort: reducing scarring trachoma to below 1 case per 1,000 population and reducing active trachoma below 5 percent in children ages 1 to 9.

Nevertheless, significant progress is being made in providing interventions such as latrine construction that offer broad public health benefits in addition to onchocerciasis control, Hopkins observed. For example, following an "explosion of latrine building" under way in the Amhara region of Ethiopia that has produced 1.8 million latrines since 2002, public attitudes toward hygiene have changed dramatically, he said, and similarly rapid and crucial behavioral changes occurred in response to the Guinea worm eradication program.

On the other hand, audience member Sheila West of the Johns Hopkins

University noted that some recent studies suggest that latrines are not as effective in controlling trachoma as once believed. West asked Hopkins whether other environmental measures to combat trachoma had been considered. Whatever their effectiveness against trachoma, latrines provide important public health benefits, he replied, "so I'm still a partisan of [latrine building], even if . . . the impact on trachoma is 20 percent rather than 60 or more percent." Moreover, he added, latrines promote public understanding of the impact of hygiene on water-borne and water-washed diseases. "They are understanding that by these kinds of behavioral changes, they can improve their lives and the lives of their families," he observed.

Hopkins noted that the antibiotic used to treat trachoma, azithromycin (Zithromax®), has been donated by its manufacturer Pfizer for use in MDA campaigns. These campaigns currently consume about 75 million doses per year and, as of 2008, reached approximately 40 million people, or 33 percent of the at-risk population, he reported. According to current estimates, 75 percent of the trachoma burden falls on 10 countries. In Ethiopia, perhaps the most severely affected country, an aggressive campaign has begun in the Amhara region, where the disease is most widespread and entrenched. This effort follows an important principle of elimination and eradication programs, which is, "if you can't start in both highly endemic and low endemic areas simultaneously, start in the most highly endemic areas first, because it's going to take the longest amount of time there," Hopkins observed.

"Much more remains to be done," Hopkins concluded. "Halfway to 2020, the global program to eliminate blinding trachoma is still uncertain about how many countries are still endemic, which areas require interventions, and how best to monitor progress." On the other hand, West noted, a recent global scientific meeting hosted by WHO defined both targets and areas for trachoma elimination, and there has been a rapid decline in the number of cases worldwide.

Lymphatic filariasis (LF) A mosquito-borne infection is caused by the parasites *Wuchereria bancrofti* and *Brugia malayi*. It causes extreme, disfiguring swelling of the limbs and genitalia in about one-third of those infected, which can cause disability and stigma; some people suffer hidden damage from LF (Hopkins, 2010; Ottesen, 2010). Generally, LF is acquired in childhood, but its outward signs do not become apparent until adulthood. Of the 1.3 billion people at risk for LF in more than 80 countries in Africa, Asia, and the Americas, an estimated 120 million are infected.

LF can be prevented by annual MDA with diethylcarbamazine and albendazole over a period of at least five years, until the adult worms die (Hopkins, 2010; Ottesen, 2010). In Africa, except where *Loa loa* is endemic, LF is treated with ivermectin and albendazole. Merck, which produces ivermectin, and GlaxoSmithKline (GSK), which produces albendazole, donate these drugs for MDA. Albendazole and ivermectin have important secondary effects on intestinal helminths, including *Ascaris* and *Trichuris*, as well as on lice and scabies. Additional

interventions for LF include surgery to reduce disabling hydroceles in men with LF, and palliative care to mitigate secondary infections and swelling of some limbs; both tend to improve patients' emotional and social health.

The Global Alliance to Eliminate Lymphatic Filariasis (GAELF),[10] established in 2000, is a public–private partnership committed to helping LF-endemic countries achieve a minimum of 80 percent coverage for annual MDA with the appropriate drugs (Hopkins, 2010; Ottesen, 2010). Annual treatments to prevent LF rose from 10 million in 2000 to 496 million in 2008, representing 37 percent of the population at risk, he reported; however, LF-endemic areas in 15 countries remained to be mapped at that time. The group aims to conclude a successful global elimination program by 2020.

While acknowledging that "process indicators"—such as numbers of people treated—provide an incomplete (and sometimes deceptive) measure of progress against a disease, Ottesen nonetheless noted that the LF global elimination program[11] provided more than 2.8 billion treatments during its first decade. Five countries have completed their MDA courses and are under active surveillance, as are several countries that did not require MDA due to a relatively low prevalence of LF, he said. The LF-related benefits of this program have been twofold, he explained: newborns have been protected from infection with the parasite, and people with asymptomatic infections have been prevented from progressing to overt disease (Ottesen et al., 2008).

The economic value of these health benefits for individuals treated during the first eight years of the program's operation, and projected over the course of their lifetimes, is an estimated US$22 billion, and for health systems, US$2 billion (Chu et al., 2010). "This is an excellent investment in global health, with impressive economic rates of return," Ottesen observed. Documenting both the health and the economic impacts of the global LF elimination program are crucial to ensuring its future and, indeed, that of any program targeting NTDs, he concluded.

Current status Table WO-3 summarizes the current status of elimination efforts against dracunculiasis, onchocerciasis, blinding trachoma, and LF. "These times of exceptional opportunities and inspiring progress are as exciting for us professionals as they are important to improving the human condition for this current

[10] GAELF is a public–private partnership created in 2000 to assist in advocacy, resource mobilization, and program implementation. GlaxoSmithKline and Merck & Co. Inc., have pledged all the albendazole and Mectizan® (in Africa where onchocerciasis is prevalent) necessary to achieve elimination—the largest drug donations in history, valued at more than $1 billion. http://www.filariasis.org/who_we_are/index.htm (accessed November 15, 2010).

[11] In 1997, the Global Programme to Eliminate Lymphatic Filariasis was created in response to a specific resolution by the World Health Assembly. At that time WHO, having recently devised a strategy aimed at achieving LF elimination through MDA, received extraordinary pledges from two pharmaceutical companies (GlaxoSmithKline and Merck & Co., Inc.) for long-term drug donations of unprecedented size to jumpstart this nascent program (Ottesen et al., 2008; http://www.plosntds.org/article/info%3Adoi%2F10.1371%2Fjournal.pntd.0000317, accessed November 15, 2010).

TABLE WO-3 Four NTDs Slated for Eradication or "Elimination"

		Onchocerciasis			
Disease Program	Dracunculiasis	OEPA	APOC	Lymphatic Filariasis	Trachoma
Goal	Eradication 2009	Elimination (interrupt transmission) 2012	Control (public health problem) 2015	Elimination (public health problem) 2020	Elimination (blinding trachoma) 2020 (TF <5% in 1–9 y/o)
Endemic Countries Known?	Yes	Yes	Yes	Mostly	Uncertain
Status of Surveillance	Very good	Excellent	Good	Incomplete	Incomplete
Coverage Target for Intervention	100%	>85% × 2	65%	80%	80%
Extent of Intervention	98% filters (2009)	93% (2009) (0.626 m/ 0.672 m)	63% (2008) (57 m/ 90 m)	29% (2009) (385 m/ 1.333 b)	33% (2009) (40 m/ 120 m)
Monitor Disease/ Intervention	Monthly	Monthly	Annually	Annually	No

SOURCES: Hopkins (2010); Carter Center.

generation," Hopkins observed. "Most NTDs cannot be eradicated or eliminated, but all can and should be much better controlled. The few NTDs that may be vulnerable to elimination or eradication should be pursued ruthlessly."

Human African Trypanosomiasis (HAT) (Sleeping Sickness)

Caused by single-celled protozoan parasites belonging to genus *Trypanosoma*, HAT is transmitted to humans through the bite of the tsetse fly (genus *Glossina*) (Simarro et al., 2008). HAT is fatal if left untreated. Tsetse flies inhabit remote sub-Saharan rural areas where health systems are weak or non-existent (Simarro et al., 2008). People who live in these areas and who depend on agriculture, fishing, animal husbandry, or hunting are frequently exposed to the bite of the tsetse fly and therefore to HAT. Thirty-six sub-Saharan countries are considered endemic for HAT, although some of them have reported no cases in the last decade.

Together, HAT and the animal form of the disease, called nagana, have sig-

nificantly hindered development, agricultural productivity, and food security in Africa. Increased HAT transmission is associated with human migration, war, and poverty (Berrang-Ford et al., 2010; Simarro et al., 2008). As part of his presentation on the NZDs (see below), Forum member Lonnie King of the Ohio State University remarked that African trypanosomiasis has rendered cattle production unsustainable in parts of Africa that are heavily infested with tsetse flies. As a result, he said, human and animal populations have migrated from these areas in order to survive.

The vast majority of HAT infections involve the parasite *Trypanosoma brucei gambiense*, which causes a chronic infection that may remain asymptomatic for months to years (Simarro et al., 2008). Symptoms—such as severe headaches, sustained fever, sleep disturbances, and neurological disorders—may not emerge until the disease reaches an advanced stage and begins to affect the central nervous system. *Trypanosoma brucei rhodesiense*, which causes fewer than 10 percent of HAT cases, produces an acute infection (Simarro et al., 2008). Symptoms of its first stage occur within weeks to months and include chancre, occasional headaches, irregular fevers, pruritus, and the development of adenopathies. As with *gambiense* infections, the parasites eventually cross the blood–brain barrier and invade the central nervous system, producing severe neurological disease that is fatal if left untreated.

In the early part of the 20th century, HAT decimated populations in many parts of sub-Saharan Africa (Simarro et al., 2008). In his workshop presentation, Jean Jannin of WHO explained that, in the 1930s, colonial administrations established disease control programs that enabled the systematic screening, treatment, and follow-up of millions of people across the African continent; as a result, by the mid-1960s, HAT transmission was nearly stopped. (Dr. Jannin's contribution to the workshop summary report can be found in Appendix A, pages 310–323.) Soon thereafter, however, many HAT control efforts were abandoned as many African countries achieved colonial independence and took on more immediate challenges. The disease slowly returned to past endemic areas, leading to outbreaks that began occurring in the 1980s. Social upheaval, war, and migration, combined with a lack of awareness and poverty, hindered the public health response to HAT and permitted its further spread.

Following a 1997 World Health Assembly resolution strongly advocating access to diagnosis and treatment for HAT and the reinforcement of surveillance and control activities, WHO established a network to strengthen coordination among all stakeholders, which led to stronger public- and private-sector support for HAT surveillance, control, and research (Simarro et al., 2008). Aided in part by the abatement of social upheaval and civil war in many countries where HAT was endemic, control of the disease has greatly improved in recent years. Between 1995 and 2006, the total number of new cases reported declined by 68 percent. Today, with fewer than 10,000 cases reported per year for the first time in 60 years, Africa is poised to eliminate HAT, Jannin observed.

Although a field diagnostic for HAT exists and is widely used for population screening, it is neither applicable to *rhodesiense* disease nor sufficiently sensitive to establish a definitive diagnosis (Simarro et al., 2008). A confirmatory diagnosis requires the microscopic evaluation of blood and lymph for parasites and, when positive results are found, assessment of the stage of infection, which requires a lumbar puncture and cerebrospinal fluid examination. Four parenteral drugs are used to treat HAT: suramin (developed in 1921) for first-stage *rhodesiense* disease; pentamidine (1940) for first-stage *gambiense* disease; melarsoprol (1949) for the second stage of both forms of HAT; and eflornithine (1990), which is only effective in the second stage of the *gambiense* form. Use of any of these drugs is cumbersome and risky, necessitating the support services of a well-trained staff. Over the past decade, WHO has distributed more than 175,000 HAT treatments, according to Jannin. All the drugs are donated to WHO by their manufacturers, sanofi-aventis (eflornithine, melarsoprol and pentamidine) and Bayer AB (suramine).

Jannin emphasized, however, that "we are killing—there is no other word—eight percent of our patients due to the toxicity of melarsoprol, and we are sure to face an increased number of resistant cases." Halting the use of melarsoprol entirely would end treatment for second-stage *rhodesiense* infections and switch treatment of *gambiense* infections to eflornithine, which requires 56 infusions over a two-week period, he said. This would be "quite impossible for the health-care facilities to do." To address the latter dilemma, WHO and sanofi-aventis developed eflornithine kits to provide these facilities with everything they needed to administer the drug. In 2006, he said, such a kit weighed 20 kilograms and cost US$700. This load was lightened somewhat by the recent development of the drug combination nifurtimox[12]-eflornithine for HAT, which reduced the treatment kit's weight to 9 kilograms and the cost to US$360. This combination also facilitates the administration of the drugs. Despite the considerable challenges associated with distributing these kits to remote locations, "everybody now, even in South Sudan or Democratic Republic of Congo can access these drugs," Jannin said. "But it's not enough to provide the drugs," he continued. Patient management is a challenge, because it requires delivering the drugs by catheter over the course of days. To meet this challenge, WHO organized regional trainings for individuals who are now instructing health care providers at the country level, he said.

Currently, 19 African countries are reporting no cases of HAT, but only 7 of them are continuing regular surveillance, according to Jannin. To confirm these findings, WHO is developing regular surveys of historical foci. Eleven countries have fewer than 100 HAT cases per year, and 3 are reporting between 100 and 500, he observed. Only 2 countries—the Central African Republic and the DRC—are reporting more than 1,000 cases per year. Chad is reporting between

[12] Nifurtimox, manufactured by Bayer, is used to treat Chagas disease (American trypanosomiasis).

500 and 1,000 cases per year. At this rate (given that current prevalence and incidence estimates for HAT are considered accurate), elimination of HAT now appears feasible, Jannin said.

Among the steps currently being taken to pursue that goal, Jannin described the nearly complete "Atlas of Sleeping Sickness," which maps 122,000 cases reported in the past decade. Efforts are also under way to develop new diagnostics for HAT that can be used in rural African treatment centers—ready to use, stable at room temperature, operable by workers with minimal training, and affordable by national health systems—and which provide a clear diagnosis of both forms of HAT (Simarro et al., 2008). To support the development of such diagnostics, WHO established a sample bank, currently housed at the Institut Pasteur in France, containing samples of relevant bodily fluids from hundreds of HAT patients and controls, Jannin reported. Attempts are also under way to develop a safe, affordable, orally administered drug effective against both types of HAT at both disease stages (Simarro et al., 2008). Although progress has been made in controlling the tsetse fly by various methods, none is ideal or universal; thus, vector control is also a subject of research and development to address HAT.

The quest to control HAT is now at a turning point, Jannin observed: should the world be content to maintain HAT at low levels, or should attempt to further reduce the number of cases? Moving forward means addressing the considerable limitations of HAT diagnostics, drugs, and their distribution. He added, though, that holding treatment back means risking the re-emergence of the disease, much as occurred in the last decades of the 20th century. This is a particular concern, he added, because of a looming drain on human resources to fight HAT. "The average age of our technicians is around 55 or more," he said. "We have a system which is now working well. We have fantastic achievements. But it's very, very fragile." Despite the graying of the workforce and the fragility of the system, he concluded, the sustainable elimination of HAT can be achieved, and he anticipated that such an announcement would be made by WHO's Director General in the coming months.

"To look at what has been accomplished against a terrible disease, but an almost even worse treatment, is incredible," Hopkins observed in discussion following Jannin's presentation. "It points to the other intangibles, besides the tools," Hopkins continued. For example, he said, "look at what it takes to treat human African trypanosomiasis and compare it to what it takes to treat yaws (see Box WO-6): a single injection of long-acting penicillin, full stop. It doesn't even require refrigeration. Yet there is still a lot of yaws in the world."

Schistosomiasis

Caused by several species of tremotodes ("flukes"), the parasitic worms of the genus *Schistosoma*, schistosomiasis (also known as bilharzia) may infect as many as 600 million people in Africa, the Middle East, South America, South-

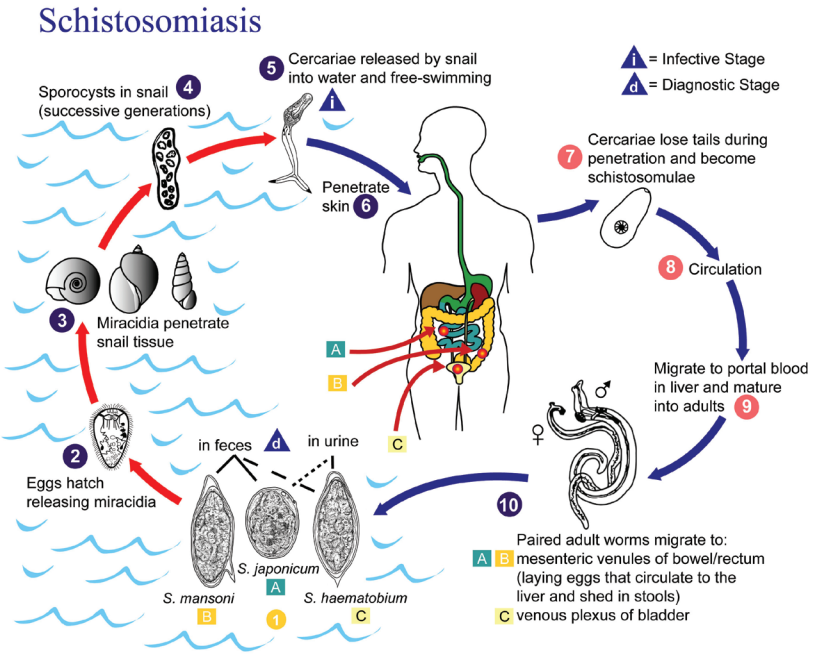


FIGURE WO-8 Life cycle of schistosomiasis.
SOURCE: Centers for Disease Control and Prevention.

east Asia, and the Philippines (King, 2007, 2010). Humans acquire this infection through contact with water infested with the parasite's free-swimming larval stage. Eggs released into freshwater infect aquatic snails and develop into larvae. After leaving the snails, the larvae can live for about 48 hours before penetrating the skin of a mammalian host, such as a person who is bathing or swimming (CDC, 2008). Within several weeks, worms grow inside the blood vessels of the body and produce eggs. Some of these eggs travel to the bladder or intestines and are passed into the urine or stool, completing the cycle. The life cycle of schistosomiasis is illustrated in Figure WO-8.

Schistosomiasis is closely tied to the unsanitary disposal of human waste, and its spread has been closely linked to the construction of dams and irrigation systems. Following the construction of the Aswan High Dam in Egypt in the 1960s, which was intended to control alluvial flooding and to generate hydroelectric power from the Nile River, environmental changes allowed aquatic snails to proliferate (Malek, 1975). Soon after the dam's completion, schistosomiasis, which previously had been rare in the region, spread widely and became endemic to the area. More recently, dam construction in Nigeria has dramatically altered

the freshwater environment, allowing freshwater snails to proliferate, which has resulted in an increase in the prevalence of schistosomiasis in the region (Oladejo and Ofoezie, 2006).

Speaker Charles King, of Case Western Reserve University, described recent progress in understanding this challenging disease. (Dr. Charles King's contribution to the workshop summary report can be found in Appendix A, pages 323–342.) "We are rethinking what schistosomiasis is all about, which in turn helps to drive some of the decision making about who needs treatment, when they need treatment, and for how long," he said. In the 1970s and 1980s, efforts to address schistosomiasis assumed that "the more infection you had, the more disease you had," he observed. Therefore, rather than treating entire communities for schistosomiasis, control programs overlooked large numbers of people with subclinical infections and focused on the few with advanced disease, who were identifiable because they were passing high numbers of eggs. Indeed, he noted, some researchers concluded that the vast majority of people infected with schistosomiasis were not ill (Gryseels, 1989) and, consequently, that the disease did not represent a significant public health problem.

"This approach was wrong," C. King concluded, because it ignored the physiological importance of subclinical disease and, in particular, its effects on development. Most people acquire schistosomiasis before the age of 5, he said. As a result, he said, these individuals suffer a host of systemic and organ-specific pathologies associated with the parasite's presence, including anemia, stunting, wasting, lack of fitness, cognitive impairment, infertility, and genital lesions. Infection brings about a lifetime of disease, he observed, "starting when you are born, with poor vaccine response; as you start to become affected after the age of four, getting into problems with anemia, growth stunting, lack of fitness. This can persist as long as you are infected. You begin to lose schooling due to persistent symptoms. There is intermittent pain, then chronic organ dysfunction. As you get to reproductive years, there is genital schistosomiasis, both male and female, and infertility in women, with both primary and secondary infertility, probably due to mechanical obstruction." As previously noted by McDonald, schistosomiasis takes a particularly heavy toll on women, for whom it is associated with increased risk of HIV infection, ectopic pregnancy, and painful intercourse. In Zimbabwe, Hotez reported on studies conducted by scientists at the University of Oslo who showed that female genital schistosomiasis has increased horizontal transmission of HIV/AIDS by at least threefold in Zimbabwe (Hotez et al., 2009a; Kjetland et al., 2006). These problems typically occur before the onset of advanced disease, which tends to occur after age 30, C. King observed. Therefore, "if we focus only on advanced disease," he said, "that's a very small subset of the population. It's also a very small subset of the disease."

These insights prompted C. King to redefine schistosomiasis as "a preventable, chronic, inflammatory condition caused by present or previous infection with metazoan parasitic blood flukes of *Schistosoma* species." He estimated that

more than 440 million people fit this description and that many of them suffer complications from past infection. "We are beginning to refocus on the lifetime impact and the ecology of infection and disease, because, as it turns out, these are actually the more important outcomes that we need to be using as markers in our monitoring and evaluation," he observed.

C. King then went on to discuss how a broader understanding of schistosomiasis was being translated into efforts to control the disease and mitigate its effects. Mathematical simulations suggest that children treated for schistosomiasis every one to two years through adolescence will attain full growth and experience reduced symptoms, he said. Because schistosomiasis is embedded in ecosystems, he added, "we are beginning to talk about issues of transmission control, not elimination or eradication. We need to do more than just drug therapy to really protect the people in these communities." An integrated approach, combining education, behavior modification, sanitation, a protected water supply, snail habitat modification, and molluscicide treatment, could significantly reduce transmission of schistosomiasis in endemic communities, he stated. According to their model, reducing child-to-child transmission by 75 percent would effectively eliminate the disease. Ultimately, he said, schistosomiasis demands the same suite of interventions that liberated the American South from hookworm, malaria, and pellagra: disease control, micronutrient supplementation, agricultural extension programs, education, and rural electrification (in part to ensure clean water).

Chagas Disease

Sometimes called "American trypanosomiasis," Chagas disease is also caused by a trypanosome parasite, *T. cruzi*, and spread by an insect vector—not by a fly, but by members of the family Reduviidae commonly known as "kissing bugs" or "assassin bugs." Speaker Rick Tarleton, of the University of Georgia and the Chagas Disease Foundation, explained that reduviid bugs, which feed on warm-blooded animals, infest the walls and roofs of houses in areas where Chagas disease is endemic. (Dr. Tarleton's contribution to the workshop summary report can be found in Appendix A, pages 505–522.) Parasites present in the bug's feces can be transmitted to mammals as the insect feeds on them, or through ingestion of contaminated food. In its mammalian host, the parasite cycles between a brief extracellular stage that circulates in the bloodstream and the disease-producing intracellular stage that penetrates muscle, fat, and sometimes nerve cells, causing cardiac disease—the most common consequence of infection—as well as gastrointestinal disorders. These symptoms, which result from years of accumulated tissue damage due to the body's immune response to low levels of parasites (which it can suppress, but not easily clear), typically arise decades later and tend not to be treated, he said.

Surveillance for Chagas disease is poor, according to Tarleton, who estimated that 10 to 20 million people, most of whom live in Latin America, are infected

with the parasite. The southern United States is endemic for Chagas disease, and the parasite is present in many animal species in that region. He noted, however, that good housing conditions in the region often limit transmission to humans. However, physician awareness of Chagas disease is low and screening and treatment capabilities are limited in the United States and in other wealthy countries (e.g., Spain, Canada, Australia, and Japan) where the disease infects relatively few people, most of whom are immigrants. Transmission of Chagas disease within these countries occurs mainly congenitally or between blood and organ donors and recipients, he said.

Nevertheless, Hotez observed, Chagas disease transmission does appear to be occurring at low levels in areas of the United States inhabited by reduviid bugs. He noted that zoonotic transmission from dogs is also a concern in the United States, as is the possibility that climate change will expand the geographic range of reduviid bugs, thereby increasing the potential distribution of Chagas disease.

Owing to the low parasite load typical of *T. cruzi* infection, diagnosis is difficult, Tarleton observed. The standard for detection is a blood smear, which is often inconclusive (CDC, 2010c).[13] Positive results on at least two of three different serological tests is often accepted as a definitive diagnosis, he explained. Different groups use different sets of tests to determine seropositivity or negativity for Chagas disease, he said. Even using best-two-out-of-three, it may not be possible to detect every infected individual. The most sensitive method for *T. cruzi* diagnosis, known as xenodiagnosis, involves allowing lab-reared (sterile) reduviid bugs to feed on patients, according to Tarleton; if the bugs become infected, the parasite will multiply to detectable levels within four to six weeks. This technique is still used frequently, especially on young children, he noted—and, like all other parasite detection methods for Chagas disease, it is not sufficiently sensitive to monitor treatment efficacy.

As Tarleton pointed out, the upside of the diagnosis dilemma for Chagas disease is the lack of need for rapid or point-of-care tests; most patients with symptoms are already chronically infected, and the treatment course lasts 30 to 60 days. There is no urgency to treat them at the point of detection, he explained; testing and treatment can be performed at centralized locations. He added, however, that disease diagnosis needs to involve a single, uniform, and rigorously certified test that is quantitative so that it can also be used to monitor changes during and following treatment. Rather than attempt to detect small numbers of parasites, it might be preferable to identify robust protein or gene-expression markers and incorporate them into multiplex serodiagnostic assays, he added.

[13] The diagnosis of Chagas disease can be made by observation of the parasite in a blood smear by microscopic examination. Thick and thin blood smears are made and stained for visualization of parasites. However, a blood smear works well only in the acute phase of infection, when parasites are seen circulating in blood. CDC Chagas Disease—Diagnosis. http://www.cdc.gov/chagas/diagnosis.html (accessed November 15, 2010).

"Development of a test that absolutely certifies parasitological cure is also going to be very difficult," he concluded, "but I don't think this is unique to *T. cruzi* or Chagas disease."

Two drugs are widely used to treat Chagas disease, Tarelton stated: benznidazole, the mainstay of current treatment, and nifurtimox, which was used in the past and has recently returned to use. Both produce considerable but generally manageable side effects, he added, and they require a 30- to 60-day course of treatment. Their biggest drawback stems from the lack of diagnostic methods to assess their efficacy. "It's easy to tell if somebody is acutely infected and has the circulating parasites that a drug works," he observed. "It's not so easy when you can't monitor what happens in somebody who is chronically infected . . . [and for whom] knocking down the parasites below a detectable level is not a cure." There is, however, evidence from a long-term study (that was neither randomized nor placebo-controlled) that treatment with benznidazole reduces the cardiac sequelae of Chagas disease, Tarleton noted. In this study, patients were followed for up to 15 years to compare the progression of clinical disease after treatment with the drug, or in the absence of treatment (Viotti et al., 2006). The researchers found that progression toward cardiac disease was reduced by approximately 75 percent in patients who received benznidazole. However, he added, "you certainly can't test a drug this way, so one thing that is really needed is accessible tests of cure, in order to evaluate new therapeutics [for Chagas disease]."

There are much improved high- and medium-throughput screening assays available to find leads for Chagas disease drugs, Tarleton continued, as well as good *in vivo* screens with which to follow up promising candidates. He noted that several companies, public–private partnerships, and nonprofits have begun to pursue this route. However, he added, inability to determine parasite load represents a major stumbling block to drug development for Chagas disease.

Treating houses with insecticide is the most effective means available for controlling *T. cruzi* infection, Tarleton said. This was demonstrated in initiatives coordinated by WHO and PAHO in the Southern Cone of South America in the 1980s and 1990s. However, he continued, reduviid bugs have developed insecticide resistance in some locations—a situation that is likely to worsen, particularly because the same insecticides are used in agriculture. Moreover, spraying houses is time-consuming, labor-intensive, and effective only for a few months. Integrated and sustainable vector control will be necessary to address Chagas over the long term, and it must be based on data, rather than anecdote, he concluded.

We are "just at the tip of the iceberg" in understanding Chagas disease, Hotez observed, and particularly its associated burden of disability. Speaker Mauricio Barreto, of Federal University of Bahia in Salvador, Brazil, recalled that in the 1970s, when his country experienced intense transmission of Chagas disease, it was estimated that more than 5 million people were infected with the parasite. An intensive vector control program eliminated its main vector, which (along with

monitoring of the blood supply) reduced transmission to very low levels, he said. Nevertheless, it is important to recognize the chronic nature of Chagas disease and to develop treatments for its sequelae in addition to preventive measures, he concluded.

NTDs in the United States

In a workshop presentation titled "Left Behind in America: Our Nation's Neglected Infections of Poverty," Hotez described how he came to the conclusion that several NTDs and related neglected infections of poverty remain highly prevalent among the poorest residents of the United States (Hotez, 2008b, 2009a). Following a database search through PubMed over 25 years using terms such as "neglected diseases" and "poverty," as well as specific geographic regions, racial, ethnic, and socioeconomic groups, and the names of the 30 NTDs listed on the website of *PLoS Neglected Tropical Diseases*, he estimated disease prevalence rates among selected communities in which studies had been done. He then multiplied these local rates by published estimates of at-risk populations in socioeconomically disadvantaged groups to produce the estimates shown in Table WO-1.

"The diseases that really stuck out from this analysis were what we sometimes now call the three C's and the three T's," Hotez said. Two of the Ts, toxocariasis and trichomoniasis, are prevalent among impoverished African American populations, as is congenital cytomegalovirus, particularly among women and children; among impoverished Hispanic Americans, he found relatively high rates of cysticercosis, Chagas disease, and toxoplasmosis. Hotez provided the following brief descriptions of these diseases as manifested in U.S. populations (see above for a discussion of Chagas disease in the United States).

Toxocariasis Although "not a disease most people think about," Hotez said he believes toxocariasis to be the most common helminth infection in the United States (Hotez and Wilkins, 2009). The parasite is transmitted from infected dogs and cats—in the United States, dogs in the inner city and stray dogs in the South—which shed eggs that people ingest; the larval stages then migrate either through internal organs or the central nervous system (visceral larva migrans) or they migrate to the eyes or optic nerve (ocular larva migrans). Several European studies (Buijs et al., 1994, 1997; Taylor et al., 1988) link toxocariasis to asthma and developmental delays, he reported. A recent CDC survey found an age-adjusted seroprevalence for the disease of 21 percent among non-Hispanic blacks versus 12 percent among whites, with the highest rates in the American South (Won et al., 2008); Hotez noted that the risk factors associated with infection included low levels of education, poverty, and elevated lead levels. His own estimates suggest that about 2.8 million African Americans in the United States have been exposed to or infected by toxocariasis.

Trichomoniasis African American women have a 10-fold higher prevalence of this parasitic sexually transmitted infection compared to whites, according to Hotez, with some of the highest rates occurring in Louisiana. Apparent risk factors for trichomoniasis infection in the United States include low educational levels and poverty. Hotez called his original estimate of approximately 900,000 cases in African American women "very conservative." Trichomoniasis is associated with preterm delivery and low birth weight, he reported, and the disease has also been identified as an important risk factor in the HIV/AIDS epidemic in the American South, because of increased viral shedding associated with co-infection (Kissinger et al., 2008; Sutton et al., 2007).

Congenital cytomegalovirus (CMV) infection A leading cause of hearing loss, vision loss, and mental retardation, CMV occurs at strikingly high rates among African American women, Hotez said. "There are an estimated 27,000 new CMV infections among seronegative pregnant women every year who acquire the virus during pregnancy," he noted, reflecting a 50-fold increase in risk among pregnant African American teenagers and a fourfold increase in risk overall (Colugnati et al., 2007). CMV is therefore "extraordinarily common and a major reason why kids are institutionalized here in the United States," he concluded.

Cysticercosis This parasitic infection of the brain currently represents the leading cause of epilepsy among Hispanic Americans, Hotez reported, adding that approximately 10 percent of seizures now presenting to emergency departments in Los Angeles result from cysticercosis. According to Hotez's estimates, between 40,000 and 169,000 Americans are infected by the tapeworms *Taenia solium* (the pork tapeworm) and *Taenia saginata* (the beef tapeworm).

Congenital toxoplasmosis Hotez estimates that about 4,000 cases of this disease, caused by the protozoan parasite *Toxoplasma gondii*, occur in the United States each year. According to L. King, toxoplamosis is the nation's third leading cause of death attributed to food-borne illness. A fetus can become infected with toxoplasmosis if the mother becomes infected during pregnancy, which may occur through improper handling of cat litter, or by touching or ingesting contaminated meat. Domestic cats contract the parasite from eating infected rodents or birds. Up to half of the fetuses infected with *T. gondii* are born preterm, and it can damage their eyes, nervous system, skin, and ears (National Library of Medicine, 2009).

Hotez noted that newborns with toxoplasmosis are often asymptomatic at birth; it can take up to a year for clinical manifestations, such as retinitis or intellectual deficits, to become apparent. "You actually have a year of opportunity to intervene with specific antiprotozoal chemotherapy," he observed, yet in the United States, only two states—Massachusetts and New Hampshire—routinely

screen newborns for toxoplasmosis.[14] "The cost-effectiveness studies are there to show that we should be doing screening throughout the United States," he asserted. Moreover, rates of disease—and consequences for children—are probably far higher in other countries. "This is probably an extremely important infection that we are just beginning to understand the full extent of," Hotez said, adding that congenital toxoplasmosis is not included in current global burden of disease assessments.

Hotez reported on new legislation, titled "The Neglected Infections of Impoverished Americans Act of 2010," which was introduced by Rep. Hank Johnson of Georgia and just passed in the U.S. House of Representatives. The legislation requests that the Secretary of the Department of Health and Human Services report to the U.S. Congress on the state of the neglected infections of poverty, especially the three Cs and Ts, as a beginning for understanding the true extent of these conditions, their modes of transmission, and research needs.

Dengue

A vector-borne viral disease spread by mosquitoes, dengue currently threatens 40 percent of the global population and causes up to 100 million infections and 25,000 deaths each year (WHO, 2010a). Dengue differs from other NTDs in that it causes acute illness rather than chronic disease (as noted in previous discussion regarding the inclusion of dengue among the NTDs); these include the complications dengue hemorrhagic fever (DHF) and the frequently fatal and more severe manifestation of the disease as dengue shock syndrome (DSS) (Morens and Fauci, 2008). Dengue incidence has increased rapidly over recent decades, and explosive outbreaks have occurred. As several workshop participants observed, dengue is underreported throughout the world (see below).

Brazil has been hard hit by dengue, particularly in its urban centers (Teixeira et al., 2009). The most recent epidemic in Rio de Janeiro, which occurred in 2008, claimed more than 200 lives, Mauricio L. Barreto of the Instituto de Saúde Coletiva, Federal University of Bahia, Salvador, Brazil, said. Dengue re-emerged in Brazil in the early 1980s when the DENV-1 serotype was introduced into the country, preceded a few years earlier by the re-introduction of *Aedes aegypti*; it has since spread throughout the country, transmitting three of the four dengue viruses (DENV-1 through DENV-3). Barreto reported that the presence of DENV-4 was officially confirmed as of July 2010. Although dengue is a very important disease intervention priority, Barreto observed that its control in Brazil presents major intervention challenges: its range has expanded rapidly, its vector is ubiquitous, and the factors that influence why some cases develop into a deadly hemor-

[14] Forum member Eduardo Gotuzzo, of Universidad Peruana Cayetano Heredia in Lima, Peru, noted that pregnant women in France are tested routinely for toxoplasmosis in order to detect subclinical infections.

rhagic fever have yet to be determined.[15] He expressed concern that a "massive epidemic in large cities in Brazil" could occur as early as 2011.

In his presentation to the workshop, the chief of the CDC's dengue branch, Harold Margolis, discussed the possible re-emergence of dengue in the continental United States. In his formal remarks at the workshop, he noted that more than 4 million Americans live in the dengue-endemic areas of Puerto Rico, the Virgin Islands, and the Pacific islands. In Puerto Rico, dengue is prototypically seasonal (with low rates of ongoing transmission during cooler, drier periods), prone to epidemics, and under-recognized, he said. The epidemiology of dengue in Puerto Rico (as well as Brazil) differs from that of other dengue-endemic locations in the region—nearly half of all cases occur in older children, young adults, and adults, he observed. In Asian countries such as Thailand and Vietnam, as well as in Central America, nearly all dengue infections and disease occur in very young children. In Puerto Rico, dengue "jumped the epidemic threshold" in July 2010, following heavy El Niño rains, Margolis said. At the time of his presentation, in mid-September 2010, more than 14,000 cases had been reported.

Between 1946 and 1980, there were no reported cases of dengue acquired in the continental United States and, until 2009, no locally acquired cases beyond the Texas–Mexico border (CDC, 2010a). In 2009, a locally acquired case of dengue was detected in Key West, Florida, heralding a local outbreak involving 27 residents; locally acquired cases have continued to be reported there. Margolis described the response to this outbreak, which included a serologic survey of 240 residents in which 13 were found to be seropositive for DENV-1. At the time of the workshop, Margolis stated that despite intensive vector control efforts a total of 44 locally acquired cases had been reported in 2010.

Based on the serologic survey, CDC estimated that 5 percent of Key West residents were seropositive for DENV-1 (CDC, 2010b). Hotez noted that DENV-2 has been prevalent along the Texas–Mexico border for several decades, particularly in low-income communities lacking window screening and garbage pickup (let alone air conditioning). These circumstances, Hotez warned, could precipitate urban dengue outbreaks throughout the Gulf Coast region that could become especially severe if the two viruses—DENV-1 and DENV-2—overlap, increasing the risk for DHF.

The potential for dengue to spread further into the United States depends to a large extent on the ranges of its vector species, *Aedes aegypti* and *Aedes albopictus*, Margolis said. *Aedes aegypti* is the fittest vector for dengue transmission, because it feeds exclusively on human blood. *Aedes albopictus*—also known as the Asian tiger mosquito—has a much wider range; it feeds on other warm-blooded animals and undergoes diapause during the winter, he explained. Where the two species overlap, or where only *A. albopictus* lives, dengue transmission is

[15] Various hypotheses regarding the pathogenesis of DHF and DSS are discussed by Morens and Fauci (2008), who note that these complications may result from a "complex interplay between viral phenotype, viral virulence, and host immunity."

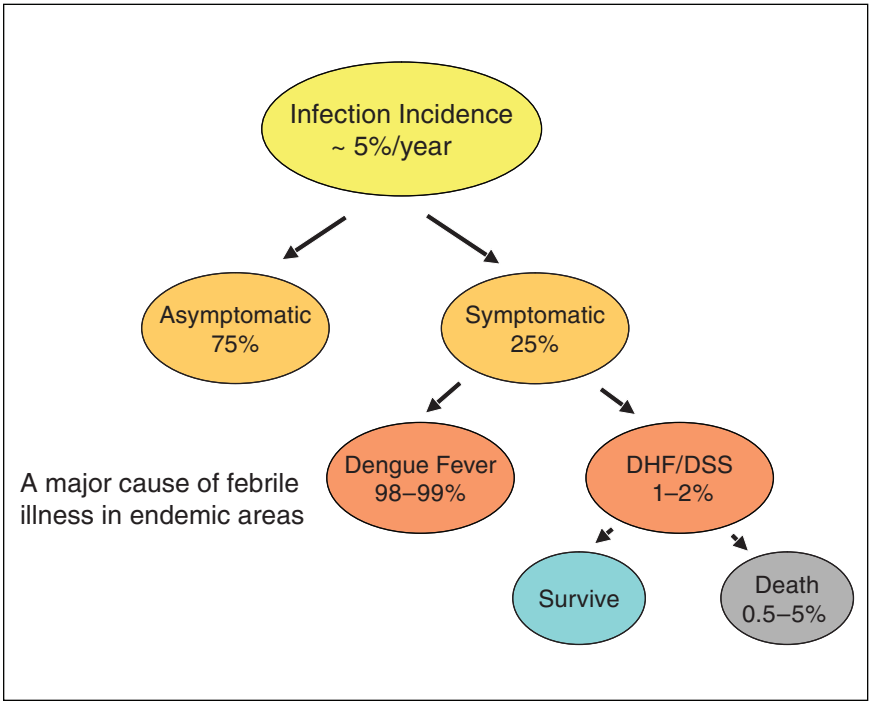


FIGURE WO-9 Dengue virus infection.
SOURCE: Margolis (2010); adapted from *Vaccine* 2002; 3043–3046.

not sustained as it is in areas inhabited solely by *A. aegypti*, such as Puerto Rico and Key West, Margolis stated.

Turning to the global re-emergence of dengue, Margolis discussed its under-recognition, which represents a significant barrier to addressing the disease. Figure WO-9 depicts the symptomatic cascade that results from dengue infection in endemic areas.

Only about one in four infections is symptomatic, he said; even so, dengue is a major cause of febrile illness in many tropical areas, sometimes co-circulating with influenza. Comparisons of laboratory-confirmed dengue in study sites with national incidence figures from several endemic locations, shown in Table WO-4, reveal major discrepancies suggestive of widespread under-diagnosis. Similarly, case reviews of suspected dengue deaths in Puerto Rico indicate that dengue-associated mortality is under-reported, much to Margolis' dismay. "In a country where you ought to be recognizing a severe disease like this, we are not recognizing it," he acknowledged.

TABLE WO-4 Laboratory-Confirmed Dengue Fever in Study Sites Compared to Reported National Incidence

Study Site	Design	Age Group	Incidence	Incidence (National Surveillance)
Patillas, Puerto Rico	Enhanced surveillance	All	0.8%	0.07% (10)
Managua, Nicaragua	Cohort	4–16 years	0.9%	0.026% (34)
Kolkata, India	Cohort	All	0.5%	0.002% (250)
Ratchaburi, Thailand	Cohort	3–13 years	1.7%	0.075% (23)
Kampong Cham, Cambodia	Active surveillance	0–15 years	1.0%	0.028% (33)

SOURCE: Margolis (2010); Pediatric Dengue Vaccine Initiative Field Site Consortium data.

On a more positive note, Margolis described some recent improvements in the "dengue toolbox," comprised of integrated vector control, case management, diagnostics, vaccines, and antivirals. Although integrated vector control has been the mainstay of primary prevention for dengue, "it has really not prevented nor has it ever stopped an epidemic that is in progress," he said. Integrated vector control might be possible through the release of genetically modified, sterile mosquito vectors, which are currently being developed. He also held out hope that reclassification guidelines from WHO, introduced in 2009, might improve identification of dengue cases and, therefore, their outcomes, because good case management has been demonstrated to reduce dengue mortality from 5 percent to less than 0.3 percent. Margolis further noted that primary care physicians in Puerto Rico, in order to maintain their medical licenses, must now take a course in dengue case management by 2013.

Margolis also cited recent improvements in dengue diagnostics, which he characterized as having been complicated, difficult to interpret, too slow for clinical diagnosis, and expensive. "Dengue is tough," he said. "You get viremia that actually goes on for a fairly long period of time at high titers. There is a soluble antigen, a nonstructural antigen . . . [but] IgM [immunoglobulin M] doesn't become detectable until about day 4. We don't know if it's not produced or if our tests aren't that good." As a result, dengue diagnosis previously required two specimens: one from the acute stage, and one from the convalescent stage—fine for surveillance, he observed, but no help to clinicians. Moreover, he added, in subsequent infections, IgM titer tends to be lower. However, a combined virus

detection strategy, using a molecular or NS1[16] test with the IgM anti-DENV,[17] circumvents the need for paired samples (Lima et al., 2010). Margolis added, however, that this detection method has not yet been commercialized or sold in Food and Drug Administration (FDA)-approved kit form. Its availability, therefore, is quite limited, especially in low-income countries.

Margolis reported that several companies are developing tetravalent dengue vaccines, although most are in early (Phase I) stages of evaluation. Dengue vaccines must overcome some significant challenges including

- interference, as multi-valent formulations of live, attenuated vaccines result in decreased immunogenicity and increased number of vaccine doses;
- the need to protect against multiple DENV types; and
- the distribution and delivery of vaccines to low-resource settings.

There is also a theoretical potential for vaccination to cause immune-enhanced disease, which Margolis said could be studied in animal models. In the course of these vaccine trials, about 800 children have been immunized with monovalent vaccines and challenged with another dengue infection. None of these children, now adults, has had severe dengue upon reinfection. These data suggest (although with small numbers and large confidence intervals) that immune-enhanced disease will be a rare event, he concluded—although active surveillance is being conducted to confirm this suggestive evidence.

In response to Margolis' presentation and the ongoing discussion about whether dengue should be included among the NTDs, Dr. Lorenzo Savioli, Director of WHO's Department of Control of the Neglected Tropical Diseases, related discussions at WHO's NTD Strategic and Technical Advisory Group in 2010 that dengue should be distinguished from the NTDs with a special program all its own because of its present expansion. Dengue outbreaks can be effectively contained—at least in some endemic areas—with appropriate surveillance, integrated vector management, and proper tools, Savioli observed. WHO has taken up this challenge, he said, "because indeed it's something that is getting out of control."

[16] The flavivirus non-structural protein NS1, a highly conserved and secreted glycoprotein, is a candidate protein for rapid diagnosis of dengue in endemic countries. The NS1 antigen test (the Platelia Dengue NS1 Ag assay) is a test for dengue made by Bio-Rad Laboratories and Pasteur Institute, introduced in 2006. It allows rapid detection on the first day of fever, before antibodies appear some five or more days later. For further information, see NS1 Antigen Test, http://en.wikipedia.org/wiki/NS1_antigen_test (accessed November 16, 2010).

[17] The most used techniques for dengue serodiagnosis are based on the anti-DENV IgM and immunoglobulin G (IgG) detection by using MAC-ELISA and IgG-ELISA. SOURCE: Lima et al. (2010).

Neglected Zoonotic Diseases (NZDs)

Approximately 60 percent of all human pathogens are zoonoses: microbes that are naturally transmitted between animals and humans. Zoonotic diseases such as anthrax, bovine tuberculosis, brucellosis, cysticercosis, echinococcosis (hydatid disease), and rabies are endemic in many developing countries of Africa, Asia, and South and Central America. Neglect of their control persists because of a lack of information and awareness about their distribution, a lack of suitable tools and managerial capacity for their diagnosis, and a lack of appropriate and *sustainable* strategies for their prevention and control. Furthermore, many of the most affected countries have poor or non-existent veterinary public health infrastructures. This situation has marginalized control of zoonoses to the gap between veterinary responsibilities and medical needs, generating a false perception that their burden and impact on society are low. As a result, neither the human and animal health resources nor the research needed for their control are available, spawning a category of NZDs.

Introducing a workshop presentation that described individual NZDs and issues in their control as a group, Forum member Lonnie King of the Ohio State University characterized these diseases as a subset of NTDs. In particular, he noted, NZDs disproportionately burden the poor, who are more at risk of acquiring these illnesses because of their frequent contact with infected animals, and because poverty reduces opportunities for effective treatment. A general lack of awareness of the importance of NZDs has resulted in a concomitant dearth of suitable diagnostic tests and surveillance for these diseases, and of appropriate and sustainable prevention and control strategies to address them, he stated.

NZDs are doubly burdensome, as they sicken and kill valuable livestock as well as humans. This impact falls largely on the rural poor in developing countries, many of whom depend on animals for food, transportation, and farm work. NZDs, moreover, also affect the urban poor through their consumption of contaminated meat and milk products (WHO, 2006, 2010d,e). Agricultural development programs, a potential source of support for animal health in developing countries, have tended to focus on crops rather than livestock.

Because NZDs largely affect impoverished livestock caretakers and their families, prevention and control of these diseases can save lives, secure livelihoods, and help alleviate poverty, L. King observed. He estimated that livestock contributes to the livelihoods of 70 percent of the world's poor people, and that approximately 800 million poor livestock keepers are dependent upon their animals and animal agriculture. The animals, in turn, support farmers, consumers, laborers, and trade in developing countries in major ways. According to the United Nations Food and Agriculture Organization (FAO), livestock numbers will need to increase by 50 percent in the next decade to meet increased global demand for proteins from animal sources (FAO, 2002), increasing the opportunity for transmission of a broad range of zoonotic diseases, he added. To meet these challenges, the unique position of NZDs at the interface between human and

animal health must be recognized,[18] and the two constituencies must engage in effective collaboration, he concluded.

L. King provided the following descriptions of representative NZDs (see also discussion of African trypanosomiasis, above, and disease descriptions in Box WO-6), and he noted that all zoonotic diseases in animals are neglected in developing countries.

Anthrax Caused by the spore-forming *Bacillus anthracis*, anthrax is almost always fatal in animals. In humans, the disease occurs in three forms: inhalation anthrax, an occupational disease that affects humans only in industrialized countries; gastrointestinal anthrax, which results from eating meat from an infected animal; and cutaneous anthrax, acquired through contact with skin lesions of infected animals, which comprises 95 percent of cases in developing countries.

Bovine tuberculosis Caused by the bacterium *Mycobacterium bovis*, this form of TB produces extra-pulmonary infection that seldom causes death in cattle but can cause significant morbidity in cattle in developing countries. In humans, bovine TB may be clinically indistinguishable from *M. tuberculosis* infection or it may be manifested as an extra-pulmonary infection. Patients often do not respond to common TB drugs. As a result, improper diagnosis and treatment may prove fatal. Effective treatment of bovine TB in humans requires specific and expensive drugs. Both forms of human TB infections appear to be increasing worldwide, and at similar rates, but both diseases are known to be under-reported. Prior to the establishment of milk pasteurization in the United States, an estimated 20 to 30 percent of domestic TB cases resulted from infection with *M. bovis*.

Brucellosis Caused by bacteria of the genus *Brucella spp.*, this disease infects cattle, sheep, pigs, and goats, among other species. Livestock infection contributes to abortion, permanently reduced fertility, and chronically reduced milk yields. Brucellosis is transmitted from infected animals to humans by direct contact, or by drinking their milk. In humans, the resulting chronic debilitating disease in tropical areas is often mistaken for drug-resistant malaria. In disease-endemic areas, brucellosis results in large losses to livestock producers.

Cysticercosis Caused by the pork tapeworm *Taenia solium*, cyticercosis infects humans who consume food contaminated with *T. solium* eggs. After the larvae hatch in the digestive system, they migrate to the muscles, brain, or eyes, where

[18] Control of zoonotic diseases requires coordination between the veterinary and human medical and public health sectors, which is particularly difficult to achieve under conditions of limited resources and inadequate governance structures. The lack of animal health infrastructure in many developing countries fosters the perception that zoonotic diseases do not impose a significant health burden. On the contrary, evidence-based studies on some NZDs have determined that their true incidences can be 100-fold higher than reported (WHO, 2006).

they form cysts. Cyst formation in the brain can induce seizures. Cysticercosis represents a major cause of preventable epilepsy, especially in developing countries. An estimated 50 million people are infected with *T. solium*, most of whom live in areas distinguished by inadequate sanitation and poor pig husbandry practices and that lack effective systems for meat inspection and infection control. Because the disease travels with both humans and pigs, it spreads easily. In the United States, livestock in some border areas have relatively high rates of cysticercosis because of their increased exposures to infected people.

Echinococcosis Also known as hydatid disease, echinococcosis is caused by the tapeworm *Echinococcus granulosus*,[19] which moves from sheep, to dogs, to people who ingest tapeworm eggs through contaminated water and food. The resulting cysts, typically located in the abdomen, grow slowly but ultimately must be surgically removed. The disease can be controlled by deworming dogs and keeping them from eating sheep offal. Echinococcosis is distributed globally and is associated with a significant burden of disease, especially in northern Africa and the Middle East.

Rabies Although well-controlled in developed countries, rabies causes an estimated 55,000 to 60,000 deaths per year in the developing world. Domestic dog bites are responsible for more than 95 percent of human infections, although bats are a major reservoir for the virus. Post-exposure prophylaxis for rabies is administered to approximately 10 million people each year. In developing countries, veterinary care tends to be poorly supported and there is little collaboration between animal and human health sectors. Not surprisingly, rabies is endemic in settings where large groups of unvaccinated and unconfined domestic dogs are present, coupled with few sustainable control measures, a lack of rabies education among traditional healers, and political or economic instability.

L. King also briefly discussed several diseases he termed animal-associated NZDs. These include dengue, toxoplasmosis, Chagas disease, and toxocariasis.[20] Highlights of his remarks on some of these diseases, and disease agents not discussed elsewhere in this overview, are noted below and in Box WO-6.

***Bartonella* and other rickettsial diseases** These infections—among them, cat scratch disease, spotted fevers, typhus, and scrub typhus—are caused by related organisms, which include members of the genera *Bartonella*, *Anaplasma*, and *Ehrlichia*. A wide range of vectors including sand flies, lice, fleas, biting flies, and ticks transmit the organisms to humans. As more is learned about *Bartonella*, L. King observed, the diseases associated with these bacteria appear to be "more

[19] Also *E. multilocularis*.

[20] In subsequent discussion, participants suggested the addition of plague and Rift Valley fever to the list of animal-associated NZDs.

widespread in the world than anybody ever thought especially in immunocompromised populations."

Q fever *Coxiella burnetii* bacteria, which are shed in the milk, urine, feces, amniotic fluids, and placental materials of animals, can infect humans, causing the flu-like symptoms of Q fever. About 1 percent of infected individuals develop chronic infection. The bacterium is distributed worldwide and has recently caused major outbreaks of disease in the Netherlands, where more than 50,000 pregnant sheep were slaughtered in 2010 in an attempt to curb its spread; 8 percent of sheep in the Netherlands are estimated to be seropositive for *Coxiella*. A recent U.S. study determined that more than 3 percent of the general U.S. population (~9.5 million people), and about 22 percent of U.S. veterinarians, were seropositive for the bacterium.

Leishmaniasis Recognized by Hotez as "one of the most important protozoan infections of humans after malaria," leishmaniasis (also known as kala-azar) is actually a complex of diseases involving more than 20 parasite species, more than 30 vector species of sandflies, and a broad range of animal hosts including wild rodents, marsupials, hyraxes, edentates, and dogs, as well as humans. A disfiguring and sometimes fatal disease, leishmaniasis mainly affects residents of low- and middle-income countries who reside in areas where housing and sanitation are inadequate. The disease tends to disproportionately affect the very young and very old.

Leptospirosis Perhaps the most under-reported NZD in the world, leptospirosis is a bacterial infection that is usually transmitted to humans through contact between skin or mucous membranes and water contaminated with the urine of an infected animal. Because leptospirosis is a febrile illness without any "unique" early signs or symptoms of infection, it is difficult to diagnose. Moreover, surveillance for leptospirosis is poor, and its prevalence remains unknown. It is, however, perceived to be a growing threat in peri-urban settings with large rodent populations.

Food-borne trematodes More than 70 species of trematodes (flukes) are known to be associated with a variety of diseases in people. Transmission occurs through a complex life cycle that involves snails as carriers, and, secondarily, animals that transport infected snails along with mud in their hooves. Trematodes currently infect an estimated 40 million people; 10 percent of the world's population is at risk of contracting such infections, with opisthorchiasis and clonorchiasis linked to high rates of cholangiocarcinoma (bile duct cancer) in China, Southeast Asia, and elsewhere.

Hepatitis E[21] While L. King noted only that the number of cases of this disease appears to be increasing rapidly in both developed and developing countries, Forum member Rima Khabbaz, of CDC, observed that hepatitis E is a potentially vaccine-preventable disease and that several promising candidate vaccines have been developed. The lack of a well-defined burden of disease associated with hepatitis E, or a clear picture of its geographic distribution, serves as a disincentive for vaccine development. Manufacturers have been reluctant to continue studies necessary for vaccine licensure if the market for hepatitis E vaccine is limited to developing countries alone, she noted.

Several of L. King's descriptions of NZDs demonstrate that, while many zoonoses pose a particularly serious risk to humans, the most effective way to control these diseases in humans is to address the disease burden of livestock and wild animals. Interventions designed to prevent and control NZDs require concerted action between veterinary, livestock, and human health sectors through a comprehensive, integrated, and interdisciplinary approach, he contended. Working across disciplines and professions—a skill he characterized as "meta-leadership"—will be essential.

L. King identified the following "critical actions and approaches" for addressing NZDs:

- Raise global awareness;
- Improve impact measures to better determine the burden of disease associated with NZDs and to inform cost-benefit analyses for interventions;
- Implement surveillance to systematically collect incidence data and identify populations at risk for NZDs;
- Invest in developing more accurate, affordable, and easy-to-use diagnostics; and
- Build effective animal health infrastructure.

Reflecting on the need for better surveillance of NZDs, Hotez observed that the determination of prevalence and disease-burden estimates for the largely nonzoonotic NTDs such as schistosomiasis, soil-transmitted helminthiases, and LF raised awareness of these diseases and increased support for addressing them. "I don't see that with the zoonotic diseases," he said. "I think that's what is holding back the community in a big way." He suggested that the zoonotic diseases make a "hit-list" of the top five zoonotic infections to be targeted for control in order to focus awareness and galvanize advocacy for this group of truly neglected diseases.

L. King agreed with this notion, but he said that the dearth of funding for

[21] According to L. King, "hepatitis E is a growing problem and . . . could become one of the neglected diseases in the future—I don't consider it as one of the traditional group of NTD at present especially because the disease is also found in developed countries but it is an emerging zoonosis that we need to watch carefully and address it as we develop comprehensive actions and interventions."

animal health would prove a barrier to such efforts. He added, however, that overcoming the "downward spiral of lack of appreciation, and consequently . . . lack of advocacy" might be possible if agencies such as FAO and WHO joined forces with the World Organization for Animal Health (OIE). He also noted that integrated control programs (described in the next section of this overview) could address NZDs along with other more "visible" NTDs. The "toolkit" of approaches to controlling NZDs is growing, L. King said, but its rate of growth reflects accessibility to markets and the marketability of animal health products.

Animal health in general has received comparatively little philanthropic encouragement compared with human health, King observed. Control of zoonotic diseases requires coordination between the veterinary and human medical and public health sectors, which is particularly difficult to achieve under conditions of limited resources and inadequate governance structures. The lack of animal health infrastructure in many developing countries fosters the perception that zoonotic diseases do not impose a significant health burden. On the contrary, evidence-based studies on some NZDs have determined that their true incidence can be 100-fold higher than reported, as was the case for rabies in Africa (WHO, 2006).

NZDs are doubly burdensome, as they sicken and kill valuable livestock as well as humans. This impact falls largely on the rural poor in developing countries, many of whom depend on animals for food, transportation, and farm work. NZDs, moreover, also affect the urban poor through their consumption of contaminated meat and milk products (WHO, 2006, 2010d,e). Agricultural development programs, a potential source of support for animal health in developing countries, have tended to focus on crops rather than livestock.

The under-diagnosis (and therefore, under-treatment) of NZDs in humans, another aspect of poverty, adds to the cumulative burdens they impose. The magnitude of that burden remains unknown since NZDs are also under-reported. The following statistics from WHO (Box WO-4) illustrate a variety of adverse consequences of some NZDs (WHO, 2010f).

With the projected rapid growth of animal populations to supply the protein demands of the expanding human populations in the developing world, the return on investment for supporting animal health becomes increasingly clear. Controlling zoonotic diseases will not only reduce livestock and human illness but will also improve the livelihood of millions of impoverished livestock keepers and their families. This, in turn, could lead to broad-based improvements in public health. In addition, L. King said, because zoonoses can travel as widely as their hosts, controlling NZDs where they normally occur can reduce the threat of global disease proliferation.

Approaches to Integrated Control of NTDs and NZDs

The experiences of the Rockefeller Sanitary Commission in its attempt to eradicate hookworm from the American South in the early 20th century (dis-

BOX WO-4
Cumulative Burdens of the NZDs

- In today's world the rural poor represent 911 million people, of which 411 million are poor livestock-keepers (almost half in south Asia and one-third in sub-Saharan Africa).
- At least 55,000 people are dying of rabies in Asia and Africa, and expenses related to the prevention and control of this disease is estimated at US$590 million annually on these two continents.
- The total cost of an average rabies post-exposure prophylaxis course is US$40 in Africa and US$49 in Asia. This amounts to a substantial fraction of per capita gross national income (5.8 percent in Africa and 3.9 percent in Asia).
- The annual societal cost (agriculture and health) of porcine cysticercosis/taenosis is estimated at about US$150 million in India alone.
- On the Tibetan plateau, the annual combined human and animal losses due to echinococcosis equate to approximately US$3.47 per person or 1.4 percent of per capita gross domestic product.
- Echinococcosis in Tunisia causes significant direct and indirect losses in both humans and animals of between US$10 million and US$19 million annually. The reported incidence in humans is 1.5 to 2.05 cases per 100,000 inhabitants, and between 12 percent and 17 percent of the cattle at slaughter is found to be infested.
- Disability-adjusted life-years (DALYs) and monetary losses resulting from human and livestock cystic echinococcosis have been calculated at the global level assuming substantial under-reporting. The estimated global human burden of echinococcosis may be as high as 1,009,662 DALYs—or an annual loss of US$763,980,979. A maximum annual livestock production loss of US$2,190,132,464 is also estimated.
- More than 50,000 cases of human brucellosis were diagnosed in only eight countries located south and east of the Mediterranean Sea in 2003.

SOURCE: WHO (2010f).

cussed earlier) highlight key aspects of current attempts to control neglected diseases of poverty and to mitigate their health and economic consequences. These efforts employ two basic approaches, either singly or in combination: mass drug administration and environmental interventions, encompassing both human-built and natural environments (Spiegel et al., 2010). Over the past two decades, mass administration of drugs has been the mainstay of NTD initiatives that have achieved, for example, the successful control and elimination of onchocerciasis and significant reduction of LF in parts of Africa. Some of the unmet needs for the control of NTDs in sub-Saharan Africa are illustrated in the map in Figure WO-10 (from Fenwick et al., 2009). Meanwhile, dracunculiasis—for which no vaccine or therapy exists—stands at the brink of global eradication following the widespread adoption of a suite of measures to provide safe drinking

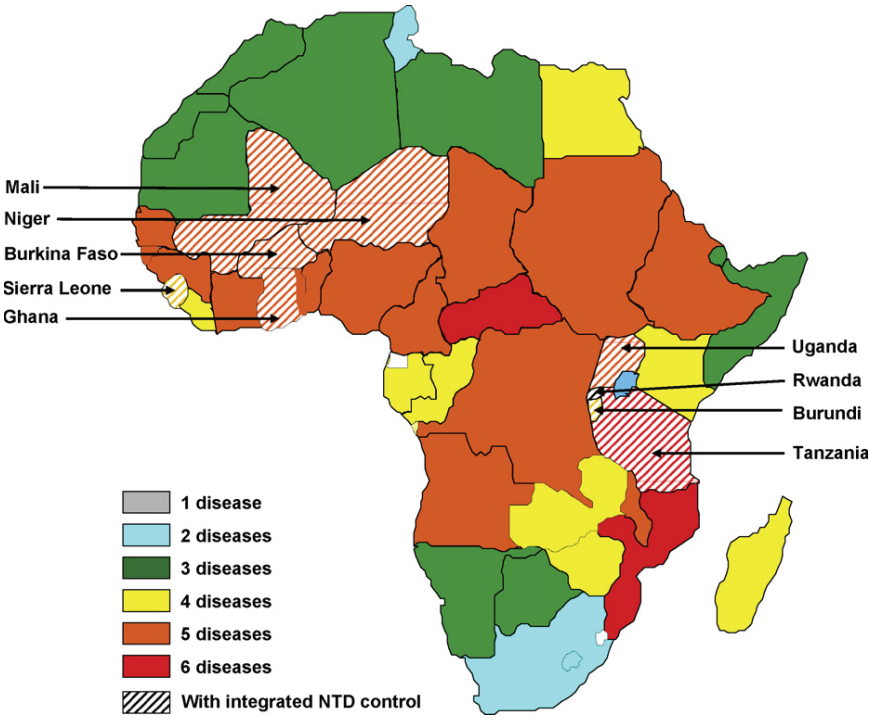


FIGURE WO-10 Distribution of NTDs in Africa (modified according to Figure 1 in Molyneux et al., 2005) and countries with integrated NTD control programs in sub-Saharan Africa. Those currently covered by the integrated NTD control programs assisted by the Schistosomiasis Control Initiative (SCI) and other organizations are indicated. Zambia was included in the SCI schistosomiasis and STH control program, but because of funding the program is currently interrupted. The NTD control program in southern Sudan is not indicated on the map.
SOURCE: Fenwick et al. (2009). Reprinted from *International Health*, 1/1, Fenwick A, Zhang Y, and Stoever K, Control of the Neglected Tropical Diseases in sub-Saharan Africa: the unmet needs, pp. 61–70, Copyright (2009), with permission from Elsevier.

water for at-risk populations (WHO, 2009). Vector control and other preventive environmental measures remain the only options for controlling several NTDs, including dengue and trachoma.

Every NTD and NZD presents unique challenges and is represented by a specific public health constituency. Because these diseases are often found in overlapping geographic areas and host populations, and frequently polyparasitize the same individual or animal host(s), groups of these diseases sharing similar

BOX WO-5
Common Features of Integrated Control Programs for Overlapping NTDs and NZDs, Malaria, and Other Infectious Diseases of Poverty

Principles for Integrating Actions:

- Available plans, guidelines, and tools
- Evidence-based decisions
- Reduction of inequalities in health
- Primary health care system
- Community participation
- Gender and ethnicity
- Interprogrammatic and intersectoral interventions to address the social determinants of health
- Cooperation between countries
- Global partnerships in the fight against neglected infectious diseases

Common Interventions:

- Screening plus drug treatment
- Mass drug administration
- Morbidity (case) management
- Integrated vector management
- Combined water supply, sanitation, hygiene, and education initiatives (known by the acronym WASHED)
- Education and school health (e.g., deworming)
- Vitamin A and/or other nutrients plus deworming
- Integrated population, health, and environment programs

Common Delivery Platforms:

- Primary health care
- Vector control
- Nutrition
- Immunizations
- Maternal-child health, family health and wellness
- Chronic disease clinics
- Food security, food safety
- Healthy schools, healthy cities

SOURCE: Adapted from Ault (2010).

"lifestyles" may be most effectively and efficiently addressed through a coordinated intervention strategy composed of a "rapid impact" package of drugs and other interventions (Hotez, 2009b; Hotez and Pecoul, 2010; Hotez et al., 2007a; Spiegel et al., 2010). A central tenet of global strategies to reduce the burden of NTDs and NZDs—integrated control—reflects common principles, interventions, and platforms, as described by speaker Steven Ault of PAHO (see Box WO-5). (Dr. Ault's contribution to the workshop summary report can be found in Appendix A, pages 115–131.)

Workshop presentations and discussions considered integrated control from a variety of perspectives. These ranged from discussions of MDA to control multiple NTDs, which represent the narrowest interpretation of "integration," to broad-based strategies combining biomedical, vector control, and behavioral interventions to address neglected diseases of poverty as a social phenomenon. Many reflected a point of view expressed by L. King, who endorsed a coordinated response to NTDs and NZDs rather than dealing with "one outbreak at a time." As a model for such a strategy, he invoked the One Health Initiative, which emphasizes connections between human, animal, and environmental health (One Health Initiative, 2010). One Health, he explained, is "the collaborative effort of multiple disciplines, especially on the veterinary and human health side, working collaboratively, nationally, locally, globally, to attain optimal health of people, animals and our environment."

Addressing "Tool-Ready" Diseases

Among the speakers who presented various classification schemes of NTDs, Savioli offered a practical distinction: "tool-ready" versus "tool-deficient" diseases. Tool-ready diseases can be addressed without disease-specific services or even individual diagnosis, he explained. These include LF, leprosy, onchocerciasis, schistosomiasis, soil-transmitted helminthiasis, and trachoma, along with yaws. These diseases can be controlled through MDA, which Savioli characterized as treatment that can be given "by non-specialized teams and integrated through other systems, using either community volunteers, schools, or other means to ensure treatment and expansion of intervention." Other diseases—including leishmaniasis, HAT, Chagas disease, and Buruli ulcer—are "tool-deficient," according to Savioli, because they are difficult to diagnose and/or complicated and costly to treat. Tool-deficient diseases are not amenable to preventive chemotherapy, he explained. Controlling these diseases requires more innovative methods, such as the interventions developed to address dracunculiasis—a disease for which no vaccine, treatment, or diagnostic tools exist. Hotez pointed out, however, that in reality all NTDs are tool-ready, meaning that there are interventions available for each of the major human NTDs, including the major kinetoplastid infections such as HAT and Chagas disease, while (ironically) almost all of the NTDs are also tool-deficient, including hookworm and schistosomiasis, referring to the fact that high rates of drug failure and emerging resistance occur for most of the NTDs that have drugs available for purposes of MDA (Hotez and Pecoul, 2010).

In her keynote address to the workshop, Christy Hanson, of USAID, described her agency's efforts to target seven of the high-prevalence NTDs—three soil-transmitted helminthiases (ascariasis, trichuriasis, and hookworm), LF, onchocerciasis, schistosomiasis, and trachoma—for MDA. (Dr. Hanson's contribution to the workshop summary report can be found in Appendix A, pages 183–208.) Describing the growth of USAID's NTD program from an initial

federal investment of $15 million in 2006 to the expected influx of approximately $100 million from the Global Health Initiative in 2011, Hanson noted that the program initially focused on "five countries where there was an overlapping burden of at least three of the seven NTDs that we wanted to deal with, where the governments were committed to an integrated approach, where at least one of the pillar programs [addressing individual NTDs] was functioning well . . . [and was] something that we could build upon, and where there were technical partners already on the ground, with good working relationships with the ministries." As a result, she continued, "we felt we could get technical assistance, partner with the governments, and really move quickly."

After three years at that funding level, followed by a near-doubling of funding in 2009, the program is now active in 14 countries and has delivered more than 255 million treatments for NTDs, according to Hanson. "We found tremendous efficiency gains both by integrating the different NTD programs and, more importantly, we look in every country at the existing infrastructure and the existing health platforms and education platforms," she said. "We work through the schools. We work through child health days. We work through existing programs, existing partners, existing infrastructure. . . . [W]herever we can, we piggyback on what is already working at the country levels. This adds to sustainability, but it also has allowed us to expand rapidly at very low cost."

The mapping of disease-endemic areas, as illustrated in Figure WO-11, has been crucial to these efforts, Hanson explained. Such maps ensure that governments satisfy the requirements of pharmaceutical companies that donate drugs, and they support ongoing NTD control efforts by the governments of disease-affected countries. "Even if we were to walk out the door tomorrow, they are able to access those drug donations," she said. USAID continues to track host-country contributions toward these NTD programs to ensure ongoing commitment to disease control. "We do not want to see the government commitment to NTDs go down," she observed, "we want to see it shift [to other NTD targets]." Typically, ministries of health in countries supported by USAID contribute one-third of the cost of NTD control, Hanson stated.

Mobilizing individual communities to undertake MDA requires time and commitment, Hanson observed, but once the intervention is accepted, it is a relatively efficient and inexpensive process, because most of the drugs used are donated.[22] This has enabled USAID to build considerable capacity at the community level, she said. "It's not just about passing out the pill. It is the health education messages, the safe strategies, the hygiene practices . . . along with how

[22] Praziquantel, used to treat schistosomiasis, is an exception; only a fraction of what is needed is currently donated (Burns, 2010). Emanuel stated that the U.S. Office of Management and Budget was "vigorously" trying to obtain praziquantel on the same terms as other drugs for NTDs: free, for as long as necessary. He noted that purchasing the drug, which costs eight cents per pill, currently consumes 15 to 20 percent of U.S. funding to address NTDs.

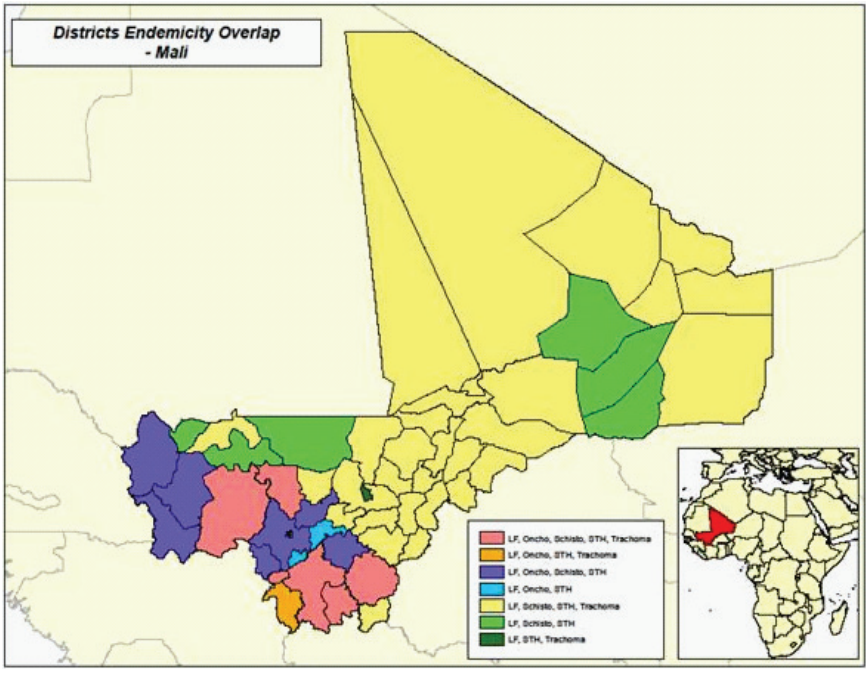


FIGURE WO-11 Endemic zoonotic diseases by district in Mali.
SOURCES: Hanson (2010); Ministry of Health, Mali (2010).

you deliver the drug," she noted. At the ministerial level, USAID is developing an international training course to educate program managers in the financial and resource planning skills required for coordinating an integrated disease control program.

In partnership with WHO, Hanson and her colleagues are also developing a "rollout package"—consisting of guidelines for action, budgeting, obtaining drug donations, logistics, and reporting—that is designed to streamline the implementation of national MDA programs. Savioli of WHO also emphasized the importance of capacity building to ensure that there is an adequate workforce in place to sustain these programs. Noting that many experts in this field—himself included—are nearing retirement, he said, "We need a new generation of people that will take over from us."

Summing up the impact of USAID's NTD control efforts, Hanson noted that, while they are proud of the number of treatments they have been able to provide, their goal is to reduce NTD prevalence to low enough levels that MDA is no longer necessary. In addition, the agency is focused on increasing the efficiency of the program in ways that can be documented and reproduced, and encouraging

sustainable support by the governments of the affected countries. Ultimately, she said, USAID wants to be able to demonstrate that gains against NTDs advance the broader aims of development, poverty reduction, and education, as expressed in the MDGs.

Regional Control Efforts

The principles of integrated control have been widely adopted to address NTDs, but the targets of such efforts vary on a regional basis, Savioli observed. Diseases targeted for elimination by PAHO differ from likely candidates in Africa, he noted. Moreover, outside of the Caribbean region, schistosomiasis elimination is currently possible in the Middle East, Asia, and South America but not yet in Africa south of Sahara, only in the eastern Mediterranean region. The leishmaniasis elimination activities currently under way in WHO's Southeast Asia region (SEARO) will not yet be possible in either Africa or the Americas, he observed. "We have to recognize that regions have their own targets," he concluded, while acknowledging that such specificity complicates global efforts to reduce the burden of NTDs. Quoting the advice of Ferrari formula one driver Niki Lauda—"If you think you have everything under control, you are not going fast enough"—Savioli added, "that's the way we need to deal with the issue sometimes."

Africa's NTD burden has received disproportionate attention, Savioli contended, even though—based on current burden of disease estimates—Southeast Asia's NTD burden is comparable. The attention focused on Africa is appropriate, he continued, because many different NTDs are endemic to the continent, but this should not be at the expense of other parts of the world that need to control "their" NTDs in order for their economies to grow. He therefore applauded the expansion of USAID's NTD program to include Bangladesh and Nepal, as well as Haiti (USAID, 2010).

Latin America and the Carribbean (LAC), another key region for NTD control, was the focus of Ault's workshop presentation. Soil-transmitted helminth infections, Chagas disease, and schistosomiasis (which frequently occur as a coinfection with hookworm) are the most prevalent and burdensome NTDs in this region, afflicting many of its poorest people (Hotez et al., 2008b). Onchocerciasis and LF, as well as schistosomiasis, persist in LAC as legacies of the transatlantic slave trade, Ault noted.

Ault predicted that recent successes in controlling such infectious diseases as smallpox, polio, and measles in LAC would bode well for targeted control efforts to address NTDs. To date, onchocerciasis transmission has been interrupted in 7 of 13 LAC foci; transmission of Chagas disease by both vector and blood transfusion has been significantly reduced, as have dog-transmitted rabies cases, he reported.

PAHO has been engaged in an effort to map diseases it has designated

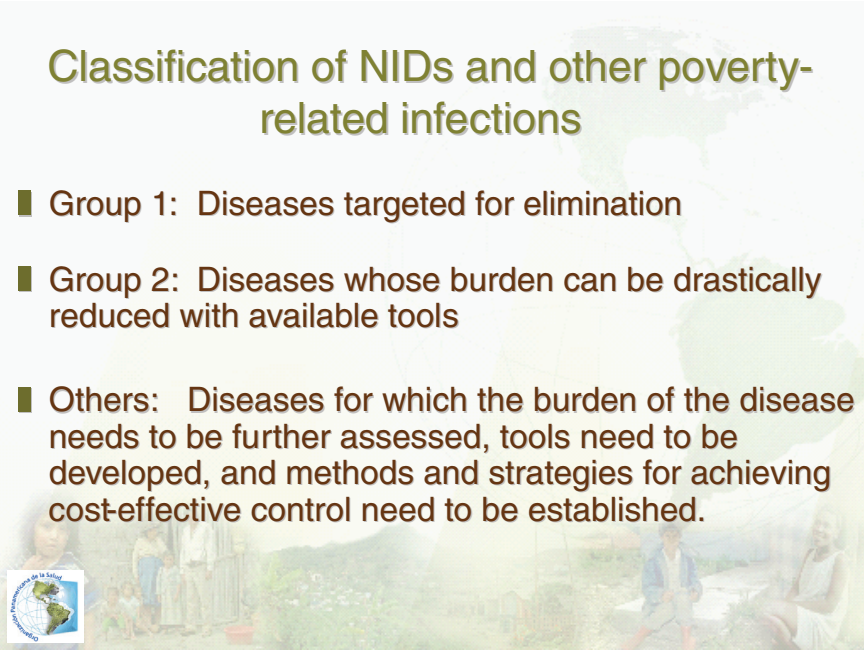


FIGURE WO-12 Classification of NIDs and other poverty-related infections.
SOURCE: Ault (2010).

"neglected diseases and other infections related to poverty," or NIDs, to the first administrative level in 14 LAC countries (PAHO, 2009), Ault said. In addition to collecting key epidemiological data, it has also identified major operational strategies to control each disease. Based on these results, PAHO grouped the NIDs into three categories (see Figure WO-12).

Group 1—illustrated in Figure WO-13—is composed of diseases targeted for elimination of transmission or elimination as a public health problem[23] in LAC.

- Lymphatic filariasis
- Onchocerciasis
- Trachoma
- Chagas disease (elimination of transmission by domestic vectors and blood transfusion)

[23] According to Ault, "elimination as a public health problem" is the "drastic reduction of the burden of disease to a certain level considered as acceptable given the current available tools and the Region's health situation. This level should be such that it does not constrain social productivity nor community development. Specific goals for each disease are established."

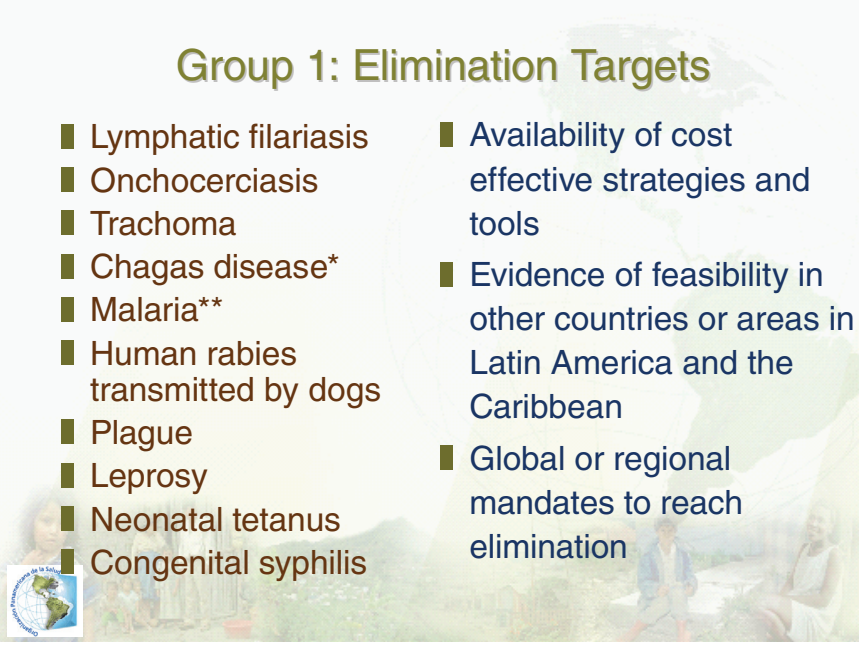


FIGURE WO-13 Group I: elimination targets. *Elimination of transmission by domestic vectors and blood transfusion; **elimination in Hispaniola and Central America.
SOURCE: Ault (2010), taken from the draft report for the 144th Executive Committee, 2009, on Elimination of Neglected Diseases and Other 10 Infections Related to Poverty.

- Malaria (elimination in Hispaniola and Central America)
- Human rabies transmitted by dogs
- Plague
- Leprosy
- Neonatal tetanus
- Congenital syphilis

Group 2—diseases for which prevalence and burden of disease remain to be determined—includes schistomiasis caused by *S. mansoni* and soil-transmitted helminthiases caused by *Ascaris*, *Trichiuris*, and hookworm (see Figure WO-14).

"We are assuming for practical purposes that all countries in the region are at risk [for these diseases, and] that there is some burden," Ault stated. "Whether it represents a public health problem or not is a question that has to be investigated." Ault estimated that at least 13 million preschool-aged children and 33 million school-aged children in LAC are at risk for soil-transmitted helminthiases, based on their lack of access to basic sanitation. Mexico and Nicaragua provide preven-

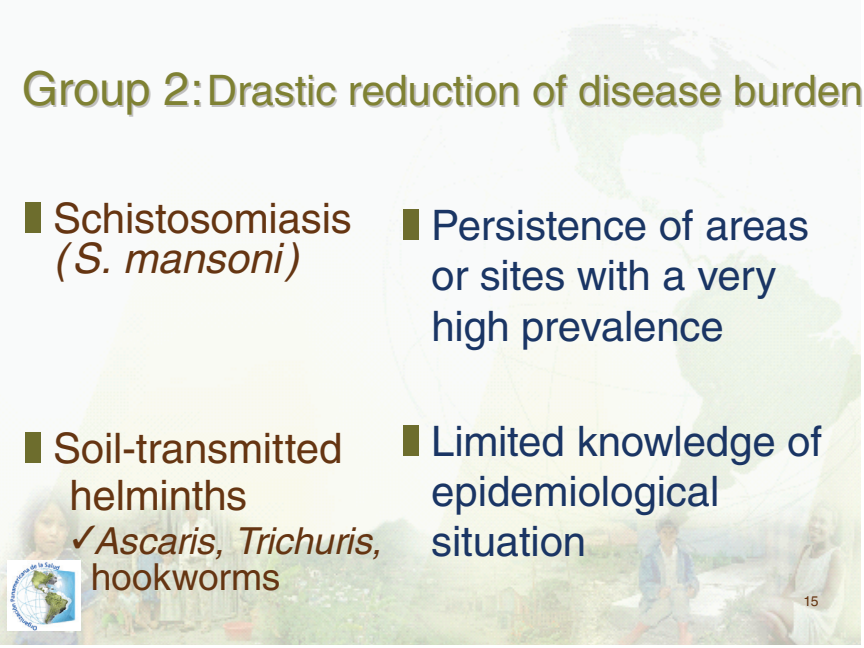


FIGURE WO-14 Diseases targeted for drastic disease burden reductions.
SOURCE: Ault (2010), taken from the draft report for the 144th Executive Committee, 2009, on Elimination of Neglected Diseases and Other Infections Related to Poverty.

tive STH treatment for all schoolchildren, he added, but this must be extended to other countries, as well as to preschoolers. The diseases in Group 3—which Ault characterized as "diseases for which new strategies and tools [were] needed for sustainable control"—included leishmaniasis, cysticercosis, echinococcosis, and food-borne trematodiasis, and other parasitic zoonoses.

In addition to ongoing mapping of NTDs and analysis of progress toward their control, Ault reported, PAHO is conducting demonstration projects on integrated approaches to NTD control in Chiapas, Mexico, and Recife, Brazil. He went on to state that the goal of this regional collaboration involving PAHO, the Inter-American Development Bank, and the Global Network for Neglected Tropical Diseases is "to see how well this integration functions and what outcomes we can actually measure as a result of the integrated implementation."

Recognizing and Addressing the Social Determinants of NTDs

Brazil stands out among the LAC countries for its heavy burden of NTDs, Hotez observed (Hotez, 2008a). "I realize Brazil is the biggest country in the Western Hemisphere, accounting for about 30 to 40 percent of the population in Latin America," he said. "They still have more than 50 percent, in some cases up to 97 percent of the neglected tropical diseases in the Western Hemisphere . . . [including] almost all of the trachoma, most of the leprosy, hookworm, and schistosomiasis." The social and environmental determinants of infectious disease occurrence in Brazil, which contribute to its high NTD burden, were a focus of Barreto's workshop presentation. Like McDonald, speaker Jerry Spiegel, of the University of British Columbia, characterized social determinants of NTDs as profoundly influencing not only disease prevalence but also the ability to carry out effective and sustained interventions, and therefore as essential targets of integrated control efforts. (Dr. Spiegel's contribution to the workshop summary report can be found in Appendix A, pages 490–505.)

Social and environmental factors in Brazil Barreto noted several key changes in Brazil's population in recent decades: a shift to more than 80 percent of people living in cities, as compared with 31 percent in 1940; a rapid decline in fertility over the past 20 years; and an increase in income and life expectancy such that both now approximate the global mean. Although many Brazilians have access to a high-quality water source, many lack adequate sanitation, he reported. Nonetheless, mortality due to infectious disease accounts for only about 8 percent of the deaths in the country, and it continues to decrease.

Brazil, a federation of 26 states and one federal district, comprises five major regions, which differ markedly in terms of their socioeconomic status—and also in terms of their patterns of infectious disease occurrence, Barreto observed. The south and southeast regions, where gross domestic product (GDP) is highest, have the highest rates of HIV/AIDS-related mortality and the lowest number of deaths associated with NTDs such as schistosomiasis and leishmaniasis, as well as with diarrhea, malaria, and TB; these figures are reversed in the poorer north and northeast. Chagas disease deaths are concentrated in the central west. "In terms of infectious disease epidemiology, there are marked regional differences in this large country," he concluded.

Examples of infectious diseases that have been successfully controlled in Brazil include vaccine-preventable diseases and Chagas disease, Barreto said. In each such case, he observed, a clearly defined and effective prevention strategy (e.g., vaccines, elimination of an intradomiciliary vector, and provision of water and sanitation) was effectively implemented through policies that either addressed key determinants of disease (e.g., water quality, basic sanitation, or vector elimination) or that provided access to preventive resources such as vaccines or that expanded access to primary health care. For example, he noted,

following implementation of a major sanitation project in the city of Salvador, diarrhea incidence and prevalence declined rapidly in the poorest parts of the city, where sewer coverage had been increased from 26 percent to 80 percent of all households (Barreto et al., 2007; Genser et al., 2008). Within 5 years of the project's completion, the prevalence of several parasitic infections—including ascariasis and trichuriasis—were found to have declined more than 50 percent (Barreto et al., 2010; Mascarini-Serra et al., 2010). Moreover, Barreto reported, "in Salvador there is no more hookworm in small kids—practically zero." These results suggest that investments in environmental interventions such as sanitation have a major impact on NTDs, as well as on other common infectious diseases, he concluded.

Barreto also identified NTDs that have been less successfully addressed in Brazil, including leprosy and schistosomiasis, which he characterized as partial successes, and dengue and leishmaniasis, which he described as failures. Leprosy and schistosomiasis are chronic infectious diseases with long infectious periods and, in the case of schistosomiasis, transmitted by vector species that have proven difficult to control, he said; dengue and leishmaniasis have eluded control in part through urbanization, and also because they lack safe and/or specific treatments.

Addressing social determinants of NTDs through integrated control strategies "To understand the challenges of NTDs in women and children, we must understand how health is transmitted across lifetimes and generations," McDonald observed. "Adult health is shaped by the social and economic opportunities that adults face, along with living and working conditions experienced. Adult health, in turn, shapes family health and well-being. Family health and well-being, in turn, shapes childhood health, which forms the basis of health in the adult (RWJF, 2008). The global cycle of poverty and substandard living conditions is what we must break in order to address NTDs and make them neglected no more."

Taking a closer look at these relationships, Spiegel examined NTDs from a social perspective and urged that integrated control strategies address factors—such as poverty, lack of infrastructure, and inadequate community-based primary care—that "predispose the ill health that we are trying to address." Without attention to such social determinants of health, he argued, interventions cannot be effectively sustained (Spiegel et al., 2010). To illustrate this point, Spiegel recalled a Jewish folk tale about the mythical, backward village of Chelm, which stood at the edge of a dangerous precipice. When the wisest men of Chelm were asked how to prevent people from falling to their deaths, they replied, "build a hospital at the bottom of the precipice."

To truly evaluate the impact and outcomes of integrated control strategies in promoting health, rather than simply measure activity in responding to illness (e.g., counting the number of treatments distributed), four basic questions must be answered, Spiegel said:

- Do we have an efficacious treatment?
- Is it safe?
- Do we have the services and systems to bring that to bear?
- Do we have a way of addressing the conditions that are producing the effect that's calling for this attention?

A "yes" to all four ensures capability to scale effective interventions to sustainably control disease, not just to stifle transmission and treat victims, he explained. This is important, because populations most vulnerable to NTDs have been neglected not only because drugs and diagnostics have not been developed for these diseases, he observed, but also because their health systems and infrastructure have similarly not received adequate attention. "We are really dealing with more than an individual's illness," he added, "because all individuals are stamped by the insecurity of acquiring that illness." Therefore, he argued, health represents "an excellent platform for developing a common security globally [*sic*]."

To comprehensively consider biomedical, environmental, and social determinants of health, Spiegel and his colleagues work with a framework called the "ecosystem approach to human health" (Lebel, 2003; Webb et al., 2010) that emphasizes transdisciplinarity, participation, and equity. Applying these principles in Havana, Cuba, they created an integrated surveillance system for dengue (Bonet et al., 2007), establishing a socially connected network and linking people in various capacities—from government epidemiologists, local physicians, and environmental officers to resident citizens. Information derived from this system was used to identify "hot spots" and monitor transmission trends and to develop a geographic information system for mapping the disease. The researchers then conducted a mosquito breeding site case-control study to help them identify social and environmental risk factors that could be reduced to improve community dengue control (Spiegel et al., 2007). In addition to such expected factors as lack of larvicide in water tanks, the researchers found that practitioners of the Afro-Caribbean religion Santeria placed themselves at higher risk for dengue through the use of ceremonial flower vases, in which mosquitoes could breed. Therefore, they concluded, efforts to reduce dengue in Havana should involve community religious leaders to help promote safe practices, and local actions to do this were conducted.

While cautioning against exclusive reliance on short-term medical solutions to neglected diseases of poverty, Spiegel acknowledged that, in a crisis, affected individuals must be treated as quickly and effectively as possible. However, he continued, it is important to recognize that taking such actions may exhaust possibilities for intervening at other levels. "One of the concerns of having an overemphasis on a technical cure-all, as effective as it may be, [is that] circumstances change," he said, noting, for example, that dengue flourished after its mosquito vector developed resistance to DDT. In addition, providing technical "fixes" encourages communities to rely on a "paternalistic provision of things," rather than

involve themselves in identifying and targeting systemic risk factors for disease, Spiegel said. "Can we really achieve the outputs that we want to achieve, without having some fundamental infrastructure in place?" he asked. "I don't think so." His argument is supported by the legacy of the Rockefeller Sanitary Commission for the Eradication of Hookworm, which failed to eradicate hookworm from the American South solely through MDA.

In order to research and fund interventions directed at the social determinants of NTDs, Spiegel and colleagues have proposed a mechanism they call "social offsets," by which a proportion of funding for any NTD research program is set aside to address related socio-environmental and health system factors (Spiegel et al., 2010). For example, in order to gain permission to distribute NTD drugs in a country, pharmaceutical companies would need to contribute to funding its health systems or to addressing other social determinants of NTDs. However, he added, there is no advantage to addressing the social determinants of NTDs if it does not produce demonstrable benefits. He insisted that, like biomedical interventions, social and environmental approaches to NTDs must be held to account, evaluated, and adjusted to ensure that they lead to desired outcomes and complement other interventions.

In an informal luncheon address to workshop participants, Forum member Jesse Goodman, Chief Scientist at FDA, applauded the inclusion of efforts to address social determinants of health in the development of integrated disease control programs. "If you just go into a community and say, 'I'm going to make you healthy,' but it's not going to be tied to other efforts to help in other ways in that community, efforts which actually may address even more important determinants of health, that's a missed opportunity," he observed. Moreover, he said, "You really want to build an integrated system that isn't just for 15 infectious diseases, but will work as people transition from one set of health problems to another."

Addressing Unmet Needs

Increasing recognition of the health and socioeconomic consequences of NTDs and NZDs is spurring efforts to identify and develop medical products, strategic plans, and workforce to reduce this significant burden of disease. The two previous sections of this overview ("Profiles of Neglected Diseases" and "Approaches to Integrated Control of NTDs and NZDs") describe a range of disease- and setting-specific needs for preventive and therapeutic treatments and diagnostics, as well as opportunities to maximize the impact of such interventions through integrated control programs. In a workshop session devoted to "unmet needs," presentations and discussions reviewed recent advances in the development of drugs, vaccines, and diagnostics to control and treat NTDs and NZDs. Participants also considered the essential role of partnerships—involving industry, governments, nongovernmental organizations (NGOs), academic

researchers, and funding agencies—in developing tools and strategies to address neglected diseases, and ways to improve and expand current models of cooperation and collaboration.

Drug Development Through Partnership

Pharma perspective Using examples from his company's considerable experience in developing drugs and vaccines for neglected diseases, Forum member and speaker Mark Feinberg, of Merck & Co., Inc., examined lessons learned from these public–private partnerships, as well as current challenges and future opportunities in addressing the diseases of poverty. In addition to the significant hurdles that any drug candidate confronts along the development pathway, products targeted to treat NTDs face several additional obstacles, Feinberg observed. First, he noted, it is often difficult for regulatory authorities in the developed world to assess the relative risks and benefits of products targeting diseases that are largely or exclusively present in developing countries. "It's not that [regulatory officials] aren't working at it," he added, "but there aren't a lot of models where that [process] has been successfully navigated so far." In addition, he said, evaluating treatments for the several NTDs that do not present as clinical disease until long after the onset of infection requires the identification of appropriate surrogate endpoints, of which very few have been approved by regulatory authorities. Finally, target profiles for NTD products have historically often failed to address factors that strongly influence implementation efforts, such as cost, scalability, route of administration, duration of treatment, or delivery logistics.

Despite these odds, Merck and other companies are engaged in a range of product-development partnerships (PDPs), spanning every stage of development, to produce drugs, vaccines, and diagnostics to treat diseases that are largely restricted to the developing world and, therefore, unlikely to be profitable, Feinberg observed. One of the best-known—and in many ways pioneering—examples of such a partnership began in 1987, when Merck first committed to supply the drug ivermectin (Mectizan) free of charge, and for as long as it is needed, to campaigns against onchocerciasis (also known as river blindness). In addition to its having an important impact on the control of onchocerciasis, Feinberg also noted that this partnership helped bring together partnerships and support the development of country-level health delivery infrastructure that has also provided a pathway to deliver ancillary interventions, including vitamin A supplementation and vaccination programs, to communities receiving ivermectin treatment.

To date Merck has donated more than 600 million ivermectin treatments (worth more than US$3 billion) for use in 34 countries, Feinberg reported. Treatment with ivermectin is estimated to prevent 40,000 cases of river blindness each year and allows farmers to reclaim significant areas of arable land previously rendered uninhabitable because of the presence of the black fly, he added. In 1998,

Merck launched an additional ivermectin donation program for the treatment of LF in combination with albendazole, which is donated by GSK.

Feinberg summarized lessons learned over the course of two decades of ivermectin donations by describing the factors that contributed to the success of this PDP (Thylefors et al., 2008):

- A broad partnership with clearly recognized common agenda and identified roles for all parties;
- Appropriate assessment tools to easily identify target populations for treatment;
- An appropriate community base for treatment with motivation and local support;
- Streamlining of all drug management aspects;
- An ongoing operations research agenda to address present and upcoming challenges; and
- Long-term commitments and long-term investments.

He also noted that this partnership has raised several important questions and implications:

- Would the program have been so successful if it was not predicated on a drug-donation model?
- Is drug donation, in and of itself, a viable model for addressing NTDs, or is it insufficiently sustainable?
- If novel agents to address NTDs are developed through PDPs, who will be responsible for their production, procurement, and delivery?
- Who will assess their impact and safety?

"I think none of those questions are available for answer now," he concluded.

Feinberg then examined Merck's participation in several initiatives to increase access to important vaccines in developing countries. These include an agreement, reached in the late 1980s, to provide the Chinese government with technology for producing recombinant hepatitis B vaccine. Merck did not profit or receive royalties from this partnership, which today provides about 65 percent of China's supply of the vaccine, he stated. The vaccine produced in this venture has prevented an estimated 30 million chronic hepatitis infections and is estimated to have averted approximately 3 million deaths, he added.

Another partnership, involving a new rotavirus vaccine produced by Merck, was launched to show that a vaccine could be rapidly and effectively introduced into a developing country to demonstrably reduce disease burden, Feinberg said. Although almost all children worldwide will become infected with rotavirus before the age of 5 years, the greatest impact of the infection is seen in low-income countries where an estimated 600,000 children die of rotavirus gastroenteritis

each year. To help demonstrate the feasibility and impact of rotavirus vaccine in a low-income country, Merck partnered with the Nicaraguan government to provide rotavirus vaccine and administrative support so that every child born within a three-year period was immunized and the impact on rates of severe rotavirus disease were monitored thereafter, he explained; additional studies conducted by PAHO and CDC were also conducted to examine the vaccine's impact (Patel et al., 2009). Importantly, rates of rotavirus disease have fallen substantially in Nicaragua since introduction of the vaccine, and immunization rates quickly reached and have been maintained at rates among the highest in the world (including in much wealthier countries such as the United States), he reported. Efficacy studies of the rotavirus vaccine have also been conducted through the Global Alliance for Vaccines and Immunization (GAVI) in Mali, Ghana, Kenya, Vietnam, and Bangladesh (Armah et al., 2010; Zaman et al., 2010); based on their outcomes, along with other data demonstrating the efficacy in GAVI-eligible countries in Africa of a different rotavirus vaccine produced by GSK, WHO now recommends immunization for every infant worldwide, he said. Nevertheless, he added, the rollout of rotavirus vaccines in developing countries has, to date, been disappointingly slow, largely because the current global financial crisis has severely curtailed GAVI's financial resources to support new vaccine introduction.

Merck's experiences introducing hepatitis B and rotavirus vaccines to developing countries revealed "tremendous opportunities and tremendous needs to develop new and better vaccines for low-income countries," Feinberg said, as well as the potential to develop new and better models to meet these needs. This is the aim of its recent joint venture, the MSD Wellcome Trust Hilleman Laboratories. Located in India and funded by Merck and the Wellcome Trust,[24] this facility is specifically dedicated to the development of new vaccines targeting diseases prevalent in low-income countries and of optimized versions of existing vaccines so that they may be more effectively implemented in resource-limited settings, he explained. In addition to the financial support provided by both Merck and the Wellcome Trust, Merck provides the laboratories with technical support, enabling technologies, and access to relevant intellectual property.

The Merck–Wellcome partnership is intended to bring together diverse partners from academic and government laboratories as well as other industrial partners (both multinational companies and developing-world manufacturers) and to serve as a model for collaborative engagement—to provide innovative products to address important unment medical needs in developing countries, Feinberg said. "The goal here is to really recapitulate the end-to-end view that exists in typical drug-development or vaccine-development programs in industry," he observed—in particular, to support proof-of-concept determinations, which tend to be a major stumbling block in the drug development pathway.

"There are opportunities to broaden the definition of the partnership model

[24] A global charitable foundation dedicated to improving animal and human health.

[to accommodate] a broader vision of integration and prioritization," Feinberg observed. "Certainly there can be public–private partnerships. There can be partnerships between private-sector entities," he added. "There can be partnerships that bring together multiple private-sector entities, with potentially private-sector partners, public-sector partners, when you have people who have the greatest potential to contribute."

Organization perspective The Drugs for Neglected Disease initiative (DNDi) is a collaborative, non-profit drug research and development (R&D) organization that establishes partnerships with industry, governments, and private funders to develop new treatments for neglected diseases including malaria, visceral leishmaniasis (VL), HAT, and Chagas disease (DNDi, 2010).[25] In his workshop presentation, Shing Chang, DNDi's director of research and development, described their efforts to develop new drugs for three of the deadliest NTDs: HAT, leishmaniasis, and Chagas disease.

Chang began with an explanation of DNDi's tripartite approach to drug development. In some cases, he said, it is necessary to adopt the long-term strategy of screening of compound libraries for leads that can be adapted to produce simplified, cost-effective, short-course treatments that also contribute to disease elimination, if possible. DNDi also pursues novel formulations and new indications of existing drugs, beginning with the pre-clinical phase of development, he said. For the short term, they identify drugs that are already approved in one geographic region that can be made available in another, in order to expand available treatment options.

For HAT—which, as Jannin previously noted, has lacked good treatment options—DNDi developed a less expensive, more easily administered alternative, nifurtimox-eflornithine combination therapy (NECT). This is still a stop-gap measure, according to Chang, because the drug must be infused, limiting its use to patients who have access to health care facilities and skilled medical personnel. Ideally, HAT will be treated orally with a combination of two drugs, he said, but there are few promising oral candidates in development.

For VL, the most severe and potentially fatal form of leishmaniasis, current treatments are difficult to administer and often poorly tolerated, Chang observed. DNDi is pursuing a range of region-specific strategies to improve the efficacy of existing VL drugs while attempting to identify promising novel compounds. In India, where resistance has arisen to one of the key drugs—pentavalent anti-

[25] DNDi was established by the following founding organizations: five public-sector institutions—the Oswaldo Cruz Foundation of Brazil, the Indian Council for Medical Research, the Kenya Medical Research Institute, the Ministry of Health of Malaysia, and France's Pasteur Institute; one humanitarian organization—Médecins sans Frontières ("Doctors Without Borders"); and one international research organization—the United Nations Development Programme/World Bank/WHO's Special Program for Research and Training in Tropical Diseases (TDR), which acts as a permanent observer to the initiative.

monial—DNDi is attempting to develop combinations of existing treatments for VL, he said, while in Africa, they are registering drugs available in India and using them to develop combination therapies. In Latin America, the organization is participating in the clinical investigation to determine the efficacy of the standard treatment and compare it with a combination. In Asia, DNDi is testing combinations of three VL drugs. However, collaboration with another organization that focuses on developing drugs for tuberculosis (TB Alliance) has yielded two promising compounds that are orally active against VL, Chang reported, "so we're looking forward to potentially having a VL oral drug."

The challenge of Chagas disease Several partnerships are pursuing much sought-after treatments for Chagas disease (see previous discussion in "Profiles of Neglected Diseases"), for which only two drugs are currently available: nifurtimox and benznidazole. Both require a long treatment period, are toxic, and are unavailable in pediatric formulations, Chang noted. DNDi has developed pediatric-strength benznidazole, which should be available by early 2011. Meanwhile, DNDi, Merck, and others are also investigating a group of antifungal drugs, the azoles, which have promising activity against the Chagas trypanosome in animal models.

Merck owns one of these compounds, posconazole, which has the double advantage of a long half-life and extensive distribution throughout the body, according to Feinberg. Posconazole is licensed in the United States, the European Union, and in other countries for the prevention of invasive fungal infections and for the treatment of oropharyngeal candidiasis, he said. A Phase II proof-of-concept study for the treatment of Chagas disease is slated to begin in late 2010, with results anticipated by 2012.

Although these developments are promising, Feinberg observed, they raise a new set of challenges—how does one assess the efficacy of a Chagas drug in the absence of a robust, validated, and accepted surrogate laboratory measure to assess drug efficacy in an infection for which clinical disease can take years to develop after initial infection? In the planned proof-of-concept study to assess the efficacy of posaconazole in the treatment of chronic Chagas disease, Merck will monitor parasite levels using polymerase chain reaction (PCR), he noted, but he wondered if a proof of concept based on such a surrogate endpoint would be sufficient to support licensure of the drug in the many countries—including the United States—where Chagas disease is also present.

Antipoverty Vaccines

In a second presentation to the workshop, Hotez described progress toward the development of vaccines to control the helminth infections hookworm and schistosomiasis, which, measured together in terms of DALYs, rank closely behind malaria as the world's most prevalent parasitic diseases (Hotez et al., 2008a).

Currently, two drugs, albendazole or mebendazole, are the only treatment options available to the more than 1 billion people infected with hookworm, he said, while praziquantel is the sole option for the nearly 800 million people chronically infected with schistomiasis.

Although resistance to these drugs has not yet occurred on a large scale, it does present a significant threat to the "massive scale-up" required to treat vast numbers of people infected with these diseases, Hotez said. In particular, he noted, albendazole and mebendazole are members of a class of drugs known as antihelminthic benzimidazoles, which have been used for decades to deworm cattle and sheep throughout the Southern Hemisphere and to which "widespread resistance" has already arisen. Even so, he observed, "What are we doing to monitor for resistance in humans? Essentially nothing! There are a couple of research groups around the world, but there is, for all practical purposes, no resistance monitoring in place [for anthelminthic benzimidazoles]." Moreover, Hotez continued, several analyses show that mebendazole, administered in a single dose (a common practice of annual MDA programs in developing countries), failed to cure or even significantly reduce worm burden in the vast majority of many cases (Keiser and Utzinger, 2008).

Responding to the significant limitations of antihelminthic drugs, the Sabin Vaccine Institute, which Hotez directs, is seeking to develop vaccines that target hookworm and schistosomiasis, as well as a vaccine for malaria. "There [are] now good evidence and a lot of data showing how neglected tropical diseases impair intellectual and physical development in children," he observed; for example, chronic hookworm infection in childhood has been shown to reduce future wage earning by 40 percent and also to contribute to adverse pregnancy outcomes (Hotez et al., 2009b). Thus, Hotez and his colleagues refer to the products they pursue as "antipoverty vaccines."

To produce these vaccines, the institute established a PDP known as Sabin Vaccine Development, Hotez explained. With the strong support of the Brazilian and Dutch governments, the National Institutes of Health (NIH), and the Bill & Melinda Gates Foundation, as well as individuals and family foundations led by Mort Hyman and Len Blavatnik, the PDP engages in all phases of vaccine discovery, from antigen discovery through genomics and proteomics, and to Phase I and II trials and beyond, he said. Other groups pursuing "antipoverty" vaccines include the Hilleman Laboratories, as described earlier by Feinberg, Novartis Global Health Vaccines, the Infectious Disease Research Institute, the International Vaccine Institute of Korea, and the Program for Appropriate Technology in Health, together with its subsidiary, the Malaria Vaccine Initiative. Hotez noted that a key advantage of such partnerships is their ability to propel vaccine development through the notoriously difficult transition from R&D to production. In Brazil, this transition is simplified because two public-sector, not-for-profit vaccine manufacturers produce two-thirds of the country's vaccines. Brazil—

despite its high rates of poverty and NTDs—stands out as a so-called innovative developing country (IDC).

Focusing on the human hookworm vaccine, Hotez observed that making a vaccine against a parasite, rather than an antigen, requires a novel approach—in this case, attempting to interfere with its ability to feed on human blood. Using this strategy, the PDP has identified two effective vaccine antigens (Asojo et al., 2007; Hotez et al., 2010; Loukas et al., 2005), has completed manufacture of one of the antigens in preparation for Phase I trials in Brazil, and anticipates completion of a large Phase II study by 2017, he reported.

"Wherever you find hookworm, you find schistosomiasis," Hotez observed. "If you have hookworm, you are more likely to have schistosomiasis, especially intestinal schistosomiasis caused by *Schistosoma mansoni*." Therefore, he reasoned, "if we are going into these endemic areas to vaccinate people against hookworm, why not try to do this for schistosomiasis as well?" Taking advantage of the complete genome sequence of *S. mansoni*, Alex Loukas, Jeff Bethony, and their colleagues working with Sabin Vaccine Development identified a promising target in the form of a family of proteins that span cell membranes, called tetraspanin surface antigens. They also determined that, by disabling these proteins using RNA interference, they could disrupt the integrity of the surface membrane and thereby halt worm development (Tran et al., 2010). Additional research demonstrating that some people who are apparently resistant to schistosomiasis possess antibodies to tetraspanin surface antigens (Tran et al., 2006) supports the viability of this target.

An anti-schistomiasis vaccine could also provide a "back door" route to AIDS prevention, Hotez speculated, because genital schistomiasis appears to increase risk for HIV infection in women. "If you actually look at a map of schistosomiasis with HIV/AIDS, it's amazing how the two, especially in rural areas, overlap so tightly," he said. Similarly, he continued, a hookworm vaccine might reduce the impact of malaria, because many people suffer co-infections of those parasites.

"The dream, moving forward, is to ultimately create a multivalent, antihelminthic antipoverty vaccine," Hotez concluded. He anticipated that such a vaccine could save 26 million DALYs, or about half the DALYs attributed to malaria or HIV/AIDS, and lift a significant portion of Brazil's overall burden of disease. If an antihelminthic vaccine were added to "rapid impact" packages, which currently consist of drugs targeting the seven most common NTDs, the resulting "vaccine-linked chemotherapy" package could be administered through school-based health systems or on designated Child Health Days, Hotez said.

Diagnostics: Essential to Progress

Speaker Patrick Lammie, of CDC, observed that precise, robust, field-friendly, affordable diagnostics are needed across the NTD portfolio to direct

treatment and also to support surveillance. (Dr. Lammie's contribution to the workshop summary report can be found in Appendix A, pages 346–356.) Diagnostics appropriate for individual case management differ from those used to guide and monitor MDA programs in which entire communities are treated, he said; both types of diagnostic tools may be employed at different stages of a disease control program, supported by appropriate sampling methodologies. In the initial disease-mapping phase of control programs, convenience sampling provides enough information to make appropriate decisions, he said. However, determining when and how to alter MDA frequency requires more precision (i.e., measuring a diagnostic marker indicative of infection), whereas post-MDA and surveillance diagnostics must capture transmission, he explained. Thus, he said, as the control program progresses, sampling becomes more systematic, and decision-making demands more robust information.

Although "19th-century" microscopic diagnostic techniques currently used in the initial phases of NTD control are adequate for the task, recent advances in genomics, proteomics, and metabolomics could vastly improve monitoring efforts in the late stages of control programs, Lammie said. Antigen-detection assays can be developed to monitor residual levels of infection in communities where MDAs are conducted, to inform decisions about altering treatment frequency or stopping it altogether, he said. He noted that such tests exist for LF, and that another is in development for schistosomiasis. There is a critical need for a similar tool to monitor trachoma transmission, he noted; currently, parasite presence is gauged by inflammation, a symptom that may persist beyond the infective stage. L. King also observed that the lack of specific tests for zoonotic parasites means that cases of febrile illnesses tend to be diagnosed as malaria, based on clinical signs and symptoms, but may actually result from zoonotic infections such as leptospirosis and Q fever.

To achieve elimination of NTDs through MDA, infection prevalence must be driven below levels capable of sustaining transmission in a host population, Lammie explained. "We are not going to be measuring . . . the number of [transmission] cycles and the initial prevalence with enough precision that we are really going to be able to rely on a standard algorithm to make decisions about when it's safe to stop [treatment]," he observed; rather, data must drive decision making. Surveillance at this stage of a control program is intended to detect any recrudescent transmission. Unfortunately, he said, researchers largely lack the tools to conduct that sort of surveillance in the field.

In an earlier discussion, audience member Joel Breman of the Fogarty International Center at NIH stated that "[i]t is essential that diagnostic tests be able to detect particularly low-level microbe infections when one gets down to the final mile, much less the final inch, in [NTD elimination or eradication] programs, and, in fact, discern where those microbes have come from." He observed that PCR for malaria can detect infection better than microscopy or even rapid diagnostic tests,

and he concluded that similarly sensitive tests are needed to detect low levels of microfilariae (for onchocerciasis and LF).

Describing his own experiences working on diagnostics for LF, Lammie recounted the results of a multi-center tool validation trial of rapid diagnostic tests in several different developing-country settings. Much to the researchers' dismay, test concurrence proved lower than anticipated, suggesting that technicians had been inadequately trained to perform the tests and that the commercially manufactured tests had not been well standardized. Lacking laboratory capacity to conduct serologic tests, the researchers concluded that point-of-care diagnostics would be a better choice for field settings—except that they are not available for onchocerciasis, schistosomiasis, or trachoma. NTD colleagues have now developed a statistically robust survey protocol, based on detection of antigen-positive (or antibody-positive) children that program managers can use routinely to determine whether any MDA program (regardless of its disease target) should be continued.

After stopping an MDA program, surveillance for incident infections must continue, Lammie observed; however, with current diagnostics, such events are difficult to detect in their early stages. In theory, antibody-based tests offer an early, sensitive indicator of exposure to pathogens and could be multiplexed to test for several diseases, but existing antibody tests for NTD pathogens are neither sufficiently robust nor specific for this purpose, he said.

In addition to improving patient care and programmatic decision making, better diagnostic tools will advance understanding of NTD transmission dynamics, Lammie observed. For example, he said, when transmission is reduced to "islands" within a geographic area where a disease is otherwise eliminated, it remains to be determined whether and how long transmission persists within those foci, or if they represent potential sources for resurgence of transmission within the surrounding population.

The Role of Regulatory Science

Goodman discussed FDA's current and potential role in addressing NTDs, working with innovators as they develop novel products and devising tools to evaluate products. He also drew scientific and policy parallels between the development of medical countermeasures against biological, chemical, radiological, and nuclear threats and emerging infectious diseases (Hamburg, 2010)—a major initiative undertaken by FDA—and efforts to develop drugs, vaccines, and diagnostics for NTDs.

Both pursuits demand and benefit from collaboration within government agencies and between governments and non-governmental entities to overcome significant barriers to development, Goodman observed. "Showing safety and effectiveness of [both NTD drugs and medical countermeasures] . . . is something that we often don't have the tools and models and methods to do," he said.

"Doing clinical trials in less developed countries is something that is a challenge that we frequently don't have the regulatory structures or methods to address." Manufacturing capacity, quality, and oversight present additional challenges to product development, as do the environments in which the products must be effective as delivered and used.

The medical countermeasures initiative seeks to address these challenges through a series of measures that are directly relevant to neglected diseases, Goodman stated. The FDA Medical Countermeasures Initiative (MCM) provides resources to support interactive science-based review and regulatory science to aid in translation from basic science into practical products, since there are often little or uncertain economic incentives to develop such products. Also, basic scientists may not recognize potentially powerful applications for their discoveries that could help enable MCM or NTD product development. In addition, FDA is providing interactive regulatory and technical support for planned DHHS-funded and other efforts to develop advanced development and manufacturing facilities and approaches for medical countermeasures using novel platform technologies such as flexible, modular, scalable, and disposable methods that may also prove appropriate for manufacturing products needed for both emerging threats and NTDs, including in other areas of the world, he observed.

FDA will work with the sponsors of each countermeasure in development, and with colleagues in the Department of Health and Human Services (HHS) and the Department of Defense (DOD), to develop a regulatory science plan that identifies gaps in applied science and determines how to fill them, Goodman said. This effort is being substantially resourced for medical countermeasures and for emerging infectious diseases, he continued. Ideally, it would extend to all diseases of global health importance. In the meantime, the medical countermeasures initiative should benefit the cause of neglected diseases by raising awareness that the health of each country affects the health of the world, and by advancing regulatory science and driving multi-use technological innovations and supporting companies that engage in it.

Goodman encouraged the NTD community to view FDA as a resource to help guide improvements in the quality of treatments and in the manufacturing processes that produce them. "We are putting a tremendous amount of energy into issues like information sharing with our regulatory partners, developing approaches to jointly assess new products so that we work together with the rest of the world in using science-based approaches to assessing product safety and efficacy," he said. Indeed, he emphasized, FDA accepts the results of clinical trials conducted overseas, as long as they include the appropriate protections and methods. The agency also evaluates and approves products for the United States even when they may be used primarily outside the United States. "Our regulatory decisions are risk/benefit decisions, not risk decisions," Goodman insisted. "We look at a decision, if it's a drug for onchocerciasis or a vaccine for malaria, in

terms of whether there is a favorable risk/benefit situation. We don't apply some U.S. standard that says things have to have no risk and 100 percent benefit."

Goodman also noted that FDA works with WHO on a number of issues with relevance to NTDs, including vaccine pre-qualification, establishing standards (e.g., for regulating blood testing and screening for Chagas disease), prequalifying drug and vaccine manufacturing facilities, and efforts to reduce drug counterfeiting. Ultimately, he said, FDA hopes to "make progress in educating both our country and the world that the health problems of one country are the health problems of every country." And to work together to prevent and attack those problems.

Investing to Address Neglected Diseases

In addition to the significant contributions of pharmaceutical companies to reduce the burden of NTDs, these efforts also receive support from countries, NGOs, and philanthropies, all of which were represented among workshop speakers. They described their current commitments and goals regarding research, development, delivery, and implementation of measures to control NTDs, and they considered how to coordinate investment in NTDs in order to optimize its impact. In the course of these presentations and subsequent discussions, participants examined ways to sustain and expand recent gains made against NTDs, so as to address significant unmet needs for effective measures to prevent and treat neglected diseases, and to mitigate the health and socioeconomic consequences of neglected diseases.

Current Investment in NTDs

The U.S. Global Health Initiative (GHI) In a keynote address that opened the workshop, Emanuel described the overall goals of the GHI and its areas of specific focus, which include the NTDs. Announced by President Obama in May 2009, the GHI will provide $63 billion over six years to address the following issues in developing countries:

- Increasing coverage and integration of pneumococcus and rotavirus vaccines in immunzation programs;
- Improving maternal and infant outcomes for childbirth;
- Preventing and treating malaria;
- Preventing HIV/AIDS; and
- Preventing and treating NTDs.

As Hanson had noted, this commitment dwarfs previous U.S. contributions to NTDs, which, beginning in 2003, amounted to $45 million over the course of the next five years. During that time, Emanuel said, more money was spent research-

ing NTDs at NIH than in distributing effective treatments to people in need. These meager efforts were, however, supported by donations of NTD drugs from Merck, Pfizer, GSK, and other pharmaceutical companies, and also by contributions from the British government (discussed below).

Emanuel presented the following list of NTD targets for the GHI:

- Reducing the prevalence of the seven high-prevalence NTDs,[26] by 50 percent, among 70 percent of the affected populations;
- Eliminating onchocerciasis in Latin America by 2016; and
- Eliminating LF and leprosy globally by 2017.

Achieving these goals will require the establishment of enduring and accountable public–private partnerships, Emanuel said. In an immediate step to increase its potential impact, the GHI will fund the creation of publicly accessible, global maps of NTDs overlaid with the locations of schools and health clinics where medications can be distributed.

The U.S. commitment to controlling and eliminating NTDs recognizes their significant health and economic impact, as well as the promise that this burden can be substantially reduced, Emanuel said. "We have effective treatments and treatment strategies [for NTDs]," he observed. "They are a great example of public–private partnerships, where we get much more leverage for what we spend."

The U.K. commitment to NTD control Contributions from the United Kingdom to address NTDs derive from diverse donors, including the British government, its Medical Research Council, and organizations focused on implementation of control measures, according to speaker Alan Fenwick of London's Imperial College. (Dr. Fenwick's contribution to the workshop summary report can be found in Appendix A, pages 172–183.) Since 2000, he said, the British government has been a steady source of support for the Centre for Neglected Tropical Diseases (CNTD) at Liverpool University, the Schistomiasis Control Initiative (SCI) at Imperial College (which Fenwick directs), and APOC, among others. In September 2008, Prime Minister Gordon Brown pledged an additional 50 million pounds over five years for NTDs,[27] a commitment that his successor, David Cameron, has agreed to honor, Fenwick said. The Wellcome Trust and Medical Research Council exclusively support research and development related to NTDs; neither

[26] As described by Hanson.

[27] Distributed as follows:
- £10 million for LF (through CNTD Liverpool),
- £10 million for dracuncluliasis (through WHO and the Carter Center),
- £5 million for onchocerciasis (through APOC), and
- £25 for schistosomiasis and intestinal helminths (through SCI, as well as for the purchase of praziquantel).

organization funds implementation programs. GSK, which donates its drug, albendazole, to LF control programs, also has a significant presence in the United Kingdom. Fenwick also mentioned a range of potential private donors—including individual citizens—whom he hopes can be persuaded to recognize and support the cause of NTDs in the near future.

In addition to the university-based initiatives SCI and CNTD, which specifically support the implementation of control measures against NTDs, other groups—such as Imperial College's Programme for Child Development, and two NGOs specializing in eye diseases—contribute to such efforts through integrated programs, Fenwick said. He also noted that SCI and CNTD have joined forces to direct their respective government funds toward the same recipient countries, in order to support the implementation at scale of both MDA and (in some cases) targeted chemotherapy against schistosomiasis, STHs, and LF in an integrated fashion.

As increasing numbers of organizations become involved in NTD control programs—both within and outside Britain—Fenwick urged greater coordination and collaboration, and cautioned against duplication of effort. He encouraged an expanded approach to integrated control to incorporate the provision of bed nets and nutritional supplementation for preschool-age children. In addition, he advised greater attention to the behavioral aspects of MDA, to increase compliance and ensure "that the people who are swallowing the drugs understand exactly why," he said. For example, most children treated for schistosomiasis have yet to experience symptoms, so they are being asked "to take a leap of faith and to take drugs that we are offering to them, when they can't necessarily see that they particularly need them," he said. He also echoed several other speakers and participants in emphasizing the importance of local ownership of MDA programs.

The Bill & Melinda Gates Foundation support for NTD control Speaker Julie Jacobson, of the Bill & Melinda Gates Foundation, observed that supporting efforts to combat NTDs fits the Foundation's basic premise: "Every person deserves the chance to live a healthy and productive life." (Dr. Jacobson's contribution to the workshop summary report can be found in Appendix A, pages 293–309.) Within its Global Health Division, the Bill & Melinda Gates Foundation currently awards grants for initiatives directed at a list of neglected diseases that includes WHO's "standard 13" as well as dengue and Japanese encephalitis; since 1998, the Foundation has invested US$544 million to address NTDs, she reported. Because DALYs drive the Foundation's giving strategy, she said, and as a result of the lack of firm DALY estimates for many NTDs, the Foundation is sponsoring efforts to improve those measurements. Grantees submit annual reports on their progress and receive payment from the Foundation linked to the achievement of project milestones.

Rather than set eradication or elimination goals for particular NTDs, the Bill & Melinda Gates Foundation invests strategically in drugs and treatments,

vaccines, diagnostics, biomarkers, vector controls, and implementation strategies, Jacobson explained. "We don't implement programs, but we do things to make sure that programs that are implemented can be done well and achieve more," she added. Current investments include the development of a macrofilaricide capable of killing adult worms in patients with onchocerciasis and LF, thereby dramatically reducing treatment duration (which currently can last as long as 17 years). Other grants under consideration include efforts to develop traps for black flies to permit analysis of parasite transmission in vector populations, a more sensitive diagnostic for onchocerciasis for monitoring post-MDA transmission, and an examination of the ancillary benefits gained through MDA. An ongoing project to develop a vaccine and drug to prevent and treat cysticercosis in pigs and humans has enabled the local elimination of that disease in a site in northern Peru, so it is working to expand and refine the model strategy and encourage uptake, she said.

The Bill & Melinda Gates Foundation's approach to NTDs has largely focused on research and development of new tools and strategies for integrated program development, Jacobson said, but they are increasingly cognizant of the need to reach more communities and optimize the impact of these innovations. To meet this challenge, the Foundation has developed communications and advocacy plans "to get the word out" about promising developments, she said. "If we work with a grantee to make the perfect tool, it means nothing if it doesn't get out there," she concluded.

Overview of investment in R&D Speaker Mary Moran, of Policy Cures—an independent group that provides research, information, decision-making tools, and strategic analysis for those involved in the creation of new pharmaceuticals for neglected diseases (Policy Cures, 2010)—reviewed the current state of R&D investment in NTDs, as described in a recent report from her organization (Moran et al., 2009). (Dr. Moran's contribution to the workshop summary report can be found in Appendix A, pages 388–414.) Known by its abbreviated title, G-FINDER (for Global Funding of Innovation for Neglected Diseases), the report summarizes the results of an annual survey of 208 organizations that invest specifically in the R&D of new products aimed at a group of 31 neglected diseases, of which approximately half are NTDs.

From these highly detailed data, Moran extracted several "big picture" characteristics, beginning with the bottom line: in 2008, she reported, the world spent about US$3 billion to develop new products for neglected diseases, of which nearly three-quarters was spent on HIV/AIDS, TB, and malaria. The NTDs, among which Moran included WHO's list of 15 diseases, collectively receive approximately 12 percent of this total, or just under US$350 million; Figure WO-15 shows how that amount was divided among classes of NTDs, with kinetoplastid diseases (Chagas disease, HAT, and leishmaniasis) and dengue receiving the majority of funding. "Funder investment in this area is very clearly stratified," she observed.

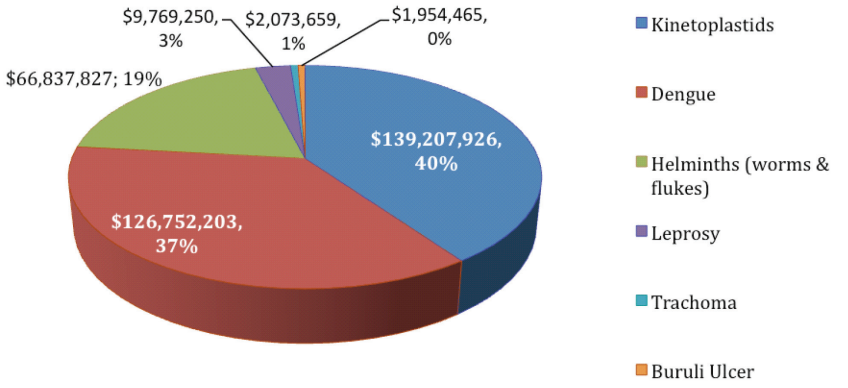


FIGURE WO-15 Global funding for NTDs by disease.
SOURCE: Adapted from Moran (2010).

The top 12 NTD R&D funding organizations are shown in Figure WO-16. NIH is the biggest funder—followed by the Bill & Melinda Gates Foundation—for nearly every disease, Moran said. She also noted that the vast majority of pharmaceutical industry funding is directed at dengue, while nearly all R&D funding for kinetoplastid and helminth diseases and trachoma derives from public and non-profit sources. "The big funders [NIH and Gates] provide about 60 percent of funding, just those two groups," she observed. "After that, you drop to very small figures. If you want to be one of the top 10 global funders [of NTD R&D], you only need about $15 million, $20 million, and, based on these figures, you will be providing more than Japan, more than Germany." On the other hand, she said, IDCs like Brazil and India now provide 10 percent of global investment in NTD R&D.

A closer examination of the breakdown of funding by disease and disease class reveals the following details, of which Moran made note:

- Whereas R&D funding for most NTDs is spent on basic research, this is not the case for kinetoplastid diseases, largely because of DNDi's efforts to develop drugs for HAT and leishmaniasis. This statistic illustrates a general trend that the existence of PDPs—which are not necessarily reflective of need—drive investment in R&D, Moran observed.
- Dengue is exceptional in receiving significant funding from the pharmaceutical industry—nearly 85 percent of its US$52 million total contribution to NTDs; this is because dengue affects wealthier countries and thus has a bigger market than most NTDs, Moran said. Dengue R&D is also relatively well-funded by Brazilian groups because of the impact of the

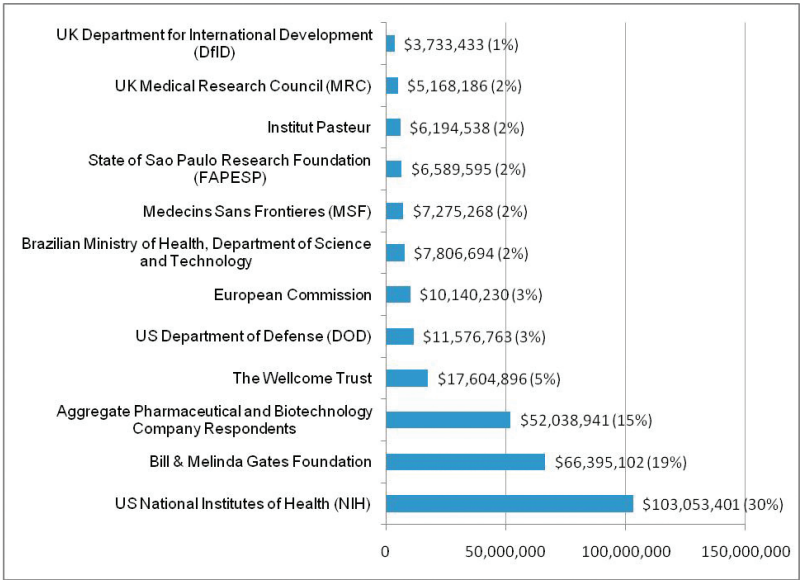


FIGURE WO-16 Top 12 funders of NTD research, 2008 (US$).
SOURCE: Adapted from Moran (2010).

disease in that country and their capacity to do research (as previously noted by Hotez), she added. Moran characterized such demand-driven funding as "much more sustainable" than funding driven by charitable grants or donations.

- Most of the relatively meager funding for helminth diseases is spent on basic research, reflecting the absence of a group devoted to applied work for most of these diseases. Here again, she observed, "the funding for basic versus applied research doesn't appear to reflect actual need. It's driven by other things."

From these findings, Moran concluded, there is a "lack of correlation between investment patterns and R&D needs and possibilities," or more simply, a "disconnect between policy and innovation." For years, out of necessity, public health policy has been focused on making do with little, she said. "Now innovations come along, and I think we are all at a bit of a loss. Policy hasn't caught up to provide the tools to stimulate investment, to guide investment, and to make sure innovations get out there quickly."

Several crucial pieces of information are needed to fill this funding gap, Moran observed. Funders need accurate assessments of health return on investment—a difficult calculation to make, she added, because the investment needed

to drive a product reflects a host of factors, including the impact of the disease (e.g., in DALYs), the severity of underfunding, and the size of the treatment gap. "If you are putting money into an area where there are already products and you are going to make a "top-up" product, your impact is much less than if you are making a product where there is nothing," she observed. Funders also need to know the state of science in the field, she said. For example, are (relatively cheap) diagnostics needed, or (relatively expensive) vaccines? "When funders think about where to put their money to get the biggest bang for the buck, there are a whole bunch of issues that they need to know about, and I don't think they clearly get this information," she concluded; moreover, funders lack the analytical tools they need to determine their health return on investment.

Those who receive funding also lack important information about how to get their products into use, Moran observed. "There is often a gap between a product being available and when it gets out there," she said, adding that a backlog of more than 100 diagnostic products currently await prequalification by WHO. However, even pre-qualified products often fail to provide potential end users with information *they* need to help them decide if the product suits their needs, she added. Moran described a promising new multi-drug resistant MDR-TB diagnostic that detects the disease in about 97 percent of patients and which a technician with very little training can perform in two hours—something public health has wanted for decades. Unfortunately, she continued, "we have the machine, but we don't have the advice. What if you are sitting in Brazil? What's the entry point for this test? Is it district hospital? Is it urban? When does it displace my existing system of testing? Who's going to fund it? Should I use it for HIV? The test is very sensitive at picking up smear-negative patients, about 90 percent. When do I use it for HIV, or should I just use it for MDR-TB? How do I scale it up? How do I implement it? Where's the entry point? How do I roll it out?"

Ministries of health need information on cost-effectiveness and implementation (e.g., if existing laboratories and/or workforce are sufficient) in order to determine whether to purchase a product, Moran explained. If this information were provided in "policy packages" accompanying each product, end-users could make better decisions as to whether or not to adopt a novel intervention, she said.

Responding to the suggestion that focusing on product development overlooks health-system approaches to NTDs, and therefore results in opportunity costs, Moran said that both approaches were needed, noting that past experience (e.g., in determining whether to emphasize treatment or prevention of HIV/AIDS) suggests that treating people leads to community mobilization to address broader health issues. "Our job as policymakers is to make sure that the innovations are brought to patients as soon as can be," Moran concluded. "For every delay in that, I actually think we're starting to be responsible for some of this mortality. We have always pointed at poor infrastructure, or lack of industry investment in R&D for neglected diseases. But now that innovations are coming along, delays in rolling them out really lay at our door."

Gauging health return on investment The concept of "health return on investment," raised by Moran, sparked considerable discussion. Forum member Carole Heilman, of NIH, noted that health return can be variously defined, but that death is the easiest way to measure it. "Preventing death is really something you can grab onto," she said. It is far easier to motivate funders to focus resources on "killer" diseases such as HIV, TB, and malaria than it is for chronic, debilitating diseases. Curing poverty is an attractive alternative, she continued, but not unless an intervention is measured using solid indicators of poverty (e.g., changes in gross domestic product [GDP] or in measures of intelligence).

"There [are] genuine data showing impressive economic rates of return when you can keep people free of these neglected tropical diseases," Hotez replied. "They truly are antipoverty measures."

But, Heilman asked, can you really demonstrate that a particular implementation measure produced those changes? Were there other confounding factors that you could control for or deal with?

That's a legitimate question, Lammie observed, but the reality is that programs are already in place under the assumption that they will alleviate poverty—so it is important to collect impact data to see if that is the case. "Do I have confidence that there are relationships between the presence of these diseases and poverty? Yes. Are they linear? Are they direct? Probably not," he concluded. "But I think, as we have seen the programs go to scale . . . the reality is that our collection of data, our gathering of data related to impact has really lagged behind. We have a long way to go to get to the point where I think we are going to be able to satisfy you with an answer."

With regard to specific interventions, Feinberg noted that, in the cases of pneumococcal and rotavirus vaccines, not only did projections derived from clinical studies anticipate economic benefits, but these were borne out in post-implementation studies by CDC. He added that he is not aware of similar efforts focused on NTDs.

Forum chair David Relman raised the possibility of conducting public health intervention experiments, controlling for as many potential confounds as possible, to explore the poverty–NTD connection. It would be unethical to perform case-control evaluations and withhold treatments from a community, Lammie replied, but it is possible to capture disease-specific impacts of integrated interventions in terms of such factors as children's growth rate or anemia prevalence. Such studies could potentially be conducted at "demographic and surveillance sites where there have been huge investments made over the last decade to look at public health interventions in the context of longitudinally monitored populations," he said.

On this point, Hopkins noted that one of the Carter Center's most powerful advocacy tools for funding dracunculiasis eradication was a UNICEF study in southwest Nigeria that was funded for US$5,000. The disease was highly prevalent in this area, which was also a very fertile rice-growing region, and the study demonstrated that rice farmers alone (among a total population of 1.6 million) were

losing $20 million per year due to dracunculiasis. When extrapolated to the entire agricultural sector of Nigeria, that figure was huge, he said—and persuasive.

"Is it indeed possible to come up with some kind of metric for health return on investment?" Moran asked. Companies gauge return on investment with one set of metrics, and cost-effectiveness with another, she observed; most governments compare the health benefit of a product with its cost. "I'm trying to look at where there is the opportunity to improve information—perfect information, no; a single number, no; a list of priorities, no—just a tool to help—because, honestly, we look at the R&D funding stats all the time, and it's just random," she said. Rather than attempt to discern precise measures of health impact, she said, she hopes to identify "simple rubrics" and "distinguishing factors" to guide investment decisions, which often come down to choosing to develop or to distribute a drug for one NTD, versus one for another.

Guiding Principles and Next Steps

In his presentation on the GHI, Emanuel described the following seven principles upon which the initiative is based. All seven were raised and elaborated upon in subsequent workshop presentations and discussion and thus may be viewed as representative of the thinking behind investment in neglected diseases, a critical component of global health strategy.

Focus on women's and children's health As both Emanuel and McDonald noted, women are primarily responsible for childrearing and for providing and seeking health care for their families; they also manage water and nutrition. It is often said that the death of a mother increases tenfold the chance that her child will die, Emanuel noted—so, if you think like an economist, you can double your return on investment by improving women's health. Since women and children suffer disproportionately from NTDs and their consequences, as McDonald observed (see previous discussion in "Defining the NTDs"), such an investment should have even greater impact. Hotez echoed the importance of NTDs as problems in maternal and child health (Hotez, 2009c).

Through support for long-term systematic change related to women and children through the monitoring and evaluation of women's health, the GHI aims to enhance productivity and social and economic participation, Emanuel said; similar gains should be realized by treating children to prevent physical and cognitive effects of NTDs that drive the poverty cycle. Ault agreed, noting that one way such gains could be realized quickly was by extending programs such as school-based de-worming to preschool-age children.

Coordination and integration The specific directives of the GHI reflect consensus on the value of coordinating efforts to reduce NTD burden and on the need to integrate approaches to simultaneously and efficiently address several diseases

(including malaria and HIV/AIDS). Under the GHI, all agencies of the U.S. government that deal with international health—the State Department, USAID, HHS—will be encouraged to work together and to coordinate their activities with host-country staff, Emanuel stated. Points of care and supply chains will be integrated, to reflect the fact that patients rarely are infected with only one parasite, nor do they have the flexibility, time, or resources to attend multiple, disease-specific clinics, he added.

Partnership The health needs of people in developing countries are too vast, and the challenges too great, for any one country or organization to manage alone, Emanuel observed; this effort must involve other countries, NGOs, private philanthropies, and the private sector. Regarding NTDs, his commitment to "coordinate activities among various donors so we don't duplicate what we are doing and we are as efficient as possible" was affirmed by several others, including Feinberg and Moran. Savioli described global efforts to address NTDs as a "roundtable of partners that are really working together as a single group," in which WHO participates by defining problems and seeking their solutions (e.g., determining whether drugs such as ivermectin can be safely administered during pregnancy and infancy).

Country ownership Many participants extolled the importance of national or local management of and participation in NTD control programs. The ultimate responsibility for health interventions rests with the countries in which they are delivered, Emanuel observed, so the United States will work closely with governments and in-country health organizations to ensure that investments are aligned with national priorities; this may involve helping countries to develop health plans and the capacity to carry them out (e.g., computers, information, budgeting strategies, and training).

Sustainability Several participants emphasized that infrastructural improvements will be necessary to sustain interventions against NTDs over the long term. "The aim isn't to manage needs, but to address them in a way that permanently reduces and eliminates these health problems," Emanuel said. "Health systems, therefore, have to be improved both institutionally and structurally." There is an especially critical need to develop adequate workforce to address health needs in developing countries, he added.

When asked how to resolve tension between disease-specific approaches to NTDs and the need to develop overall public health infrastructure, Fenwick observed that political will within each recipient country is important to striking this balance, which can only occur if there is support for infrastructural development. "There are often trained people in [developing] countries for addressing NTDs, but they don't have resources they need," he observed. "If you provide those resources, they can do great things."

Monitoring and evaluation "We need to base our policy decisions on hard, good data," Emanuel insisted. "In the end, it's not the budget numbers, it's not the number of bed nets used or the number of pills distributed that really matter to us, but it's the lives saved, the health improved, and the health system functionality that we really ultimately care about." Even more important than doing what works is figuring out what doesn't work, and stopping it quickly, he observed; on the other hand, he added, "we need to identify, take to scale, and refine proven approaches. When something works, we need to quickly disseminate it."

Exactly how to know if something works remains a challenge, Emanuel acknowledged; thus, robust metrics must be developed to measure the impact of interventions. As economist and Nobel Prize winner Joseph Stiglitz has argued, "What you measure affects what you do—if you don't measure the right thing, you don't do the right thing" (Goodman, 2009).

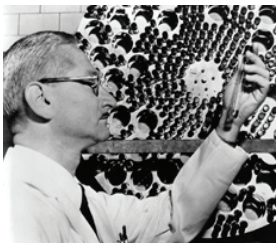
Research and innovation Anticipating a key point Moran made in her presentation, Emanuel noted several disappointing lapses in the adoption of proven measures to improve global health, such as circumcision to prevent mother-to-child HIV transmission. "We have not scaled up," he admonished. "We need to implement findings as part of our research." Under the GHI, he said, "we are going to support innovations that promote results-oriented rather that input-oriented expenditures." He also envisioned testing a variety of strategies for health services delivery involving such things as incentives to encourage people to attend clinics or to adhere to treatment.

Expanding Medical Diplomacy

In recent years, several workshop participants observed, NTDs have become increasingly less neglected. A major advance came with the recognition that NTDs represented an important opportunity for medical diplomacy[28]: the provision of needed health services as a means to developing positive international relations. Hotez took up this topic at the conclusion of his presentation on antipoverty vaccines, while displaying the quote from John Gardner in Figure WO-17.

Figure WO-17 also displayed the results of an analysis Hotez and colleagues performed, revealing that 40 percent of the world's seven most common NTDs occur in the world's Islamic countries: Indonesia, Bangladesh, Pakistan, Somalia, Sudan, West Africa, Chad, and Niger (Hotez, 2009d). Another 20 to 30 percent of the NTDs occur in large "upper middle" and "lower middle" income countries—India, China, Iran, North Korea, and Syria—that possess nuclear weapons (Hotez,

[28] Tommy Thompson claimed to have coined the term "medical diplomacy" while serving as Secretary of Health and Human Services in the Bush Administration (Iglehart, 2004), but the promotion of international relations through the provision of health services was first practiced by Cuba and has been a cornerstone of that country's foreign policy since shortly after the 1959 revolution (Feinsilver, 2006).



"There are no better grounds on which we can meet other nations and demonstrate our own concern for peace and the betterment of mankind than in a common battle against disease" John Gardner

Hotez PJ. SCIENCE 2010

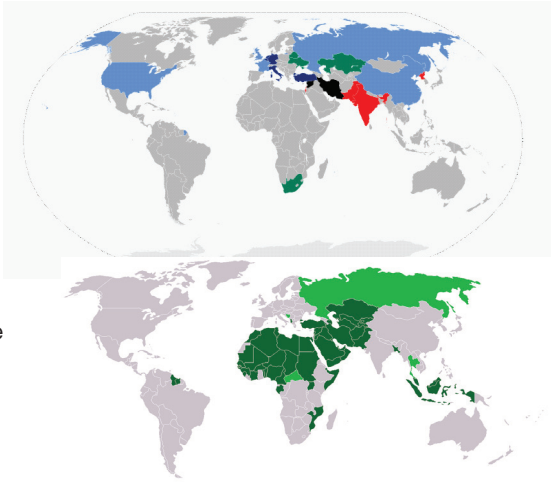


FIGURE WO-17 Opportunities for "vaccine diplomacy."
SOURCE: Hotez (2010c).

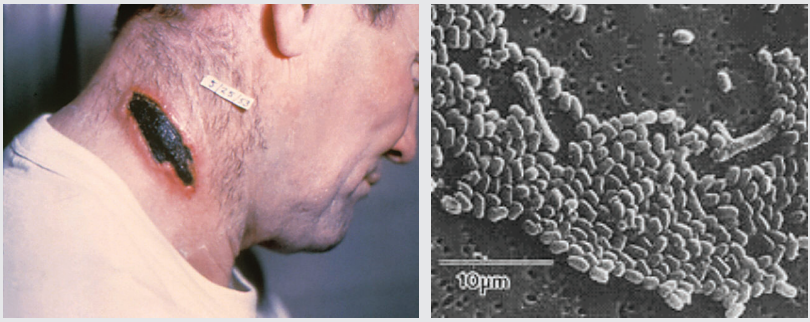
2010d). Given the geopolitical importance of these countries, health diplomacy addressing NTDs is more critical than ever, Hotez suggested; so important, in fact, that its purview should be expanded beyond MDA to include joint cooperative scientific ventures. Recalling Albert Sabin's joint effort with Soviet scientists that produced the oral polio vaccine—which occurred at the height of the Cold War—as an example of how two countries can put aside their ideologies for purposes of biomedical research, he posed the following question: "Can vaccinations help to resolve conflicts and nurture diplomacy?" (Hotez, 2010c).

Forum member Terence Taylor, of the International Council for the Life Sciences, affirmed Hotez's idealism. He offered the contemporary example of consortia on health decisions between Israel and its Arab neighbors, which have enabled them jointly to pursue leishmaniasis control and to share outbreak data on a day-to-day basis. In Southeast Asia, in southern Africa, and even in North Korea, health consortia are currently working across political divides, he added. Such groups could profitably turn their attentions to NTDs and, in particular, to the establishment of public health priorities in addressing these diseases, he said. "Health issues," Taylor concluded, "can cross the most difficult boundaries, and it is happening now."

> **In the end it is not the budget numbers, the number of bednets used, or the pills distributed that matter, but the lives saved, the health improved, and the health systems functionality.**
>
> —Emanuel keynote remarks

BOX WO-6
Key Neglected Diseases of Poverty

ANTHRAX



A B

FIGURE WO-6-1 Anthrax. (A) Cutaneous anthrax lesion on neck. (B) Bacterium, *Bacillus anthracis*, the causative agent of anthrax.
SOURCES: CDC, Public Health Image Library (PHIL 1934); Defense Threat Reduction Agency (DTRA).

Infectious agent: *Bacillus anthracis*, a bacterium

Routes of transmission to humans: Cutaneous (spores enter through skin lesions; accounts for 95 percent of cases in developing countries); eating meat from infected animals (gastrointestinal); inhaling spores (inhalation)

Health effects: Headaches, muscle aches, fever, vomiting (cutaneous); severe abdominal pain, vomiting, and diarrhea (gastrointestinal); rapid progression from cold symptoms to severe breathing difficulty and shock (inhalation). Enteric anthrax is frequently lethal; subclinical cases provide subsequent immunity

Incidence, prevalence, and mortality (estimated): Rare in developed countries. For cutaneous disease, estimated incidence ranges from 1 case per 10 livestock carcasses butchered in northern Europe to 10 cases per single carcass in Africa, India, and the southern Russian Federation

Prevention: Safe disposal of infected carcasses, vaccination of at-risk herds; human vaccine use restricted to high-risk groups

Treatment: Antibiotic therapy effective if given before or immediately after onset of illness

ASCARIASIS (ROUNDWORM)

A B

FIGURE WO-6-2 Ascariasis. (A) African child infected by *Ascaris lumbricoides*. (B) A large bolus of Ascaris worms blocking the intestinal lumen.
SOURCES: World Health Organization (WHO); Palmer and Reeder/Uniformed Services University of the Health Sciences (USUHS).

Infectious agent: *Ascaris lumbricoides*, a parasitic worm

Routes of transmission to humans: Eggs transmitted through human feces, usually hand-to-mouth

Health effects: Pneumonia, cognitive impairment, intestinal blockage, delayed mental and physical development

Incidence, prevalence, and mortality (estimated): 807 million people infected, of whom 58 million are considered "highly infected"

Prevention: Improved hygiene and sanitation; periodic drug treatment of at-risk populations

Treatment: Antihelminthic therapy

continued

BOX WO-6 Continued

BOVINE TUBERCULOSIS

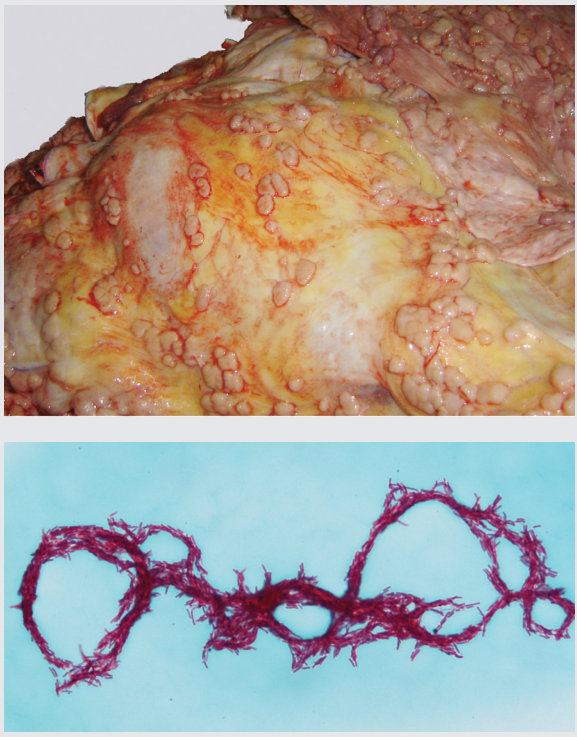


FIGURE WO-6-3 Bovine tuberculosis. (A) Pericardial lesions. (B) *Mycobacterium bovis* displaying the typical "medium rods with cording" morphology seen when cultured under normal laboratory conditions (Ziehl–Neelsen acid fast slide shown at 1,000 magnification).
SOURCE: U.S. Department of Agriculture (USDA)/Animal and Plant Health Inspection Service (APHIS); National Veterinary Services Laboratories, USDA, Ames, IA.

Infectious agent: The bacterium *Mycobacterium bovis* is a close relative of *Mycobacterium tuberculosis*, which causes most human cases of tuberculosis

Routes of transmission to humans: Consumption of unpasteurized milk and undercooked meat from infected animals; close contact with infected animals

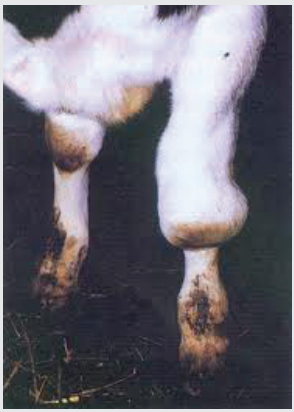
Health effects: Lesions and progression are largely indistinguishable from *M. tuberculosis* infection. Does not respond to common TB drugs, which can result in death

Incidence, prevalence, and mortality (estimated): No global estimates; rare in developed countries and likely under-reported in developing countries because of difficulty of diagnosis

Prevention: Test-and-slaughter policies; food hygiene practices

Treatment: Antibiotic therapy differs from that of TB and is far more expensive

BRUCELLOSIS (UNDULANT FEVER)



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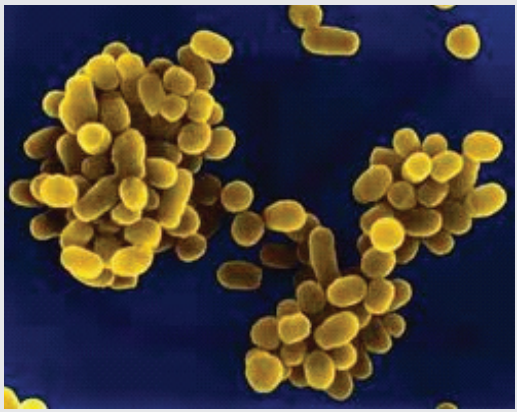


B

FIGURE WO-6-4 Brucellosis. (A) Hygromas[a] on the knee joints. (B) *Brucella melitensis/Brucella suis*.
SOURCES: Food and Agriculture Organisation of the United Nations (FAO); Defense Threat Reduction Agency (DTRA).

Infectious agent: Various bacteria of genus *Brucella*

Routes of transmission to humans: Contact with infected animals, drinking unpasteurized milk from infected animals

Health effects: Recurrent fever (often misdiagnosed as drug-resistant malaria); joint pain, fatigue, depression

Incidence, prevalence, and mortality (estimated): More than 500,000 new cases per year

Prevention: Pasteurization of milk, vaccination of cattle in high-prevalence areas, testing and culling of cattle in low-prevalence areas

Treatment: Antibiotic therapy

[a]An accumulation of fluid in a sac, cyst, or bursa.

continued

BOX WO-6 Continued

BURULI ULCER

A

B

FIGURE WO-6-5 Buruli ulcer (*Mycobacterium ulcerans*). (A) Child presenting nodule—early sign of Buruli ulcer disease, Ghana 2009. (B) A typical Buruli ulcer on the left hand of a 17-year-old boy in Nigeria.
SOURCES: WHO; Chukwuekezie et al., 2007. Originally published in *Emerging Infectious Diseases*.

Infectious agent: *Mycobacterium ulcerans*, a bacterium of the same family as TB and leprosy

Routes of transmission to humans: Unknown

Health effects: Swelling, ulcers, risk of bone deformities

Incidence, prevalence, and mortality (estimated): None determined

Prevention: Bacille Calmette-Guerin (BCG) vaccine offers short-term protection; research in progress for specific vaccine

Treatment: Antibiotic therapy; surgery to repair damaged tissue

CHAGAS DISEASE (AMERICAN TRYPANOSOMIASIS)

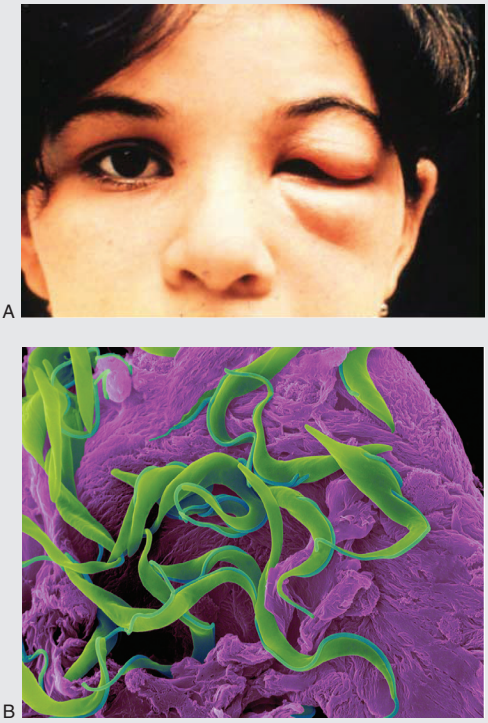


FIGURE WO-6-6 Chagas disease. (A) Acute Chagas disease in a young child. The eye sign of Romana is present. This is frequently seen in acute cases and is presumed to mark the point of entry of the parasite. (B) Trypanosome trypomastigote (*Trypanosoma* sp.) A hemoflagellated protozoan parasite that causes trypanosomiasis (Chagas disease, African sleeping sickness). SEM 800x magnification.
SOURCES: Special Programme for Research and Training in Tropical Diseases (TDR) Research Image Library (WHO/TDR); http://www.denniskunkel.com/product_info.php?products_id=13508 (accessed January 19, 2011). Copyright Dennis Kunkel Microscopy, Inc.

Infectious agent: *Trypanosoma cruzi*, a protozoan parasite

Routes of transmission to humans: Bites from insects known as "assassin bugs" or "kissing bugs"; blood transfusions; mother-to-fetus

Health effects: Cardiac or digestive complications; risk of death from heart problems

Incidence, prevalence, and mortality (estimated): 8 to 9 million people infected; up to 2.8 million with severe disease; 14,000 deaths per year

Prevention: Vector control; improved housing and food hygiene; screening of blood and organ donors

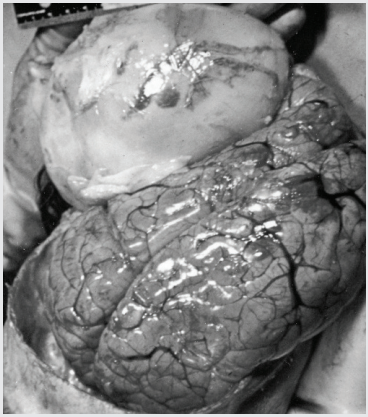
Treatment: Anti-parasitic drugs; most effective if given at onset of infection

continued

BOX WO-6 Continued

CYSTIC ECHINOCOCCOSIS (HYDATID DISEASE)

A



B

FIGURE WO-6-7 Hydatid disease. (A) An autopsy specimen from a 7-year-old girl with a huge *Echinococcus granulosus* cyst of the brain. (B) Adult cestode, *E. granulosis*.
SOURCES: Palmer and Reeder/USUHS; CDC Public Health Image Library (PHIL 11020).

Infectious agent: *Echinococcus granulosus*, a tapeworm

Routes of transmission to humans: After eating meat from infected livestock (typically a sheep), carnivores (typically domestic dogs) shed tapeworm eggs in their feces; humans ingest eggs in contaminated food and water, or through contact with infected dogs

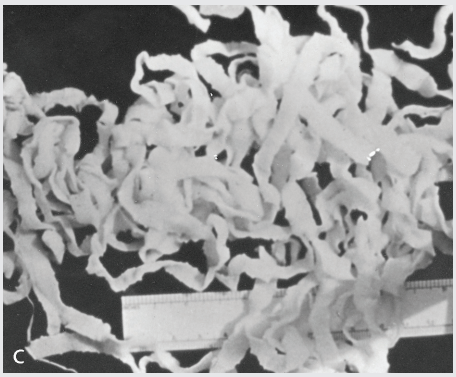
Health effects: Large cysts, usually in the abdomen, that grow slowly and can become very large

Incidence, prevalence, and mortality (estimated): Highly prevalent in poor communities in developing countries; incidence of surgical cases ranges from 0.1 to 45 cases per 100,000 and real prevalence ranges between 0.22 percent and 24 percent in endemic areas

Prevention: Sanitary slaughter conditions to prevent dogs from eating visceral organs of infected livestock, personal hygiene, avoidance of feces-contaminated water or vegetables, periodic treatment of dogs, meat inspection

Treatment: Surgery to remove cysts

CYSTICERCOSIS, TAENIASIS, AND NEUROCYSTICERCOSIS (NCC)



A

B

FIGURE WO-6-8 Cysticercosis. (A) Adult *Taenia solium* worm. (B) Mammal intestine tapeworm (*Taenia* spp.). The adult has a head (scolex) with suckers and/or hooks that are used to attach to the host (SEM 16x magnification).
SOURCES: Palmer and Reeder/USUHS, Courtesy of Dr. Herman Zaiman; http://www.denniskunkel.com/product_info.php?products_id=1173 (accessed January 19, 2011). Copyright Dennis Kunkel Microscopy, Inc.

Infectious agent: Tapeworms that infect pigs (*Taenia solium*) and cattle (*Taenia saginata*)

Routes of transmission to humans: Consumption of raw or undercooked pork (cysticercosis) or beef (taeniasis) containing larvae; contact with tapeworm carriers (who shed eggs in feces) or with egg-contaminated water or food

Health effects: Depending on the location of the larval cysts, infections can cause lumps under the skin, impaired vision, or—when cysts form in the brain or spinal cord (NCC)—neurological symptoms including seizures, headaches, cognitive impairment, balance difficulties, and swelling of the brain

Incidence, prevalence, and mortality (estimated): 50 million cases worldwide; 50,000 deaths per year

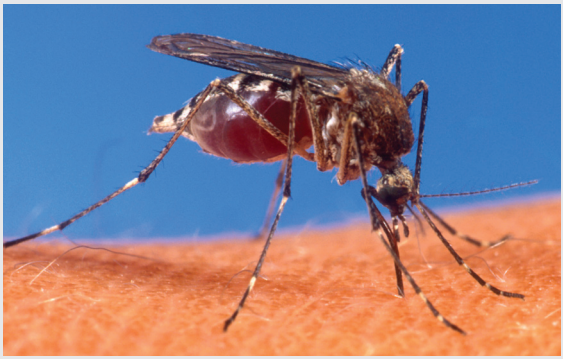
Prevention: Cooking pork and beef, hygiene and sanitation

Treatment: Cystercercosis treatment involves both antibiotics and steroids and is not always successful; antibiotic treatment of taeniasis is effective

continued

BOX WO-6 Continued

DENGUE AND DENGUE HEMORRHAGIC FEVER (DHF)



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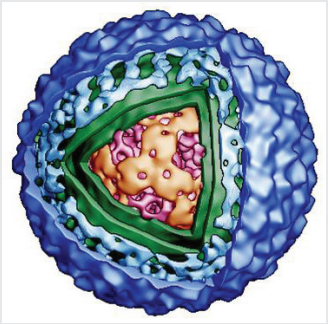

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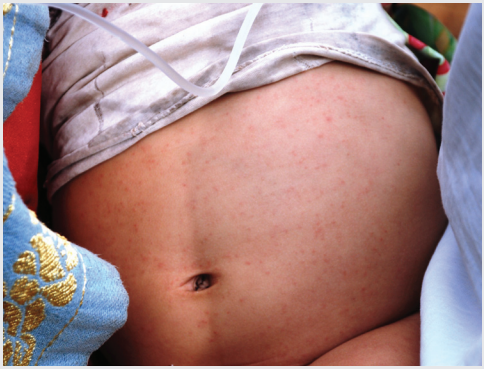


C

FIGURE WO-6-9 Dengue. (A) *Aedes aegypti* mosquito, seen feeding on a human host, is the primary peridomestic vector for dengue virus (IOM, 2010). (B) 3D electron microscopy reconstruction of a mature dengue virus. Part of the external glycoprotein shell (blue) and lipid membrane envelope (green) has been cut away to show the internal RNA nucleocapsid (red). (C) Infant with dengue rash—Cambodia.
SOURCES: USDA; Richard Kuhn and Michael Rossmann, Purdue University; USAMC-AFRIMS, Bangkok, Thailand.

Infectious agent: One of four viruses

Routes of transmission to humans: Mosquito bites

Health effects: Fever, pain; DHF frequently fatal

Incidence, prevalence, and mortality (estimated): 50 million cases and 22 million deaths per year; global incidence has risen in recent decades; 40 percent of global population at risk

Prevention: Vector control

Treatment: No specific treatment; skilled care for DHF saves lives

DRACUNCULIASIS (GUINEA WORM)

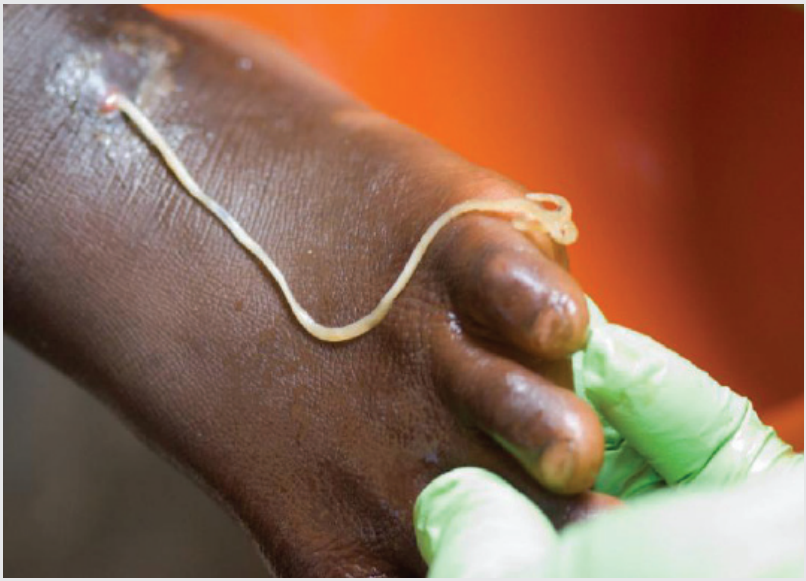


FIGURE WO-6-10 Guinea worm (*Dracunculus medinensis*).
SOURCE: Courtesy of The Carter Center/L. Gubb.

Infectious agent: *Dracunculus medinensis*, a parasitic worm

Routes of transmission to humans: Eggs live in standing water, such as ponds, and can be ingested by humans

Health effects: Pain and disability as worms exit body

Incidence, prevalence, and mortality (estimated): <5,000 people (reduced by nearly 99 percent since 1980)

Prevention: A candidate for eradication through provision of safe drinking water and case ascertainment

Treatment: None

continued

BOX WO-6 Continued

HOOKWORM

FIGURE WO-6-11 Hookworm (Nematode *Ancylostoma* caninum). The adult parasites are small cylindrical worms 0.5–1.5 mm long. The genus Ancylostoma have pairs of teeth on the ventral margin of the buccal capsule (SEM 8x magnification).
SOURCE: http://www.denniskunkel.com/product_info.php?products_id=1093 (accessed January 19, 2011). Copyright Dennis Kunkel Microscopy, Inc.

Infectious agent: *Necator americanus* (85 percent of the cases) and *Ancylstostoma duodenale*, parasitic nematodes (roundworms)

Routes of transmission to humans: Larvae in contaminated soil enter through skin

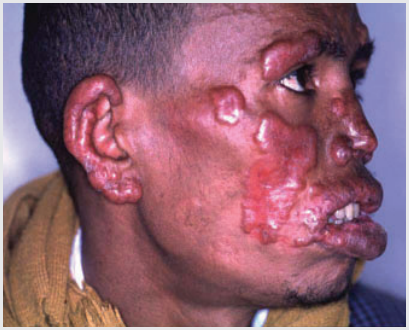
Health effects: Intestinal blood loss, anemia, protein malnutrition; cognitive impairment, delayed mental and physical development; maternal morbidity and mortality during pregnancy

Incidence, prevalence, and mortality (estimated): 576 million people infected, of which 60 million are "highly infected," with the largest number of cases in sub-Saharan Africa, South and East Asia, and in tropical regions of the Americas

Prevention: Improved hygiene and sanitation; periodic drug treatment of at-risk populations

Treatment: Antihelminthic therapy

LEISHMANIASIS AND VISCERAL LEISHMANIASIS (KALA-AZAR)



A

B

C

FIGURE WO-6-12 Leishmaniasis (*Leishmania*). (A) Patient with diffuse cutaneous leishmaniasis. (B) Patient awaiting treatment during a 2005 leishmaniasis outbreak in Libo Kemkem, Highlands, Ethiopia. (C) Parasitic promastigotes that cause leishmaniasis in humans (*Leishmania donovani*). SOURCES: WHO/TDR/Crump; WHO; http://www.denniskunkel.com/product_info.php?products_id=12507 (accessed January 19, 2011). Copyright Dennis Kunkel Microscopy, Inc.

Infectious agent: Protozoan parasites of the genus *Leishmania*

Routes of transmission to humans: Insect bites, especially those of sandflies

Health effects: Fever, weight loss, skin sores, disfigurement; visceral leishmaniasis can be fatal

Incidence, prevalence, and mortality (estimated): 12 million people infected; up to 50,000 deaths per year

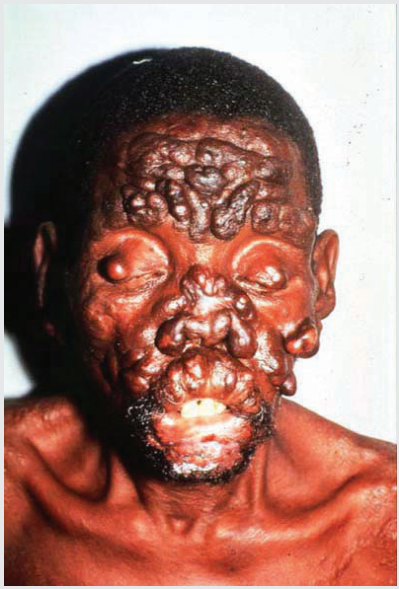
Prevention: Vector control

Treatment: Several effective drugs, all with serious drawbacks

continued

BOX WO-6 Continued

LEPROSY



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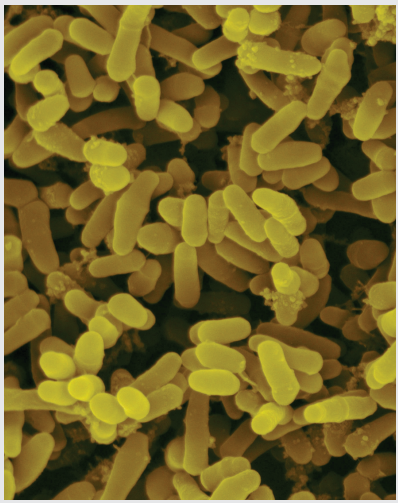


B

FIGURE WO-6-13 Leprosy (*Mycobacterium leprae*). (A) The face of a patient with active, neglected nodulous lepromatous leprosy. (B) *Mycobacterium leprae*—Gram-positive rod prokaryote, cause of leprosy.
SOURCE: WHO/TDR/McDougall; http://www.denniskunkel.com/product_info.php?products_id=8519 (accessed January 19, 2011). Copyright Dennis Kunkel Microscopy, Inc.

Infectious agent: *Mycobacterium leprae*, a bacterium

Routes of transmission to humans: Human-to-human contact via respiratory droplets; may be additional modes

Health effects: Loss of sensation leading to damage to extremities and disability; disfigurement

Incidence, prevalence, and mortality (estimated): 900,000 people infected

Prevention: None (not highly infectious)

Treatment: Antibiotic therapy (multi-drug)

LYMPHATIC FILARIASIS (ELEPHANTIASIS)

A

B

FIGURE WO-6-14 Lymphatic filariasis. (A) A patient with elephantiasis of the left leg. (B) Woman suffering from lymphatic filariasis presenting important bilateral lymphedema, Haiti.
SOURCES: WHO/TDR/Chandran; WHO.

Infectious agent: *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*, parasitic worms

Routes of transmission to humans: Mosquito bites

Health effects: Inflammation, vulnerability to bacterial infections, kidney damage, swelling of lymph tissues

Incidence, prevalence, and mortality (estimated): 120 million people infected

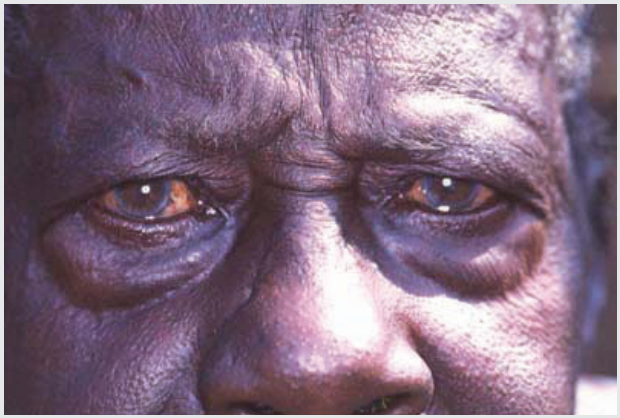
Prevention: Vector control; drug treatment for infected individuals in endemic areas

Treatment: Limiting damage from bacterial and fungal superinfection; measures to promote lymph flow; surgery

continued

BOX WO-6 Continued

ONCHOCERCIASIS (RIVER BLINDNESS)



A

B

FIGURE WO-6-15 Onchocerciasis. (A) The face of a 63-year-old male farmer, virtually blind, his eyes indicating the ocular damage that occurs as a result of long-term infection (Kanungu district). (B) Mature adult worms (*Onchocerca volvulus*).
SOURCES: WHO/APOC/TDR/Crump; WHO/TDR/OCP.

Infectious agent: *Onchocerca volvulus*, a parasitic worm

Routes of transmission to humans: Blackfly bites

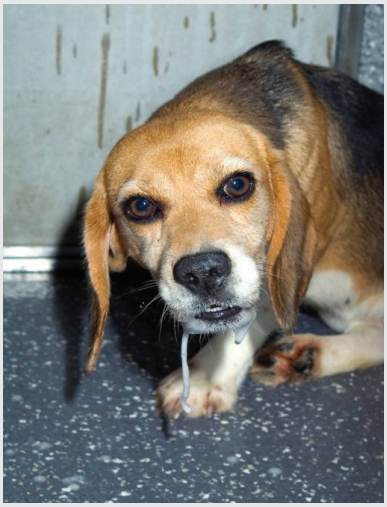
Health effects: Severe skin disease with itching; severe eye disease causing blindness

Incidence, prevalence, and mortality (estimated): 37 million people infected, mainly in Africa; includes 350,000 blind and 600,000 with impaired vision

Prevention: Vector control

Treatment: Anti-parasitic drug

RABIES



A

B

FIGURE WO-6-16 Rabies. (A) Beagle dog with clinical signs of rabies. (B) Rabies virus, purified from an infected cell culture. Negatively stained virions: note their characteristic "bullet shape." Magnification approximately 70,000x.
SOURCES: Photo courtesy of Dr. I Kuzmin, CDC; Micrograph courtesy of F. A. Murphy, University of Texas Medical Branch, Galveston, Texas.

Infectious agent: Virus

Routes of transmission to humans: Bite from infected animal, often a domestic dog

Health effects: Fatal if untreated

Incidence, prevalence, and mortality (estimated): 55,000 deaths per year

Prevention: Vaccines for animals (especially dogs) and humans

Treatment: Post-exposure vaccine immediately following contact

continued

BOX WO-6 Continued

SCHISTOSOMIASIS (BILHARZIA)

A B

FIGURE WO-6-17 Schistosomiasis. (A) Symptoms of advanced schistosomiasis (distended abdomen and muscle wasting). (B) A child suffering from *schistosoma haematobium* showing bloody urine—a symptom of chronic infection, Niger.
SOURCES: WHO/TDR/Eltoum; WHO.

Infectious agent: Parasitic worm, trematode (blood fluke of the genus Schistosoma)

Routes of transmission to humans: Waste from infected humans deposits eggs in water; eggs grow in water-dwelling snail

Health effects: Symptoms of acute schistosomiais appear two–four weeks after infection and include fever, nausea, and malaise. Chronic disease results from host-response to eggs retained in infected tissues and can result in bloody diarrhea, bloody urine (hematuria), liver and bladder disease, cancer, genital lesions, reduced growth, and anemia

Incidence, prevalence, and mortality (estimated): 207 million people infected (although the actual number may be substantially higher); mainly in sub-Saharan Africa

Prevention: Vector control, improved sanitation and health education; treatment of at-risk individuals

Treatment: Anti-parasitic drug (effective, safe, and low-cost)

TOXOCARIASIS

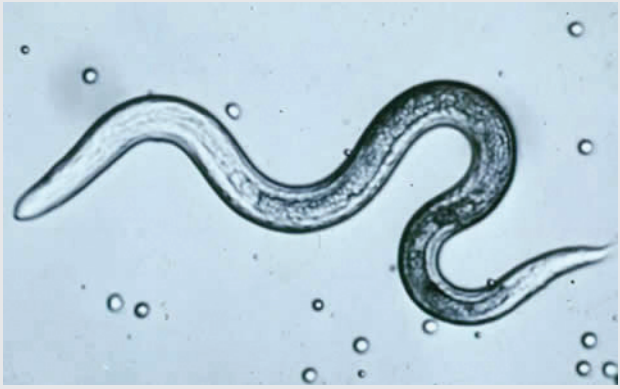


FIGURE WO-6-18 Parasitic roundworm associated with Toxocariasis (larvae). SOURCE: CDC parasite image library.

Infectious agent: Parasitic roundworm

Routes of transmission to humans: Ingestion of eggs from contaminated soil; worm embeds in wall of large intestine

Health effects: Some infections cause eye disease that results in blindness; heavy or repeated infections can result in swelling of internal organs or central nervous system

Incidence, prevalence, and mortality (estimated): No global estimates; most common human parasite in the United States; reported to infect 40 percent of the population of some middle-income countries

Prevention: Treatment (deworming) of domestic animals; personal hygiene

Treatment: Anti-parasitic and anti-inflammatory drug combination for eye infections; visceral cases treated to prevent progressive damage to eye

continued

BOX WO-6 Continued

TRACHOMA

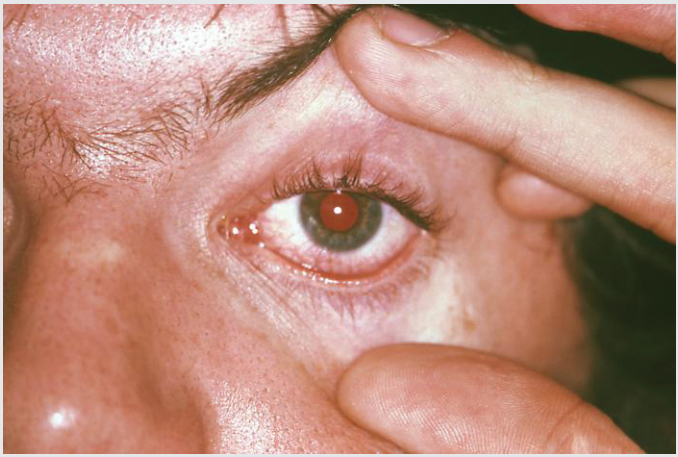


FIGURE WO-6-19 Trachoma. *Chlamydia trachomatis* infection can lead to conjunctivitis (as seen here) and to blindness.
SOURCE: CDC, Public Health Image Library (PHIL 4076).

Infectious agent: *Chlamydia trachomatis*, a bacterium

Routes of transmission to humans: Human-to-human contact; eye-seeking flies

Health effects: Scarring of cornea leads to blindness (leading infectious cause of blindness)

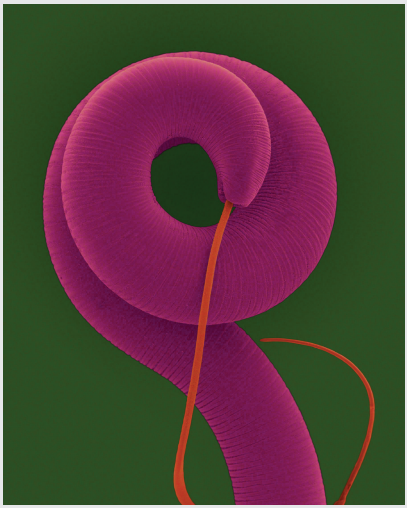
Incidence, prevalence, and mortality (estimated): 84 million people infected, of whom 2.9 million become blind and 3.5 million have impaired vision

Prevention: Access to clean water; improved sanitation and hygiene (face washing); reduction in fly breeding sites

Treatment: Surgery to correct scarring and reverse inturned eyelashes

TRICHURIASIS (WHIPWORM)

A



B

FIGURE WO-6-20 Trichuriasis (Whipworm). (A) Close-up of the prolapsed rectum of a child with numerous *Trichuris trichiura* clinging to the rectal mucosa. (B) Nematode (*Trichuris* spp.) helminth (whipworm), intestinal parasite.
SOURCES: Palmer and Reeder/USUHS, courtesy of Dr. Herman Zaiman; http://www.denniskunkel.com/product_info.php?products_id=668 (accessed January 19, 2011). Copyright Dennis Kunkel Microscopy, Inc.

Infectious agent: *Trichuris trichiura*, a parasitic roundworm

Routes of transmission to humans: Ingestion of eggs from contaminated soil; worm embeds in wall of large intestine

Health effects: Cognitive impairment, colitis and inflammatory bowel disease, delayed physical and mental development

Incidence, prevalence, and mortality (estimated): 604 million people infected of whom 27 million are "highly infected"

Prevention: Improved hygiene and sanitation; periodic drug treatment of at-risk populations

Treatment: Antihelminthic therapy

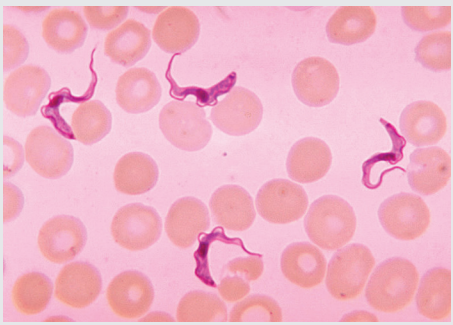
continued

BOX WO-6 Continued

HUMAN AFRICAN TRYPANOSOMIASIS (ZOONOTIC SLEEPING SICKNESS)

A

B



C

FIGURE WO-6-21 Human African Trypanosomiasis (*Trypanosoma brucei*). (A) A young woman watches over her husband who is comatose, suffering from sleeping sickness. (B) Child suffering from convulsion due to treatment toxicity, Democratic Republic of Congo. (C) Trypanosoma parasite in peripheral blood.
SOURCES: WHO/TDR/Wellcome; WHO; CDC Public Health Image Library (PHIL 613).

Infectious agent: Protozoan parasites *Trypanosoma brucei gambiense* (West and Central Africa), *T. brucei rhodesiense* (eastern and southern Africa)

Routes of transmission to humans: Insect bites, especially from tsetse flies

Health effects: Central nervous system damage; fatal if untreated

Incidence, prevalence, and mortality (estimated): Limited to Africa; 50,000–70,000 infections and up to 24,000 deaths per year

Prevention: Vector control

Treatment: First- and second-stage drug treatments; second-stage drugs, which cross the blood–brain barrier, are highly toxic and difficult to administer

YAWS

A B

FIGURE WO-6-22 Yaws infection (*Treponema pertenue*). (A) Tibial "saber" deformity as a result of yaws. (B) Child presenting lesions caused by yaws, Côte d'Ivoire, 2009.
SOURCES: Rinaldi (2008), previously published in PLoS Neglected Tropical Diseases; WHO.

Infectious agent: *Treponema pertenue*, a bacterium

Routes of transmission to humans: Person-to-person via skin contact (infects only humans)

Health effects: Chronic disfigurement due to skin and cartilage lesions; painful bone lesions; rarely fatal

Incidence, prevalence, and mortality (estimated): No recent estimates; in the 1990s, WHO determined that 2.5 million people were infected, of which 460,000 represented new cases

Prevention: A candidate for eradication via antibiotic treatment to interrupt transmission

Treatment: Antibiotic therapy

SOURCE: Adapted from *Health Affairs* (2009) with additional information from Ayele et al. (2004), CDC (2009, 2010a), Cosivi et al. (1998), Hotez (2010a), Hotez and Wilkins (2009), Pappas et al. (2006), and WHO (2008a–g, 2010c–g); The Merck Manual (http://www.merckmanuals.com/professional/sec14/ch183/ch183h.html (accessed on January 21, 2011).

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A

Contributed Manuscripts

A1

REGIONAL APPROACHES TO NEGLECTED TROPICAL DISEASES CONTROL IN LATIN AMERICA AND THE CARIBBEAN

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Neglected [tropical] diseases impose a huge burden on developing countries, constituting a serious obstacle for socioeconomic development and quality of life . . . Thus, taking decisive action to eliminate them as a public health problem in the Region, which is an achievable dream—provided the necessary political commitment and resources are in place—for which we are working in PAHO, would also be a clear reassertion of our countries' deep commitment with human rights as enshrined in international treaties and standards.

—Mirta Roses Periago, Director, Pan American Health Organization (Director's Blog, April 8, 2008, http://66.101.212.220/mirtaroses/index.php?id=69)

Background

In the Latin America and Caribbean region (LAC) at least 180 million people live below the poverty line. These impoverished and marginalized populations are often heavily burdened with neglected tropical diseases (NTDs) and other infectious diseases of poverty. This group of diseases continues to take a measur-

able toll, not only on families and communities but also on the socioeconomic development of nations.

NTDs and Their Impact

The NTDs largely comprise infectious and parasitic tropical diseases. Today, NTDs can be usefully considered as a group because they are concentrated almost exclusively among impoverished populations living in marginalized areas whether rural or peri-urban. These incapacitating diseases, such as lymphatic filariasis, onchocerciasis or river blindness, schistosomiasis (including bilharzia), soil-transmitted helminthiasis (ascariasis, trichuriasis, and hookworm infection), Chagas disease, leishmaniasis, leprosy or Hansen's disease, and trachoma continue to perpetuate poverty, generate prejudice, or inflict severe incapacity (lymphatic filariasis), disability (e.g., leprosy/Hansen's, onchocerciasis), and sometimes premature death (e.g., Chagas disease and schistosomiasis) in LAC and other regions of the world. Children with heavy intestinal worm burdens may become stunted or anemic, or they may suffer from maldigestion, malabsorption, and poor physical and cognitive development. These worms can reduce school attendance, attention span in class, and test scores. Infection with NTDs reduces income-earning capacity, and this in turn often creates a loss of the ability to care for a family.

Social Determinants

Although biologically and medically diverse, NTDs share features that allow them to persist in conditions of poverty where they frequently overlap (Brooker et al., 2006). These conditions of poverty include unsafe water, poor sanitation, and refuse disposal, which sustain transmission cycles and favor the proliferation of vectors that transmit disease. Other conditions, such as a lack of access to health services, low levels of literacy, inadequate nutrition and poor personal hygiene all help to increase vulnerability to infection and work against prevention efforts. Addressing these social determinants of poverty complements the use of existing tools to combat and eliminate NTDs. Specific technical opportunities to control and eliminate NTDs in LAC through intersectoral and multidisease approaches while addressing social determinants were recently reviewed (Ault, 2008; Ehrenberg and Ault, 2005; Holveck et al., 2007; Hotez et al., 2008), and provide background for this paper.

Legacy of Slavery

Interestingly, some of the NTDs—for example lymphatic filariasis (LF), onchocerciasis, and schistosomiasis—are parasitic diseases that were imported to the Western Hemisphere through the European slave trade, which targeted

Africa. Today, a little more than 200 years after the end of that colonial slave trade, they still cause substantial morbidity and are particularly attractive targets of elimination. As noted by Lammie et al. (2007), "the elimination of diseases that are a consequence of this trade will represent a tangible contribution to the health and well being of people and communities who, arguably, still suffer from the residual affects of slavery."

Tools and Mandate to Combat

Tools exist today to effectively combat the NTDs, including safe and inexpensive antihelminthics, dose poles, quantitative and rapid mapping methods, and rapid test kits for several parasites, and having these tools in hand makes it an ethical imperative to work toward the control and elimination of NTDs. Since 2007, the Pan-American Health Organization (PAHO) also made headway in the scientific and political debate that guided the development of an elimination agenda and made it possible to subsequently mobilize the necessary will and resources. In 2009, PAHO received a mandate in the form of a resolution (CD49-R19) from its Directing Council (composed of the Ministers of Health of the region) to support the countries in the region in eliminating or significantly reducing the burden of a group of 12 neglected diseases and other poverty-related infections. This chapter discusses this mandate and the region's plans to tackle and eliminate several NTDs over the next five years.

Elimination Agenda

Working together, the LAC countries and PAHO have had significant success in eliminating several infectious diseases in the region in the recent decades: smallpox (1977), poliomyelitis (1994, wild poliovirus), and measles (2002). As well, at the end of 2010, onchocerciasis transmission has been apparently eliminated in 8 of 13 foci among six endemic countries in the region. The number of human cases of rabies transmitted by dogs in Latin America dropped significantly, by nearly 90 percent, between 1990 and 2007 (PAHO, 2009).

A significant reduction in the transmission of Chagas disease by two important domestic vectors (*Rhodnius prolixus* and *Triatoma infestans*) in the 21 endemic countries has been achieved since 1990 principally as a result of systematic indoor spraying with residual pyrethroid insecticides of houses in rural endemic areas, infection and mortality have declined as has the population at risk (Table A1-1). As of 2010, 10 countries have eliminated these vectors and 3 others have eliminated them in parts of their national territories. A reduction in blood transfusion–origin Chagas disease has also been achieved in the region, as endemic countries began universal screening of blood donors at blood banks using a rapid Enzyme-linked immunosorbent assay (ELISA) test.

TABLE A1-1 Evolution of Change in Epidemiological Parameters of Chagas Disease in LAC

Changas Disease Epidemiological Parameters	1990	2006
Annual deaths	>45,000	12,500
Human cases of infection	30 million	15 million
New cases per year	700,000	41,200
At-risk population	100 million	28 million

SOURCE: PAHO (2009).

What Is Feasible?

There is broad technical consensus that there are available tools and strategies to combat several neglected tropical diseases that have been included in the World Health Organization's (WHO's) 2008–2015 Global Plan to Combat Neglected Tropical Diseases (WHO, 2007). Beginning in 2007, PAHO began to review the data to determine which of these NTDs and other infectious diseases of poverty we can eliminate or significantly reduce transmission of in the entire region by 2015, such as onchocerciasis, LF, and trachoma. PAHO reviewed others that can be eliminated in certain subregions or in a particular country, as in the cases of plague in Peru and Ecuador, schistosomiasis in St. Lucia and Suriname, and malaria in the Caribbean and Central America. The agency focused on identifying successful strategies for control and elimination, collecting epidemiological data on the presence and prevalence of these diseases in the region, and preparing maps down to the first administrative level of where the diseases overlapped geographically. With these data and information in hand, PAHO published its epidemiological profiles of 10 neglected diseases in 14 countries in early 2009 (PAHO, 2009).

Next, a regional elimination strategy was developed during 2009 by the agency's communicable diseases project for 10 neglected diseases of poverty with input from PAHO technical staff, managers and external experts, and the draft strategy was vetted with the Ministers of Health and approved by the Directing Council in October 2009 as Resolution CD49-R19. In approving the resolution, the Member States of the region have committed to an objective by 2015 to eliminate or reduce neglected diseases and other infections related to poverty for which tools exist, to levels such that these diseases are no longer considered public health problems. This effort requires long-term political and financial commitment and the preparation and implementation of integrated national plans of action (POAs). In 2010, several countries in the region have now established national committees with the objective to develop their POAs for the integrated control and elimination of NTDs.

The PAHO strategy uses two definitions for elimination, depending on the

disease. The elimination of a disease is a reduction to zero of the incidence of a given disease in a defined geographic area as a result of deliberate efforts, with continued intervention measures being required (WHO, 1998). Elimination of a disease as a public health problem occurs by drastically reducing the disease's burden to a level that is acceptable given the current tools available and the region's health situation. At this level, the prevalence of the disease does not constrain social productivity and community development. Achievable goals have been established for each disease. In this chapter, both definitions are used to select the diseases targeted for elimination, according to previous global and regional mandates for elimination.

PAHO considered the following criteria in selecting the diseases that could feasibly be eliminated or drastically reduced in the region: (a) the "unfinished agenda"—diseases that already had been priority targets for elimination by PAHO or WHO and for which, despite progress made, some areas lagged behind; (b) technical feasibility—including the availability of knowledge and tools for structuring interventions to interrupt or reduce transmission; (c) regional evidence of achievable elimination—existence of successful regional experiences in accomplishing elimination at country or subnational levels; (d) economic criteria—including relatively low unit cost of interventions and demonstrated cost-effectiveness; (e) unequal burden of disease—wherein the more vulnerable populations (such as indigenous and Afro-descendant populations, women, and children who have been historically excluded) suffer from a higher prevalence and social consequences of these diseases, thus perpetuating the cycle of poverty; (f) political relevance—the diseases must be recognized as being of public health importance with a broad international appeal, which could be expressed through existing resolutions approved by the World Health Assembly or PAHO's Directing Council; and (g) best practices, including those utilized in primary health care, well-accepted interventions such as mass preventive chemotherapy and high-coverage vaccination campaigns, integrated approaches for vector-borne diseases, and local projects with community participation to improve health through intersectoral action. These examples of best practices have already been developed in the region and will provide the basis for the scale-up of local and national proposals for disease elimination.

The selected diseases were classified into two groups, those with greater potential for being eliminated, and those that can be drastically reduced with available tools. *Group 1* diseases are those that have a greater potential for being eliminated: Chagas disease (vector-borne and transfusional transmission, both as a public health problem); congenital syphilis (as a public health problem); LF (as a public health problem); onchocerciasis; rabies transmitted by dogs; neonatal tetanus (as a public health problem); trachoma (as a public health problem); leprosy (as a public health problem at the national and first subnational level); malaria (elimination in Haiti and the Dominican Republic and in México and Central America); and plague (as a public health problem). Cost-effective strate-

gies and tools exist for elimination, there is evidence of feasibility of elimination in other countries or areas in LAC, or there are global or regional mandates to reach elimination. Next, we highlight two of the Group 1 diseases, onchocerciasis and lymphatic filariasis.

Onchocerciasis is endemic in parts of Africa and in 13 foci in six countries of the Americas where it was introduced through the slave trade. It is estimated that more than half a million people live in areas of México, Guatemala, Colombia, Ecuador, Venezuela, and Brazil where documented transmission of onchocerciasis occurs or has been documented in the recent past. The basic strategy for achieving elimination in this Region is mass drug administration (MDA) using a form of ivermectin (Mectizan®, a donated medicine) given twice a year to at least 85 percent of all eligible population, accompanied by health education and promotion of community participation for at least 10 consecutive years. The minimum required coverage in all the 13 foci in the Region was achieved in 2002 and has been maintained since. New cases of onchocercal blindness were eliminated since 2007. However, some cases of ocular morbidity still occur in a few foci, mainly in the Amazon region of Southern Venezuela and Northern Brazil inhabited by the Yanomami Amerindians. As of January 2011 onchocerciasis transmission has been interrupted in 8 of the 13 foci, with those currently being in the post-treatment surveillance phase. Transmission is suspected to be suppressed in two other foci: South Chiapas in México and the Central focus in Guatemala. Onchocerciasis transmission persists in the three foci (Northeastern focus of Venezuela, and the southern focus of Venezuela and northern focus of Brazil, which share the Yanomami area (epidemiologically, it constitutes one shared focus). The Yanomami area represents the greatest challenge to the regional elimination efforts.

Lymphatic filariasis, another NTD imported to LAC by the trans-Atlantic slave trade, was common in port cities, some Caribbean islands, and coastal areas in the Region until the last century when advances in sanitation began to reduce and then interrupt transmission by its *Culex* mosquito vector. In the past few decades three countries (Costa Rica, Suriname, and Trinidad and Tobago) have presented evidence of interruption of transmission, together with two cities in Brazil (Belém, Pará state and Maceió, Alagoas state). Today more than 9 million people are considered at risk for lymphatic filariasis in four endemic countries in the Region (one focus in metro Recife, Brazil, and Guyana, Dominican Republic and Haiti), with the highest proportion living in Haiti. People at risk benefit from more than 10 years of effort to eliminate transmission by MDA with the drugs diethlycarbamazine and albendazole. In 2009 about 3.4 million were treated via MDA. The January 2010 earthquake in Haiti and the Dominican Republic complicated the timely delivery of medicines. A meeting convened by PAHO in February 2010 with international partners created solidarity in support of Haiti to continue the work and reach the elimination goal, which helped enable the Haitian Ministry of Health and Population's MDA program to pick up and con-

tinue in 2010. Ministries of Health are intensifying their efforts to eliminate the remaining foci in Brazil, Dominican Republic, and Guyana.

Group 2 diseases are those whose burden can be drastically reduced with available tools: schistosomiasis and soil-transmitted helminthiasis (STH), for which there exist safe and very effective drugs and a record of success in greatly reducing intensity of infection though MDA in a strategy of preventive chemotherapy. In LAC, the parasites targeted are *Schistosoma mansoni* (the only human schistosome in the region) and the three common types of STHs (*Ascaris lumbricoides*, *Trichuris trichura*, and the human hookworms *Ancylostoma duodenale* and *Necator americanus*). They persist in some areas (poor rural communities or peri-urban shantytowns), sometimes with a very high prevalence (more than 50 percent) in vulnerable populations like children; however in many countries there is very limited or no recent epidemiological data about their distribution, prevalence, and burden, hampering awareness and adequate interventions.

Soil-transmitted helminthiasis is considered to be present in all the LAC Region's countries, with prevalence varying. PAHO estimates conservatively that 13 million preschool-age children and 33 million school-age children are at risk of STH infections in the Region, where transmission is closely associated with a lack of access to basic sanitation and safe water. A handful of countries have established national deworming programs, principally for school-age children, while in other countries various international nongovernmental organizations (NGOs) contribute to deworming efforts through their community-targeted interventions. Epidemiological information on STH is sparse, as these infections are not reportable; however, in PAHO's review of published prevalence rates some surveys have indicted prevalence higher than 50 percent in some groups of school-age children and indigenous populations, and intensity of infection varies but has been seen high enough to be associated with adverse health effects like anemia. The Region's high-risk countries are being encouraged and supported to scale-up deworming efforts to reach all vulnerable populations.

In LAC, PAHO estimates that approximately 1.8 million persons are infected, and up to 25 million are at risk of schistosomiasis. Schistosomiasis infection occurs in humans in contact with infested freshwater reservoirs when the cercarial stage of the parasitic fluke leaves the intermediate host snail and penetrates the person's skin and enters the bloodstream. The drug praziquantel is the recommended treatment, which can be provided by MDA or individual treatment. MDA with praziquantel can interrupt transmission. Today the disease is limited to four countries in LAC: parts of Brazil (principally the northeast of the country), St. Lucia, and parts of Suriname and Venezuela. Morbidity appears low, and reported deaths (from Brazil) are few. Brazil's national schistosomiasis control program has, over the decades, significantly reduced morbidity and mortality, while the other countries treat cases as encountered; Suriname and St. Lucia are taking steps to eliminate the disease while Venezuela is evaluating its epidemiological situation.

For other infectious diseases, such as leishmaniasis and leptospirosis, the burden of the disease needs to be further assessed, better tools need to be developed for diagnosis (e.g., leishmaniasis), and methods and strategies for achieving cost-effective and sustainable prevention and control need to be established (e.g., leptospirosis, cysticercosis/taeniasis). For these diseases and for others that have epidemiological relevance to some of the region's countries, more operational research needs to be conducted, new tools need to be assessed, and surveillance systems need to be improved.

Framework for Elimination

The public health strategies and interventions that are used to eliminate or reduce infectious diseases to acceptable levels go beyond routine control measures. In order to strengthen the efforts against diseases related to poverty as a group, endemic countries can develop integrated POAs under the same framework, while considering the following:

- Available plans at the global, regional, or country level to eliminate or control these diseases.
- Available guidelines for the selected diseases to support the countries in achieving the goals of elimination or control.
- Available tools such as drugs and diagnostic techniques to support surveillance systems.
- Evidence-based decisions for strengthening health surveillance systems, mapping the diseases to identify remaining foci, and identifying overlapping of diseases in geopolitical areas ("hot spots" or areas of co-endemicity) for integrated action.
- Reducing gaps in tool-ready neglected diseases in deficit areas in the region.
- Ensuring that the necessary resources are available for the primary care system to integrate NTD control and help reduce inequalities in health.
- Pursuing inter-programmatic interventions that integrate the various existing plans into a comprehensive vision based on the epidemiology and social determinants of each area identified for intervention (hot spots); interventions should tackle the factors and mechanisms through which social conditions affect the community's health and, where possible, address them through social and health policies.
- Pursuing community participation and intersectoral partnerships: the community, stakeholders and all actors and potential partners within and outside the health sector should be enlisted to make actions sustainable.
- Pursuing horizontal cooperation: identify which countries share problems or borders where the selected diseases occur, to promote joint actions and intercountry plans.

- The increase in donor support from global partners in the fight against neglected tropical diseases and other infections related to poverty.

Progress, Priorities, and Lines of Action for Elimination

PAHO partnered with the Inter American Development Bank (IDB) and the Global Network for Neglected Tropical Diseases (GNNTD, or Global Network [GN]) based in the Sabin Vaccine Institute beginning in 2008. With the IDB and the GN the partners have established a Trust Fund for Neglected Infectious Diseases in the IDB and are working to capitalize the fund in 2011. Additionally the partners have worked together and with Ministries of Health to develop a POA and demonstration project in the State of Chiapas México projects, and another demonstration project in the metropolitan area of Recife, northeast Brazil, which are meant to demonstrate or show proof of principle of integrated approaches to NTD control and elimination in the LAC Region. The Chiapas demonstration project covers trachoma, Chagas disease, leishmaniasis, rabies transmitted by dogs, onchocerciasis, and STHs. The project in metropolitan Recife tackles schistosomiasis, STHs, LF, and leprosy/Hansen's disease. Each project will become operational in 2011. Meanwhile, several countries, including Guyana, Suriname, Dominican Republic, and Haiti, are developing integrated POAs to combat multiple NTDs, and more countries will begin the process in 2011.

In collaboration with the GNNTD, in 2010 PAHO began a process to map NTDs down to lower administrative levels (municipal levels) in several countries. With the Swiss Tropical Institute and Louisiana State University, PAHO is using environmental and social parameters and Bayesian modeling to map the expected distribution and prevalence of Chagas disease, schistosomiasis and STH in Brazil, Bolivia, and Colombia. This modeling approach is expected to be extended to additional countries in 2011. Additionally, PAHO has worked with the Autonomous University of Yucatán, México, to study the social determinants of STHs, Chagas disease, and dengue in peri-urban and rural communities near the city of Mérida.

To operationalize the strategies and interventions needed to eliminate NTDs in the region, PAHO also prepared a report in 2010 analyzing progress in control and elimination of five NTDs amenable to preventive chemotherapy, prioritizing the associated endemic countries with respect to these five diseases and identifying lines of action to take to achieve elimination by 2015 (PAHO, 2010).

This report, referred to as the Prioritization Report, is a qualitative analysis of gaps and needs in technical cooperation and is presented in order to make progress toward the elimination goals for these five diseases in 33 countries in LAC: onchocerciasis, schistosomiasis, trachoma, LF, and soil-transmitted helminthiasis.

As a result of the analysis, countries were classified and prioritized into four groups.

Group 1 This group concentrates the majority of population at risk for the main NTDs. These countries have 66.8 and 67.4 percent of preschool-age children (Pre-SAC) and school-age children (SAC) populations, respectively, at risk in LAC for STHs. Four countries have foci of onchocerciasis with 421,000 people at risk. Three countries have foci of schistosomiasis with up to 25 million people at risk. Three countries have foci of trachoma with up to 50 million people living in risk areas, and four countries have foci of LF with more than 9 million people at risk. This group includes countries working to eliminate onchocerciasis, LF, and trachoma, and one country with the possibility to eliminate schistosomiasis; Suriname is expecting external verification of LF elimination. This group needs technical cooperation to develop and implement integrated, interprogrammatic, and intersectoral plans to combat neglected infectious diseases (NIDs) including STHs (Table A1-2).

TABLE A1-2 Diseases, Foci, Population at Risk, and Treatment Coverage in Group 1 Countries

Diseases in Countries of Group 1	Foci	Population at Risk	Treatment Coverage
Onchocerciasis	This group has 9 of 13 onchocerciasis foci in LAC: Brazil (1), Ecuador (1), Guatemala (4), and México (3)	421,000 people	Second Round 2009: Brazil 89%; Guatemala 93%; México 93%; Ecuador 96%
	Transmission interrupted in 6 foci: México (2), Guatemala (3), Ecuador (1)		
Lymphatic filariasis	This group has all of the lymphatic filariasis foci: Brazil, Dominican Republic, Haiti, and Guyana. Suriname is expecting validation of elimination.	More than 9 million people	MDA in 2009: Haiti 3 million people treated; Brazil 177,000; Guyana: 129,189; Dominican Republic has not carried out MDA for LF since 2007, transmission interruption is being evaluated
Schistosomiasis	Foci in 3 countries: Brazil, Suriname, and Saint Lucia. Transmission to be evaluated in Dominican Republic	Nearly 25 million people at risk	Treatment coverage: Brazil 83% cases treated of cases detected; 21 cases were treated in 2009 in Suriname
Trachoma	Foci in Brazil, Guatemala, and México	50 million people live in risk areas	No data available at national level

SOURCE: Modified from PAHO (2010).

Group 2 This group has 26.8 and 26.1 percent of Pre-SAC and SAC populations, respectively, at risk for STHs in LAC. Two countries have foci of onchocerciasis with 115,070 people at risk. One country has foci of schistosomiasis. There is no evidence of LF transmission in this group of countries. However, recently Miller et al. (2010) provided clinical evidence of trachoma in an Amerindian indigenous community in the Department of Vaupés, Colombia documenting the presence of trachoma for the first time in Colombia.

This group includes countries also eliminating onchocerciasis and targeting schistosomiasis. These countries need technical cooperation to improve current interprogrammatic and intersectoral coordination and to include STHs into NID-integrated actions (Table A1-3).

As mentioned above, most of the LAC countries have no updated results of nationwide surveys of prevalence and intensity of infection of STH and schistosomiasis and trachoma. Groups 1 and 2 have the greatest gaps in sanitation coverage and a clear opportunity to integrate intersectoral and interprogrammatic actions for integrated NTD control, in the framework of primary health care systems and addressing the social determinants of health.

Group 3 This group has 5.4 percent of Pre-SAC and SAC population at risk for STHs in LAC. There is no evidence of the presence of onchocerciasis, schistosomiasis, trachoma, or LF. These countries need technical cooperation to focus activities for NIDs at local level and rural areas, with emphasis on STHs.

Group 4 This group has 1.03 and 1.1 percent of Pre-SAC and SAC populations, respectively, at risk for STHs in LAC. There is no evidence of the presence of onchocerciasis, schistosomiasis, trachoma, or LF. Costa Rica and Trinidad and Tobago are expecting external verification of LF elimination.

TABLE A1-3 Diseases, Foci, Population at Risk, and Treatment Coverage in Group 2 Countries

Diseases in Group 2	Foci	Population at Risk	Treatment Coverage
Onchocerciasis	This group has the remaining 4 of the 13 foci of onchocerciasis in LAC: Colombia (1) and Venezuela (3) Transmission interrupted in Colombia focus	115,070 people at risk	Second Round 2009: Venezuela South focus 85%, Northeast focus 95%, North–central focus 99%. The Colombian focus is in post-treatment surveillance
Schistosomiasis	Foci in Venezuela	No data available	No data available

SOURCE: PAHO (2010).

The classification is used to define the nature of external technical cooperation that each group may require to mobilize resources needed for elimination. It is important to note that if actions were focused on all populations of Groups 1 and 2, the following groups could be reached (see Table A1-4 for details):

- 84.5 million of people at risk for four diseases (i.e., onchocerciasis, schistosomiasis, LF, and trachoma); and
- 94 percent (12,088,816) of Pre-SAC and 93.5 percent (29,927,933) of SAC populations at risk for STHs in LAC, who could be reached with deworming activities.

Opportunities for Integration

In the PAHO map below (Figure A1-1), six NTDs are shown in 14 countries for 2008: schistosomiasis, STHs, onchocerciasis, LF, trachoma, and human rabies transmitted by dogs. The diseases are mapped at the first "administrative" level of the country. Among these countries, 275 administrative units (e.g., states, provinces, departments etc.) reflect the co-endemicity of diseases. Three of the units (the states of Maranhão, Pernambuco, and Sergipe in Brazil) have the presence of four of the six NTDs selected for the PAHO study. Twelve other units present with the presence of three of the six diseases, while 41 units had two NTDs present. This 2008 analysis by PAHO revealed that, of the 580 million inhabitants of LAC, some 241 million live in units with the presence of at least one of these diseases.

The mapping efforts of PAHO have shown the potential for integrated control and elimination where two or more NTDs overlap in space and time. Efficiencies and economies of scale can be achieved, and local health workers can be trained to manage multiple diseases in the areas of endemicity.

TABLE A1-4 Pre-SAC and SAC Population at Risk for Soil-Transmitted Helminths (STHs) in LAC, 2009

Group of Countries	Pre-SAC at Risk of STH		SAC at Risk of STH	
	Number	Percentage	Number	Percentage
1	8,630,605	66.8	21,569,079	67.4
2	3,458,211	26.8	8,358,854	26.1
3	697,895	5.4	1,727,941	5.4
4	130,844	1.01	349,341	1.09
Total	12,917,455	100	32,005,215	100

SOURCE: PAHO (2010).

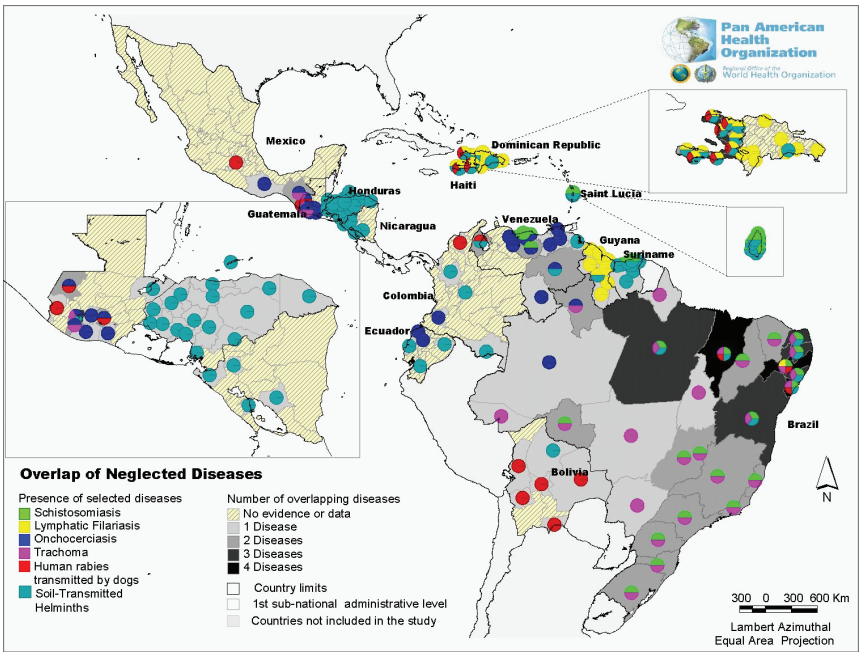

FIGURE A1-1 Overlapping of six neglected infectious diseases.
SOURCE: PAHO (2009).

PAHO has identified several principles for integrating actions for NTD control and elimination. They include the following:

- Available plans, guidelines, and tools to develop integrated POAs (instead of reinventing the wheels of successful stand-alone programs);
- Evidence-based decisions (using the data about disease overlap and burden);
- Reduction of inequalities in health (to justify resources for integrated control);
- Primary health care systems (as a principal service delivery platform for NTD control);
- Community participation (in surveillance, control, education, monitoring and evaluation);
- Gender and ethnicity (as a way to target those most likely deprived);
- Interprogrammatic and intersectoral interventions to address the social determinants of health (water and sanitation, drainage, housing, and nutrition);

- Cooperation between countries (where one endemic country is well positioned to help another endemic country); and
- Global partnerships in the fight against NIDs (allowing significant drug donations and provision of training and other resources).

The agency sees multiple approaches to integrate actions for NTD control and elimination, through inter-programmatic actions within a Ministry of Health. Common interventions may include the following:

- Screening, drug treatment/MDA
- Morbidity (case) management (LF, leprosy/Hansen's disease)
- Integrated vector management
- Water Supply, Sanitation, Hygiene, Health Education and Deworming (WASHED) strategy
- Education and school health for deworming
- Vitamin A + deworming medicine distribution
- Other micronutrients (Fe, I, Zn, multi-vitamin) distribution + deworming
- Food vouchers and complementary nutrition to combat undernutrition, combined with deworming
- Food security programs to reduce undernutrition and anemia
- Conditional cash transfers to encourage mothers to bring children to regular medical visits and receive NTD screening and deworming
- Integrated population, health, and environment programs
  - Agroforesty, home gardens, aquaculture, and beekeeping to reduce undernutrition and anemia
  - Primary environmental care to create protective environments against NTDs

To deliver such interventions, Ministries of health may use other ministry health programs as common delivery platforms for NTD services, for example, for the distribution and delivery of antihelminthics or rapid screening tests, or patient care (case management for leprosy/Hansen's and LF cases) can be delivered. Some of these platforms include

- Primary health care
- Vector control
- Nutrition/micronutrients
- Immunizations (children, adolescents, pregnant women)
- Maternal-child health, family health and wellness
- Skin disease clinics, diabetes/chronic diseases clinics
- Food security, food safety
- Healthy schools, healthy cities
- Malaria and TB programs

Piecing the Puzzle Together

The elimination and control of NTDs can be considered to consist of three categories: information and planning, delivery of services, and the development of integrated POAs. These are depicted in Figure A1-2. The information and mapping category includes an important aspect—stakeholder identification and mapping—allowing ministries to see what NGOs, faith-based groups, academia, and the private sector can bring to the table to support elimination. Additionally, the mapping of disease presence, prevalence, and burden, especially areas of overlap or co-endemicity, allows the visualization of the patches or hot spots where control efforts must be focused. Finally, the mapping of the social determinants of health (water supply and sanitation coverage, housing, agriculture and industry, and zones of malnutrition or unemployment) allows one to find and target populations most likely to be at risk of NTD infection. Delivery of health services for NTD control and elimination in poor communities is often best done through the primary care system, supplemented by other interventions as needed. Sets of minimum packages of treatment or care can be established for each group of co-endemic diseases, and these can be complemented by the necessary (and

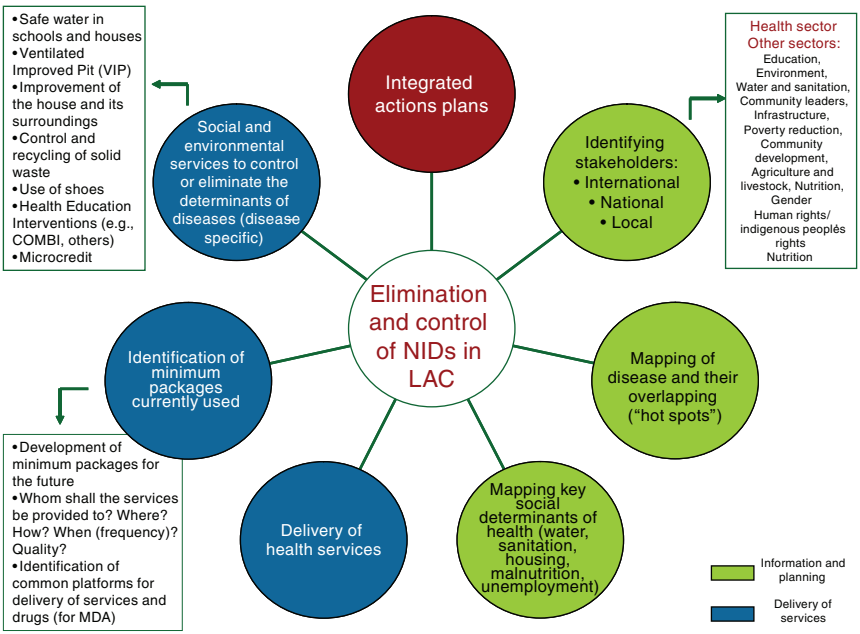

FIGURE A1-2 Elimination and control of NIDs in LAC: Putting the pieces together. SOURCE: PAHO (2010).

disease-specific) social and environmental services needed to educate and prevent or mitigate disease transmission and morbidity.

Conclusions

Through the use of existing tools, stepped-up advocacy, political commitment, development of partnerships, resource mobilization, and careful allocation of resources, and reflected in integrated plans of action, a number of NTDs can be eliminated in the LAC region, These include onchocerciasis and LF (and LF and malaria in Hispaniola) in children and adults, trachoma in school-age children, schistosomiasis in the populations of St. Lucia and Suriname, as well as domestic vectoral transmission and transfusional Chagas disease, among other NTDs. This is the most opportune moment in history to eliminate these diseases, and it is an ethical and moral imperative for the region's citizens and governments.

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A2

NEGLECTED TROPICAL DISEASES, CONFLICT, AND THE RIGHT TO HEALTH

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Introduction

The neglected tropical diseases (NTDs) are characterized by their prevalence among the poor of the most impoverished areas of the planet. These are neglected diseases of neglected populations, flourishing in the developing world but long since controlled or eradicated in the developed. NTDs generally affect the poorest people in poor societies—populations with little voice and representation. As a consequence, NTDs have until very recently received little funding and international attention. These diseases typically cause more disability than death. Their clinical features often lead to stigmatization and social isolation, which can further increase their neglect. Combined, as many as 1 billion people worldwide are at risk for NTDs or already suffer from them, and they account for 57 million disability-adjusted life-years lost (Hotez et al., 2007). However, these figures are thought to be an underestimate of the true burden (Hotez et al., 2008), because of a lack of reliable surveillance and of the research necessary to quantify their impacts (J. Jacobson, 2010).

As yet there is no internationally agreed consensus for which diseases come under this classification. In the first launch of a global report on NTDs, the World Health Organization (WHO) has defined 17 key diseases (WHO, 2010c), but several others exist. For the purposes of this review, we have opted to use the most inclusive definition possible, encompassing all NTDs that predominately affect the poor of the global south. In particular, we posit that malaria and poliomyelitis fit these criteria and may also be considered with the NTDs. Though both are less neglected than many other conditions, they affect many of the same populations as the classic NTDs, and they share many social and structural features with them.

Although evidence for the association between poverty and NTDs has been well documented, the impact of conflict on these diseases has been less well studied. With increasing prioritization of NTDs on the international agenda, these links are becoming more apparent. In the past few months, WHO has warned of several impending epidemics of NTDs in conflict settings. Of the four endemic countries for guinea worm, more than 90 percent of cases are currently in

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conflict-torn Sudan (CDC, 2010a). There has been a recent outbreak of visceral leishmainiasis in Southern Sudan (WHO, 2010b), a disease with high mortality among children. In a similar fashion, the number of cases of the cutaneous form of this disease has been soaring in Afghanistan as a result of the long-standing conflict there (WHO, 2010a).

Understanding the true burden of these diseases in conflict zones is difficult, as there are many political, logistical, and ethical barriers to conducting programs, surveillance, and research. Nonetheless, systematic evaluation of disease burden as well as effectiveness of interventions in the field is crucial to assist decisions with policy, advocacy, and providing care to these communities.

The human rights lens provides a useful ethical and legal framework to examine and address NTDs in conflict settings. Formal human rights conventions are a series of treaties, placing legal obligations on member states to ensure that they are accountable for their conduct. They define the humanitarian imperative for signatory states to respect, protect, and fulfill the basic human rights of their people. Most relevant among these instruments is the right to health, as defined by Article 12 of the 1976 International Covenant on Economic, Social and Cultural Rights. Specifically, Part c is applicable to NTDs, as it is defined by "[t]he prevention, treatment and control of epidemic, endemic, occupational and other diseases." As of December 2010, 160 of the 192 United Nations member states were party to the Covenant. Like many processes mediated by the United Nations, enforcing these rights has proven to be difficult. Many countries worldwide are arguably in violation of the right to health. Nevertheless, the rights conventions do provide policy frameworks from which to advocate for more research into this area, legal tools for signatory state accountability, and platforms for action on global initiatives, such as the Millenium Development Goals.

We first explored this subject in 2007 (Beyrer et al., 2007). In this review we reassess the current literature and describe ways forward for responding to NTDs in conflict settings. In the first part, we analyze the literature in this field since 2007. In the second part we describe, through four case studies, potential mechanisms through which conflict can affect NTDs, and we review progress in the field.

Literature Review

Methods

We searched PubMed, without restriction on language for studies published between January 1, 2007, and October 15, 2010. Our search had two main components. To assess both the direct and indirect impacts of conflict, we used the following keywords: "conflict," "war," "civil unrest," "political unrest," "political instability," "displacement camps," "refugees," "refugee camps," and "internally displaced." To assess articles that focused on NTDs, we used free text and MESH

terms (where available), for all neglected diseases listed at http://www.plosntds.org.static/scope.action. We also included additional search terms on malaria and poliomyelitis.

As a further strategy we looked at recent morbidity and mortality surveys in known areas of conflict to see if NTDs or malaria were mentioned. We also cross-referenced with a recent WHO report (WHO, 2010c) and expert editorials (Hotez, 2009; Hotez and Kamath, 2009) to see if any references were missed.

Exclusion criteria were determined a priori: if the articles described pre-1980 conflicts, or described disease in non-endemic populations (i.e., military, tourists), they were excluded. We also chose not to include editorials, viewpoints, articles focusing on guidelines, isolated case reports, or letters. Also, if primary research was published in multiple journals, only one article was selected. Our full search protocol and results are summarized in Figure A2-1.

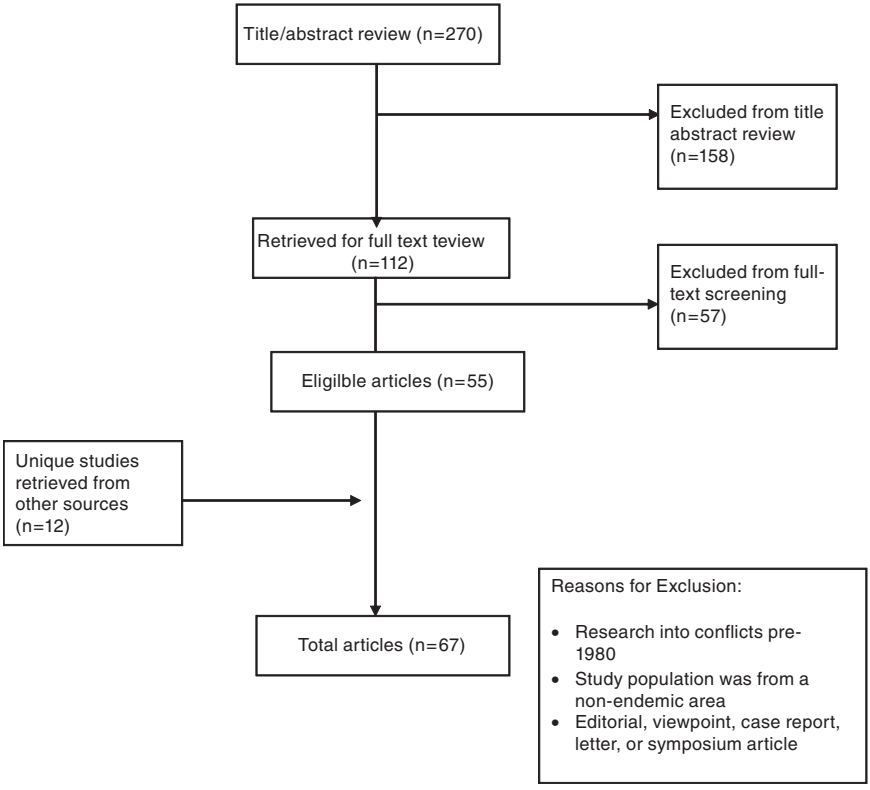


FIGURE A2-1 Search protocol and results.

Results

Table A2-1 describes new studies in the area of neglected diseases and conflict since 2007 (n = 67). Research was conducted in sub-Saharan Africa (51%), the Middle East (15%), North America and Australia (13%), Asia (11%), and on a global level (10%). The five most common disease areas investigated were malaria (39%), intestinal parasites (21%), leishmaniasis (12%), trachoma (7%), and trypanosomiasis (6%).

Studies were either classified as primary research (70%), review articles (21%), and/or routine surveillance data (9%). The vast majority of primary research reports (45/47) were based on cross-sectional surveys to investigate the burden of disease in conflict settings.

The majority of papers identified an increased burden of disease in the conflict or postconflict environment. The only exception to this was a study by Mathenge et al. (2007) looking at causes of blindness in Rwanda, in which this association was not seen.

Mechanisms

On examination of the literature it is evident that conflict can impact on neglected diseases through several intermediate factors. These factors appear to act on the two principal points of the neglected disease cycle; either to increase exposure to the infectious agent and/or increase susceptibility to disease (see Box A2-1). As a result there is increased transmission of the neglected disease, and also more severe illness in individual patients.

The precise nature of the mechanisms may depend on the type of neglected disease involved. For example, the burden of vector-borne diseases (malaria, trypanosomiasis, and filariasis) may be increased in conflicts where there is substantial migration, and where there is a breakdown in control programs with limited access to prevention and treatment (Bygberg et al., 2010). Alternatively, the conditions of crowded refugee camps favor the transmission of water-borne diseases such as cholera and intestinal helminthes (Abu Mourad et al., 2008).

Furthermore it is important to note that the effects of conflict should be described in the wider context of other socioeconomic and ecological determinants of health in these settings. Poverty is a key factor along with conflict that impacts on the existing interplay between pathogen, human host, and the environment. In a recent study investigating the impact of the war in Côte d'Ivoire on risk factors for NTDs, Fürst has elegantly provided a conceptual framework to demonstrate these interactions (Figure A2-2).

Case studies can help to explore these mechanisms in further detail. Here we describe the impact conflict has had on the two common protozoan NTDs—trypanosomiasis and leishmaniasis—in diverse conflicts settings in Africa and Asia.

TABLE A2-1 Studies in Conflict and Neglected Tropical Diseases Since 2007

Region	Disease	Author	Study Type	Outcome(s)	Journal	Year
Northern Uganda	Malaria	Akello-Ayebare et al. (2010)	Questionnaire study	Burden of disease/ access to care	Ann Trop Med Parasitol	2010
Afghani refugees in Iran	Malaria	Basseri et al. (2010)	Cross-sectional	Burden of disease	Bull Soc Pathol Exot	2010
Africa	Trypanosomiasis	Berrang-Ford et al. (2010)	Retrospective cohort	Incidence of disease	Soc Sci Med	2010
Global	Arthropod-transmitted diseases	Brouqui (2010)	Review		Annu Rev Entomol	2010
Africa	Trypanosomiasis	Brun et al. (2010)	Review		Lancet	2010
Global	Vector-borne disease	Bygbjerg (2010)	Review		UgeskrLaeger	2010
Côte d'Ivoire	NTDs	Fürst et al. (2010)	Questionnaire study	Risk factors for disease	Emerging Themes Epidemiol	2010
Afghanistan	Malaria	Howard et al. (2010)	Interview-based study	Access to care	Malaria J	2010
Middle East	Leishmaniasis	R. L. Jacobson (2010)	Review		Vector Borne Zoonotic Dis	2010
Eritrean refugees in Israel	Malaria	Kopel et al. (2010)	Case series	Burden of disease	European Surveillance	2010
Liberia	Malaria	Kruk et al. (2010)	Population-based survey	Access to care	Bull WHO	2010
Burma	Intestinal parasites and malaria	Mullany et al. (2010)	Cross-sectional	Burden of disease	PLoS Med	2010
Sudan/Mali	Guinea worm	CDC (2010a)	Surveillance data	Burden of disease	MMWR	2010
Global	Polio	CDC (2010b)	Surveillance data	Burden of disease	MMWR	2010

Afghanistan	Leishmaniasis	Reithinger et al. (2010)	Cross-sectional	Risk factors for disease	PLoS Neglected Trop Dis	2010
Global	Malaria	Speigel et al. (2010)	Review	Provision of care	Conflict Health	2010
Sudan	NTDs	Sturrock et al. (2009)	Cross-sectional	Burden of disease	PLoS Neglected Trop Dis	2010
DRC	Cholera	Bompangue et al. (2009)	Cross-sectional	Burden of disease	Congo	2009
DRC	Malaria	Coghlan et al. (2009)	Mortality survey	Mortality survey	Disaster Med	2009
Guinea-Bissau	Cholera	Colombatti et al. (2009)	Cross-sectional	Burden of disease	Afr J Med Sci	2009
Côte d'Ivoire	Cholera	Ekra et al. (2009)	Surveillance data	Burden of disease	Bull Soc Pathol Exot	2009
Côte d'Ivoire	NTDs	Fürst et al. (2010)	Questionnaire study	Risk factors for disease	PLoS Neglected Trop Dis	2009
Global	Malaria	Guthmann (2009)	Review		Med Sci (Paris)	2009
DRC	Malaria	Hawkes et al. (2009)	Prospective cohort study	Burden of disease/ diagnostic test study	Malaria J	2009
Africa	NTDs	Hotez and Kamath (2009)	Review	Burden of disease	PLoS Neglected Trop Dis	2009
Sudan	Trachoma	Kur et al. (2009)	Cross-sectional	Burden of disease	PLoS Neglected Trop Dis	2009
Burma	Malaria	Lee et al. (2009)	Scale-up of program	Disease program scale-up	Global Public health	2009
Afghanistan	Malaria	Leslie et al. (2009)	Cross-sectional	Burden of disease	Emerg Inf Dis	2009

continued

TABLE A2-1 Continued

Region	Disease	Author	Study Type	Outcome(s)	Journal	Year
East Timor	Malaria	Martins et al. (2009)	Case-based study	Incidence of disease	Conflict Health	2009
Congo (Brazzaville)	Malaria	Mouko et al. (2009)	Cross-sectional	Burden of disease	Sante	2009
Pakistan	Hydatid disease	Mumtaz et al. (2009)	Cross-sectional	Burden of disease	Trop Doctor	2009
Sudan	Cholera	CDC (2009)	Surveillance data	Burden of disease	MMWR	2009
Sudan	Trachoma	Ngondi et al. (2009)	Cross-sectional	Burden of disease	PLoS Neglected Trop Dis	2009
Refugees in Australia	Malaria, schistosomiasis	Raman et al. (2009)	Cross-sectional	Burden of disease	Aust N Z Public Health	2009
Sudan	NTDs	Rumunu et al. (2009)	Review		Trends Parasitol	2009
Kenya	Cholera	Shikanga et al. (2009)	Case-control study	Burden of disease	Am J Trop Med Hyg	2009
Kenyan refugee camp	Cholera	Shultz et al. (2009)	Cross-sectional	Burden of disease	Am J Trop Med Hyg	2009
Refugees in U.S.	Intestinal parasites and malaria	Stauffer and Weinberg (2009)	Review	Burden of disease	Curr Opin Infect Dis	2009
DRC	Buruli ulcer	Suykerbuyk et al. (2009)	Cross-sectional	Burden of disease	Am J Trop Med Hyg	2009
Palestine	Leishmaniasis	Abu Mourad et al. (2008)	Descriptive study	Burden of disease	Public Health	2008
Iraq	Leishmaniasis	Al-Hucheimi et al. (2009)	Observational study	Burden of disease/ diagnostic test study	Int J Dermatol	2008
West Africa	Trypanosomiasis	Courtin et al. (2008)	Review	Burden of disease	Bull Soc Pathol Exot	2008
Cambodian refugees in U.S.	Intestinal parasites	Goswami et al. (2009)	Cross-sectional	Burden of disease	Am J Trop Med Hyg	2008

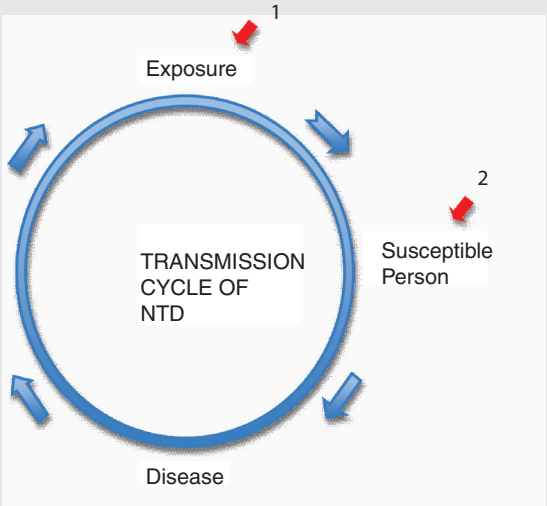
Afghanisthan	Cholera	Kakar et al. (2008)	Review		Trop Doct	2008
Global	NTDs	Gayer et al. (2007)	Review		Emerg Inf Dis	2008
West Africa	Lassa fever	Khan et al. (2008)	Cross-sectional	Burden of disease	Antiviral Res	2008
Angola/DRC	Buruli Ulcer	Kibadi et al. (2008)	Case series	Burden of disease	Emerging Inf	2008
Sudan	Trachoma	King et al. (2008)	Cross-sectional	Burden of disease	PLoS Neglected Trop Dis	2008
Uganda/Kenya	Leishmainiasis	Kolaczinski et al. (2008)	Case-control study	Risk factors for disease	Int J Epidemiol	2008
Pakistan	Leishmaniasis	Anwar et al. (2007)	Review		East Med H J	2007
Africa-Uganda	Trypanosomiasis	Berrang-Ford (2007)	Review	Burden of disease	Conflict Health	2007
Sri Lanka IDPs	Intestinal parasites	Chandrasena et al. (2007)	Cross-sectional	Burden of disease	Trop Doct	2007
Mozambique	Endemic syphilis (Bejel)	Clyti and dos Santos (2007)	Case series	Burden of disease	Bull Soc Pathol Exot	2007
Karen refugees in Canada	Intestinal parasites	Denburg et al. (2007)	Cross-sectional	Burden of disease	Can Commun Dis Rep	2007
Guinea	Lassa fever	Fair et al. (2007)	Cross-sectional	Burden of disease	Vector Borne Zoonotic Dis	2007
Sudanese refugees in U.S.	Intestinal parasites, schistosomiasis	Franco-Paredes et al. (2007)	Cross-sectional	Burden of disease	Am J Trop Med Hyg	2007
Sierra Leaone IDPs	Intestinal parasites	Gbakima et al. (2007)	Cross-sectional	Burden of disease	Afr J Med Sci	2007

continued

TABLE A2-1 Continued

Region	Disease	Author	Study Type	Outcome(s)	Journal	Year
Haitian refugees in Jamaica	Malaria	Lindo et al. (2007)	Case study	Burden of disease	Emerging Infect Dis	2007
Sudan	Trachoma	Mathenge et al. (2007)	Cross-sectional	Burden of disease	PLoS Med	2007
Burma	Malaria	Mullany et al. (2007)	Cross-sectional	Burden of disease	J Epidemiol Commun Health	2007
Burundian refugees in U.S.	Malaria	CDC (2008)	Surveillance data	Burden of disease	MMWR	2007
Sudan	Trachoma	Ngondi et al. (2007)	Cross-sectional	Burden of disease	Am J Trop Med Hyg	2007
Somalian and Sudanese	Intestinal parasites	Posey et al. (2007)	Cross-sectional	Burden of disease	Clin Infect Dis	2007
Refugees in Canada	Intestinal parasites	Pottie et al. (2007)	Cross-sectional	Burden of disease	Can Fam Phys	2007
Afghanistan	Leishmainiasis	Reithinger and Coleman (2007)	Cost effectiveness		BMC Infect Dis	2007
Burma	Malaria	Richards et al. (2007)	Cross-sectional	Burden of disease	Trop Med Int Health	2007
Refugees in U.S.	Intestinal parasites	Varkey et al. (2007)	Cross-sectional	Burden of disease	Travel Med Infect Dis	2007

BOX A2-1
The Impact of Conflict on Neglected Diseases



1. *Factors affecting exposure to infectious agent*
   - Increased contact with vector (i.e., mosquito, tsetse fly)
   - Dirty water
   - Poor shelter
   - Crowded conditions
   - Reduced access to preventative therapy
   - Migration

2. *Factors affecting susceptibility to disease*
   - Malnourishment and food insecurity
   - Reduced access to treatment
   - Exposure of nonimmune to disease through migration

Case Example: Human African Trypanosomiasis

Human African trypanosomiasis (HAT) is endemic to 36 African countries, putting 60 million people at risk. If not diagnosed early, it causes a severe debilitating disease where mortality approaches 100 percent in untreated cases. It is estimated to cost Africa $1.5 billion in lost productivity. Treatment is available at low cost, and the disease can be successfully controlled with active population screening of cases and prompt administration of care (WHO, 2010).

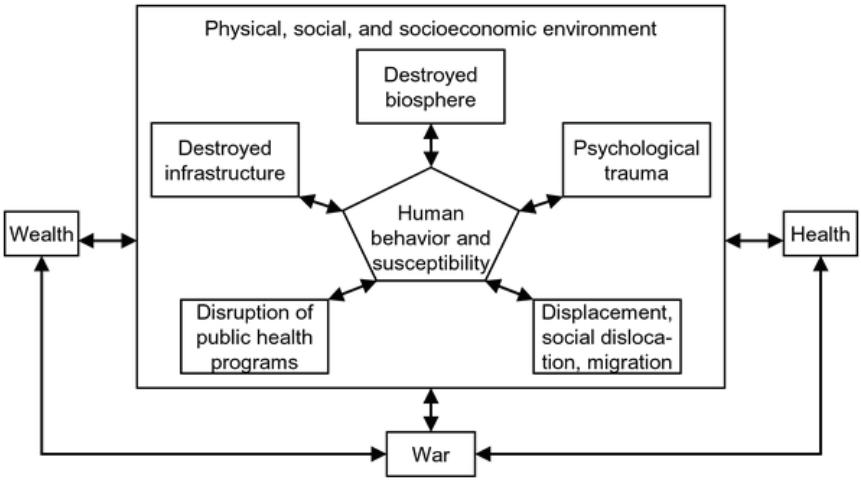


FIGURE A2-2 Conceptual framework for effect of conflict on NTDs.
SOURCE: Reprinted from *PLoS Neglected Tropical Diseases*, Fürst et al. (2009).

In the 1960s, the disease was on the verge of eradication following effective disease control programs. However, lack of sustained disease control in the postindependence area, combined with periods of political unrest, led to resurgence of HAT cases in many countries. These cases peaked in 1996. Following several WHO resolutions in 1998 advocating for stronger access to diagnosis and treatment, the number of new cases reported had been reduced by 68 percent in 2005. Nonetheless, the disease continues to pose problems in conflict regions of Africa: In 2010, the three countries with the highest burden of HAT were Congo, Sudan, and Angola, all states with active conflicts or postconflict (WHO, 2010c).

Case Study: Sub-Saharan Africa

A recent study by Berrang-Ford and colleagues (2010) investigated the relationship between HAT incidence and conflict in Africa over a 30-year time period (1976–2004) using quantative epidemiological methods. In this study, the authors were able to obtain population-level data of both HAT incidence and conflicts within the region. In the study period, they demonstrated six significant space-time clusters of disease incidence (Figure A2-3). Four of the six clusters appear to be associated with specific conflicts, and it was postulated that one of the six clusters was indirectly associated (Table A2-2).

The principal mechanism by which HAT incidence increases during and after a conflict appears because of a breakdown in disease control programs, such that transmission will continue because of inadequate diagnosis and treatment.

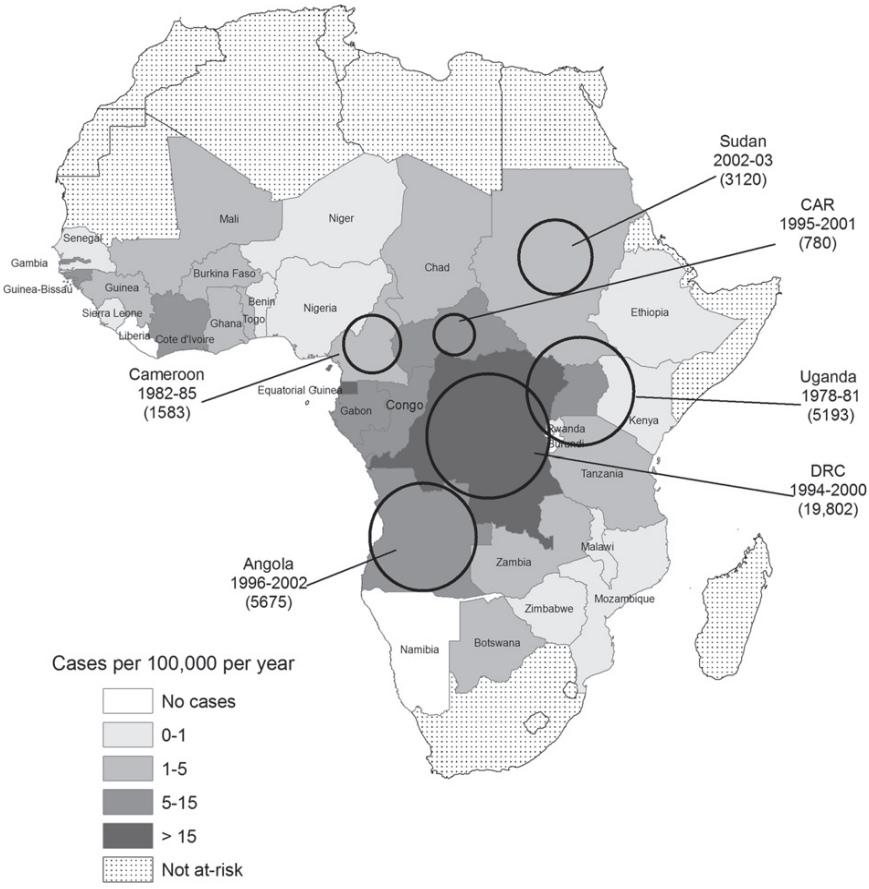


FIGURE A2-3 Map of the distribution of sleeping sickness incidence, Africa 1976–2004. SOURCE: Reprinted from *Social Science & Medicine*, Berrang-Ford et al., Conflict and human African trypanosomiasis, Copyright (2010), with permission from Elsevier.

TABLE A2-2 Summary of Six Space-Time Clusters of Sleeping Sickness Incidence, Africa 1976–2004

Country	Years of Incidence	Relative Risk	Association with Conflict	Estimated Lag (years)
DRC	1994–2000	13.3	Political and civil unrest	Unknown
Angola	1996–2002	10.2	Civil war	10
Uganda	1978–1981	10.5	Civil war	5–10
CAR	1995–2001	5.4	Neighbouring conflict	Unknown
Cameroon	1982–1985	3.9	None found	N/A
Sudan	2002–2003	2.1	Civil war	7–12

However, as shown in the epidemic of disease in the Central African Republic, major population displacement due to conflicts in neighboring countries may also be an important factor.

The study by Berrang-Ford and colleagues is a major advancement in this field, because it uses quantative methods to assess the impact of conflict on the control of an NTD. Although epidemiological research of this nature cannot prove causality, and there may be several confounding factors to explain the findings (i.e., climatic factors, education, or political systems), it does provide convincing evidence to inform future policy and research.

Case Example: Cutaneous Leishmaniasis

Leishmaniasis is a disease caused by a group of intracellular parasites, which are transmitted from the bites of infected sandflies. Leishmania parasites can cause a spectrum of disease ranging from chronic ulcerating skin lesions (cutaneous leishmaniasis [CL]) or a disease that affects the internal organs of the body (visceral leishmaniasis [VL]), which is fatal if left untreated. There are an estimated 1.6 million cases annually (WHO, 2010c), and it is considered to be second in mortality and fourth in morbidity among all tropical diseases (Mathers et al., 2007).

Treatment of the disease is complex, involving drugs with a myriad of toxic side effects, although promising new regimens have recently been developed (WHO, 2010c). Control of the disease is possible through early access to diagnosis and treatment, as well as measures to reduce exposure to the vector, using periodic indoor spraying, health education, and bednets.

Conflict and civil unrest have been thought to be important factors driving leishmaniasis epidemics throughout the world (Bern et al., 2008). A resurgence in cases of VL has been documented in times of conflict in several sub-Saharan African counties, including northern Uganda, Somalia, and Chad (Hotez and Kamath, 2009). In the Middle East, VL has been documented to increase in war-torn areas in Palestine and Iraq, while CL is a major problem in Afghanistan, Iraq, and Pakistan (R. L. Jacobson, 2010).

Leishmaniasis thrives in conflict conditions, as a result of the breakdown in health infrastructure, forced migrations, destruction of human habitats, and food insecurity. Because of the collapse of health systems, patients are unable to access treatment, and there are few disease control measures available to reduce transmission. Poor housing, combined with a mobile population of refugees and internally displaced people, leads to greater transmission of the disease because of increased exposure to the sand-fly vector. In addition, there is a great deal of stress and malnutrition during war, which impairs the human body's defense system, increasing susceptibility to the disease.

Case Study: Afghanistan

Afghanistan has been engaged in conflict for more than 30 years. Health indicators are still among the worst globally, with many preventable diseases such as malaria, measles, and polio rampant throughout the country (Waldmann, 2002).

Kabul, the capital city, is currently the worldwide largest focus of CL with an estimated 67,500 new cases per annum (WHO, 2010a). The majority of CL in Afghanistan is anthroponotic, which means the human population is the main reservoir of infection. Because of the disfiguring nature of the skin disease it causes (i.e., large cutaneous lesions that appear at the biting site of the sand fly), the disease has a significant social impact on the local population. Individuals may become ostracized from society because of stigmatization, and thus the disease may effect their psychological, social, and economic well-being (Kassi et al., 2008). A questionnaire study of individuals in the capital city portrayed the many misconceptions that exist about how the disease is transmitted. Of the 360 respondents, the most common answers were touching (n = 86) and sharing meals (n = 26). As a result of these false beliefs, social exclusion is common. For example, women with lesions may be deemed unsuitable for marriage. They may be separated from their children during the disease, leading to depression and anxiety (Reithinger et al., 2005).

Several epidemics of CL have been described in Afghanistan, corresponding to increases in the intensity of conflict. An important factor in driving the high rates seen in Kabul has been forced migrations of susceptible individuals in the capital (Reyburn et al., 2003). In a similar fashion, outbreaks of disease have been described in neighboring Pakistan and Iran among Afghani refugees (Rowland et al., 1999).

Despite the fact that epidemics of CL have ravaged Afghanistan, there have been few disease control efforts. A few stories of successful public health interventions have been reported among the occupied military forces (Faulde et al., 2008). However, for the vast majority of Afghanis suffering from the disease in neglected areas of conflict, control programs have been non-existent. Because CL does not cause high rates of mortality, control of the disease has not been deemed cost-effective by WHO criteria, further increasing its neglect (Reithinger and Coleman, 2007).

However, control programs for leishmaniasis in conflict settings can be effective. In 2003, a major outbreak of VL was prevented in southern Iraq following the Allied invasion of the country (Jassim et al., 2006). As the burden of CL in Afghanistan expands and affects more vulnerable Afghans, it is imperative that we address the problem.

Ways Forward

In this final section, we highlight some potential interventions to improve the health of those suffering from NTDs in warzones.

Case Example: Intestinal Parasites

Intestinal parasites comprise both intestinal worms (nematodes) and protozoan infections. More than a quarter of the world's population is infected with nematodes (WHO, 2010c), and data on the true burden of protozoan infections are not known because many are not diagnosed. The vast majority of these diseases are transmitted via the feco-oral route, through contact with either contaminated water or food. Symptoms are often nonspecific in the early stages and only become evident when the infection is severe. Children and pregnant women are often the most susceptible. Effects include anemia, growth stunting, reduced physical fitness, impaired intellectual development, and poor educational performance (Feasey et al., 2010). Deworming treatment is available at low cost to treat these diseases, but access is very limited to people who need it the most. Preventative strategies focus on the provision of clean water, health education, and improved sanitary measures.

Conflict often results in large numbers of internally displaced individuals and refugees. These populations are ideal targets for intestinal parasites. Overcrowding, dirty water, minimal sanitary measures, and poor sewage systems are rife in displacement camps, creating the perfect environment for transmission. Mobile populations are often malnourished, increasing their susceptibility to more severe disease. Research in these settings has been limited; however, several cross-sectional surveys have shown a high burden of intestinal parasites in displacement camps in Sierra Leone (Gbakima et al., 2007), Sri Lanka (Chandrasena et al., 2007), and Palestine (Abu Mourad et al., 2008). In a similar fashion, high rates of these diseases are seen in refugees and asylum seekers when they reach developed countries including the United States, Canada, and Australia (Franco-Paredes et al., 2007; Posey et al., 2007; Pottie et al., 2007; Raman et al., 2009; Stauffer and Weinberg, 2009).

Case Study: Burma and Helminth Control in Internally Displaced People

The Burmese government has been engaged in civil war with ethnic minority groups for almost 50 years. There has been widespread documentation of human rights violations committed by the ruling government, including murder, torture, rape, forced labor, forced displacement, and destruction of villages (United Nations, 2010). As a result, a complex humanitarian crisis has developed, and there are estimated to be approximately 2 million internally displaced persons (IDPs). There is little sign of the crisis abating, with the recent reinstallment of the military government following what the international communities describe as "sham elections."

As a result of this long-standing civil war, the health of these IDPs has suffered tremendously. The ruling party is estimated to allocate only 4 percent of the national budget on health care, even though it has been able to spend 40 percent on the military. Furthermore, in 2006 the government imposed new restrictions of international aid, forcing many aid agencies to leave the country (Stover et al.,

2007). It is only since 2009 that humanitarian agencies have returned to be able to provide care. As a result, child and infant mortality rates in the ethnic zones are estimated to be some of the highest reported in the world (Lee et al., 2006). Compared to refugees, IDPs are a particularly difficult group for humanitarian agencies to access (Spiegel et al., 2010).

Infectious diseases are abundant, with malaria, HIV, filiariasis, and other neglected diseases being the principal health problems (Beyrer et al., 2006). Owing to the lack of permanent food, shelter, and clean water supply, mobile populations are particularly vulnerable to the effects of many of these diseases. Often it is pregnant women and children who suffer the most.

As a result of the high morbidity and mortality among IDPs living in Burma, local ethnic-based organizations have empowered themselves to provide health care for their respective communities. Through collaboration with international nongovernmental organizations (NGOs) and academic centers, they have set up control programs to tackle various health care problems in the ethnic zones of Burma. One such program is an innovative project to improve coverage of key maternal health services to improve reproductive health known as the the Mobile Obstetric Medics (MOM) project.

The MOM project was set up in 2005 following an initial survey exploring the very high maternal mortality rates seen in the ethnic zones of Burma. Intestinal parasitic infestation is thought to be an important cause of maternal anemia, leading to many pregnancy-related complications. At survey baseline, the presence of maternal anemia was shown to be 7 times more likely in those populations who had experienced food security violations than those who had not (Mullany et al., 2007).

Recently the first evaluation of the MOM project was described (Mullany et al., 2010). The researchers used a two-stage clustering survey to compare the delivery of key maternal interventions, before (2005) and after (2008) the program was implemented in four distinct ethnic areas in eastern Burma. One such intervention was deworming treatment for helminth infection: compared to baseline, pregnant women were 14.2 times (95% CI, 2.69–3.54) more likely to receive antihelminth coverage than before (Mullany et al., 2010). Since albendazole is a proven treatment for intestinal worms and there is no drug resistance, this is likely to have resulted in a reduction in helminth disease.

The MOM project provides an example of how community-based organizations have been effective in improving access to key interventions for helminth control for vulnerable populations in unstable conflict settings, which were previously considered inaccessible. This is particularly promising, as the MOM project may be used as a model in other settings to deliver simple interventions for neglected diseases.

Case Example: Malaria

Malaria is a protozoan disease that affects more than a third of the world's population and is estimated to cause approximately 1 million deaths annually—

mainly among young children living in Africa (WHO, 2009). In resource-poor settings, the diagnosis traditionally has been made based on clinical symptoms alone, and confirmed by microscopy where available. In recent years, however, the introduction of rapid diagnostic tests has revolutionized diagnosis, allowing accurate diagnosis of malaria in remote field settings. Control programs are based on vector control measures such as insecticide-treated nets and health education, combined with early identification and treatment of cases. Although drug resistance to malaria has been a major problem, the use of artemisinin combination therapy (ACT) for the most severe form of malaria is still effective in most countries.

Malaria is fueled by conflict through several mechanisms. The breakdown in vector control programs and health infrastructure that occurs in wartime leads to increased transmission. In addition, the environmental destruction that occurs during a war is thought to encourage vector breeding (Rowland and Nosten, 2001). Forced displacement leads to exposure of nonimmune individuals to malaria-prevalent areas, leading to severe disease.

In 2000, WHO announced that approximately 30 percent of malaria deaths in Africa were a result of conflict or natural disasters. Malaria is often considered to be responsible for more deaths than the conflict itself. Outbreaks of malaria have recently been described in many conflict areas. Examples include the Democratic Republic of Congo (Coghlan et al., 2009), Afghanistan (Kolaczinski, 2005), and Burundi (Protopopoff et al., 2007). The increase in malaria incidence in refugees and displaced populations has been well described, for Iran (Basseri et al., 2010), Afghanistan (Basseri et al., 2010), Africa (Mouko et al., 2009), the United States (CDC, 2008), Israel (Kopel et al., 2010), and Jamaica (Lindo et al., 2007). Despite this fact, a recent study shows that almost 50 percent of national malaria strategic plans of African countries have no provision for refugees or internally displaced individuals (Spiegel et al., 2010).

The NGO sector has played a crucial role in delivering malaria care to these conflict areas where possible. There are even a few examples where NGOs have conducted basic clinical research to improve their control programs (Guthmann, 2009). However, it is not the primary agenda of NGOs to conduct such research. Furthermore, it may not be a sustainable solution, because NGOs are often only temporary providers.

The past few years have seen a dramatic increase in international funding for malaria. Despite this, in areas of conflict, malaria control remains underfunded and neglected.

Case Study: Timor Leste

During the civil conflict in Timor Leste in 2006, there was widespread street violence with more than 3,000 homes destroyed and displacement of approximately 15 percent of the country's population. In the capital city, Dili, more

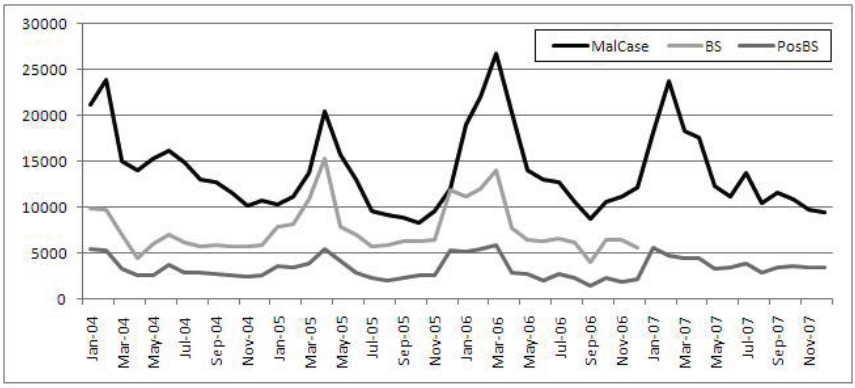


FIGURE A2-4 Malaria in Timor Leste, 2004–2007.
SOURCE: Reprinted from *Conflict and Health*, Martins et al., Malaria control in Timor-Leste during a period of political instability: what lessons can be learned? 2009,3:11, published by BioMed Central Ltd.

than 60 camps were established to provide temporary shelter for IDPs. These circumstances created the perfect environment for a malaria epidemic; however, through an array of control measures, such an epidemic was avoided (Martins et al., 2009).

Malaria in Timor Leste has always been a major public health problem. The disease incidence often follows a cyclical pattern with incidence increasing in the rainy season. In contrast to other conflict zones, the national malaria trends of 2006 showed no increase in malaria cases reported by the health system through the crisis (Figure A2-4).

The principal reason for this appears to be due to a well-galvanized and effective public health response, to prevent a malaria epidemic. This emergency response was co-coordinated centrally by the Ministry of Health (MOH) and involved all major development parties (MOH staff, WHO, international and national NGOs). Key to the success was the early provision of malaria interventions such as ACT treatment and massive ITN distribution to displacement camps. Although routine diseases surveillance was disrupted at the start of the crisis, the MOH ensured it was resumed as soon as possible, which was vital to ensure that the malaria epidemic could continue to be monitored.

Discussion

In this review, we have summarized interactions between NTDs and conflict. Conflict fuels NTDs for a variety of reasons, leading to increased acquisition of the infectious agent and increased susceptibility to disease.

Since our original assessment in 2007, there have been promising improvements in the quality of research in this area, enabling better characterization of the problem. Although many of the studies are cross-sectional, there has been an increase in the use of statistical modeling and geographic information systems, allowing diseases and conflicts to be mapped over space and time. New technology has enabled point-of-care testing for several NTDs, including malaria and trypanosomiasis. This has allowed novel methods for diagnosing these diseases in conflict settings but also better characterization of the total disease burden.

Almost all studies conducted in this field show an increase in NTDs in conflict and postconflict environments. Several studies have shown that, as a result of a conflict in one country, the control of the disease is often disrupted in the region as a whole. As such, it has been extremely difficult to enable worldwide eradication of NTDs such as guinea worm and polio, for these reasons.

There have also been some early examples of successful programmatic interventions for controlling NTDs in unstable settings. The MOM project in Burma provides an excellent model in which local communities have empowered themselves, using mobile health care workers, to provide antihelminth treatment to IDPs. With respect to vector-borne epidemics in conflict times, major outbreaks of malaria and leishmaniasis have been prevented by well-organized rapid-response measures. Ultimately, peace is the ideal intervention. However, initial outcomes may be deceptively poor as postconflict often means return of surveillance and a spike in "new" cases, which are really "newly detected cases."

Despite improvements in research, this field remains underfunded and neglected. The human rights approach places a humanitarian imperative to address these issues. Working under the premise of "shared humanity," it prioritizes the health and suffering of millions of IDPs, refugees, and victims of war. States can be made accountable to look after the health of all their individuals, regardless of their ethnicity or tribal affiliation.

Tackling NTDs in conflict should be part of a broader approach of improving basic rights to those living in conflict zones, who remain some of the most neglected individuals worldwide.

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A3

PARASITE PREVALENCE AND THE WORLDWIDE DISTRIBUTION OF COGNITIVE ABILITY[2]

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In this study, we hypothesize that the worldwide distribution of cognitive ability is determined in part by variation in the intensity of infectious diseases. From an energetics standpoint, a developing human will have difficulty building a brain and fighting off infectious diseases at the same time, as both are very metabolically costly tasks. Using three measures of average national intelligence quotient (IQ), we found that the zero-order correlation between average IQ and parasite stress ranges from $r = -0.76$ to $r = -0.82$ ($p < 0.0001$). These correlations are robust worldwide, as well as within five of six world regions. Infectious disease remains the most powerful predictor of average national IQ when temperature, distance from Africa, gross domestic product per capita and several measures of education are controlled for. These findings suggest that the Flynn effect may be caused in part by the decrease in the intensity of infectious diseases as nations develop.

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1. Introduction

Since the first publication of quantitative data on average national intelligence quotient (IQ) scores (Lynn & Vanhanen, 2001, 2002, 2006), five empirical studies have attempted to explain the global distribution of variation in intelligence. Barber (2005) hypothesized that IQ—like many other psychological traits—is a highly plastic trait that may increase onto genetically as the rewards of higher intelligence increase, and with exposure to education and other cognitively demanding environments such as non-agricultural labour. He reported that, across 81 nations, average national IQ correlated with enrolment in secondary school (r = 0.72), illiteracy (r = -0.71), agricultural labour (r = -0.70) and gross national product (r = 0.54). He also proposed that health and nutrition may affect intelligence, and found that average national IQ correlated negatively with rates of low birth weight (r = -0.48) and with infant mortality (r = -0.34). While it is plausible that formal education increases intelligence, Barber (2005) admits that it is not possible to determine from the data he used whether the correlation between education and intelligence is owing to education increasing intelligence or whether more intelligent individuals seek more education. Research has shown this relationship to be intractable (reviewed in Ceci, 1991). The same direction-of-causation ambiguity is true for agricultural labour (Barber, 2005). We agree with Barber's assertions that health and nutrition may affect intelligence, although the variables he studied—low birth weight and infant mortality—are probably rather incomplete measures of these factors.

Lynn (1991) and Rushton (1995, 2000) proposed that temperature and climate provide important Darwinian selective pressures for intelligence, with cold climates selecting for higher intelligence, because low temperatures provide more fitness-related problems for humans that must be solved through cognitively demanding means, and through more complex social organization. Templer & Arikawa (2006) tested and supported predictions of this proposal in a cross-national study and found that average IQ correlated significantly with winter high temperature (r = -0.76), winter low temperature (r = -0.66), summer high temperature (r = -0.31) and summer low temperature (r = -0.41). Templer & Arikawa (2006) also found that average IQ correlated significantly with average skin darkness (r = -0.92). The authors offered little explanation of why this trend exists, except that they believed skin colour was related to exposure to certain climates over evolutionary time.

Kanazawa (2004) hypothesized that intelligence evolved as a domain-specific psychological adaptation to deal with environments that are evolutionarily novel. This hypothesis was tested and supported at the crossnational level (Kanazawa 2008). Results showed that distance from three points in or near central Africa—

the evolutionary origin of humans—correlated positively with average national IQ (0° E, 0° N, r = 0.45; South Africa, r = 0.53; Ethiopia, r = 0.22). Kanazawa (2008) did not offer his findings as an alternative to those of Templer & Arikawa (2006), but, rather, as complementary to them. Wicherts et al. (2010a) and Borsboom & Dolan (2006) heavily criticized Kanazawa's hypothesis; for reasons they give in detail, we seriously question the ability of linear distance from sub-Saharan Africa to measure evolutionary novelty, undermining the foundation of Kanazawa's hypothesis.

Saadat (2008) and Woodley (2009) suggested that inbreeding depression and associated reduced phenotypic quality is a cause of the variation in cognitive ability across the world. They found cross-national correlations of r = -0.77 (n = 35, $p < 0.0001$) and r = -0.62 (n = 71, $p < 0.01$), respectively, between average IQ and measures of inbreeding. Woodley (2009), however, noted that rates of consanguineous marriage itself may not account for the magnitude of this variation because (i) the statistical significance of the effect disappears when education and gross domestic product (GDP) are controlled for, and (ii) the effect of inbreeding on intelligence had previously been shown to be relatively small.

Here, we offer a new hypothesis—the parasite-stress hypothesis—to explain the worldwide distribution of intelligence. The brain is the most complex and costly organ in the human body. In human newborns, the brain demands 87 per cent of the body's metabolic budget, 44 per cent at age five, 34 per cent at age ten, and 23 per cent and 27 per cent for adult males and females, respectively (Holliday, 1986). Presumably, if an individual cannot meet these energetic demands while the brain is growing and developing, the brain's growth and developmental stability will suffer. Lynn (1990, 1993) has argued that nutrition is vital to high degrees of mental development. Lynn (1990) suggested that nutrition may account for the Flynn effect (large increases in IQ over short periods of time as nations develop; Flynn, 1987), and later (Lynn, 1993) reviewed evidence showing that undernourished children have smaller heads, smaller brains and lower psychometric intelligence than sufficiently nourished children.

Parasitic infection affects the body, and hence the brain, energetically in four ways. (i) Some parasitic organisms feed on the host's tissues: the loss must be replaced at energetic cost to the host. Such organisms notably include flukes and many kinds of bacteria. (ii) Some parasites inhabit the intestinal tract or cause diarrhoea, limiting the host's intake of otherwise available nutrients. These notably include tapeworms, bacteria, giardia and amoebae. (iii) Viruses use the host's cellular machinery and macromolecules to reproduce themselves, at the energetic expense of the host. (iv) The host must activate its immune system to fight off the infection, at energetic expense. Of these, diarrhoeal diseases may impose the most serious cost on their hosts' energy budget. First, diarrhoeal diseases are the most common category of disease on every continent, and are one of the two top killers of children under five, accounting for 16 to 17 per cent of all of these deaths worldwide (WHO, 2004a). Second, diarrhoea can prevent the body from

accessing any nutrients at all. If exposed to diarrhoeal diseases during their first five years, individuals may experience lifelong detrimental effects to their brain development, and thus intelligence. Parasites may negatively affect cognitive function in other ways, such as by infecting the brain directly, but we focus only on energetic costs.

The worldwide distribution of parasites is well known. Disease-causing organisms of humans are more prevalent in equatorial regions of the world and become less prevalent as latitude increases. Ecological factors contributing to this distribution include mean annual temperature, monthly temperature range and precipitation (e.g. Guernier et al., 2004). Similar trends of parasite distribution have been shown in other host species (e.g. Møller, 1998).

Many studies have shown a negative relationship between intestinal helminth infection and cognitive ability (reviewed in Watkins & Pollitt, 1997; see also Dickson et al., 2000). Although several hypotheses have been proposed to explain this phenomenon, none have considered intestinal worms in the larger context of all parasitic infection, nor have they considered fully the energetic cost of infection and its consequences on the brain. Other studies have shown relationships between helminth infection and economic and educational factors that are related to intelligence. For example, Bleakley (2007) studied the effects of eradication of hookworm in the southern US during the early twentieth century, and found that areas where hookworm infections had been greatly reduced had higher average incomes after treatment than areas that had not received treatment. Jardin-Botelho et al. (2008) found that Brazilian children infected with hookworm performed more poorly on cognitive tests than uninfected children, and that children infected with more than one type of intestinal helminth performed more poorly than children infected with only one.

Thus, from the parasite-stress hypothesis, we predict that average national intelligence will correlate significantly and negatively with rates of infectious disease, and that infectious disease will remain an important predictor of average national intelligence when other variables are controlled for. It is the purpose of this study to introduce this hypothesis to describe the worldwide variation in intelligence, and to provide some supportive evidence using correlations and linear modeling techniques.

2. Material and Methods

National average intelligence was taken from Lynn & Vanhanen (2006), who present their methods in detail. IQ was measured directly in 113 nations, and estimated for 79 more nations by averaging the IQs of nearby nations with known IQ. These estimates were validated by Lynn & Vanhanen (2006) by comparing them to actual measurements of IQ in the same nations. At least two studies have presented evidence of validation for these data (Lynn & Mikk, 2007; Rindermann, 2007), by showing strong positive correlations between Lynn &

Vanhanen's (2006) national IQ scores and other measures of cognitive ability. Wicherts et al. (2010b) have criticized Lynn & Vanhanen's (2006) estimates of IQ in sub-Saharan African nations on the grounds that the selection criteria used to include studies in these estimations did not produce national IQ scores that were representative. Using selection criteria that they argue are more appropriate, Wicherts *et al.* (2010b) proposed new average IQ values for 17 nations in sub-Saharan Africa (but see also Lynn & Meisenberg, 2010). Analyses will be performed using three datasets: Lynn & Vanhanen's (2006) original data, including estimates (LVE; mean = 84, median = 84.2, s.d. = 11.8); Lynn & Vanhanen's (2006) data using collected data only (LVCD; mean = 86.7, median = 87.5, s.d. = 11.9); and Wicherts *et al.*'s (2010b) revisions of Lynn & Vanhanen's (2006) data with estimates (WEAM; mean = 85.0, median = 85, s.d. = 11.0).

As a measure of infectious disease levels for each nation, disability-adjusted life years lost (DALY) owing to infectious disease were used (WHO, 2004b). This measure combines years of life lost and years spent disabled owing to 28 representative and important human diseases, including tetanus, malaria, tuberculosis, hepatitis, syphilis and leishmaniasis, such that one DALY equals one healthy year of life lost per 100 000 people. Although other cross-national measures of disease exist, we believe this to be the best for our study because (i) data exist for most countries of the world (n = 192), and (ii) this variable is a reasonable measure of the physiological costs of infectious disease, which concerns the parasite-stress hypothesis applied to cognitive ability. The DALY infectious-disease measure correlates strongly with other measures of human infectious disease (e.g. Thornhill et al., 2009). This variable was log-transformed owing to an extreme skew to the right (mean = 3.36, median = 3.28, s.d. = 0.761).

As an independent measure of nutrient stress, DALY owing to nutritional deficiencies (WHO, 2004b) were used. This calculation includes mortality and healthy years lost owing to protein-energy malnutrition, iodine deficiency, vitamin A deficiency and iron-deficiency anaemia. This variable was log-transformed owing to an extreme skew to the right (mean = 2.59, median = 2.65, s.d. = 0.49).

Average winter high temperatures (mean = 15.6, median = 17, s.d. = 12.5) were taken from Templer & Arikawa (2006). Although they used four intercorrelated temperature variables in their analysis, they reported that average winter high temperature was the best predictor of IQ of the four, so we used it.

Although Templer & Arikawa (2006) found a positive relationship between IQ and skin darkness, we will not use skin darkness in our analyses for three reasons: (i) although evidence suggests that skin darkness is a measure of historical infectious disease intensity over evolutionary time, it is unclear exactly what kind of infectious diseases it is indicative of (see discussion); (ii) Templer & Arikawa (2006) argued that the relationship between skin darkness and IQ is not causal; and (iii) Templer & Arikawa (2006) did not sufficiently explain why the association between intelligence and skin darkness exists. Without a reasonable

theoretical framework for this association, we did not feel it was appropriate to compare it with other variables for which there is a better theoretical rationale.

Literacy rates (mean = 87.6, median = 96, s.d. = 15.9) were taken from World Bank (2008). This variable is defined as the percentage of the population aged 15 years and older who have at least a basic proficiency at reading. Data were from the most recent year available for each nation between 1990 and 2007. Barber (2005) used data from 1976 for his analysis of literacy because that was the average year in which IQ data were collected for all countries. We felt that a more recent date was more appropriate, however, because the IQ scores for each country we used had been modified based on recorded trends of the Flynn effect to reflect the expected modern IQ score (Lynn & Vanhanen, 2006).

Enrolment in secondary school (mean = 29.0, median = 28.5, s.d. = 16.8), completion of secondary school (mean = 12.0, median = 10.5, s.d. = 9.25) and average years of education (AVED; mean = 6.17, median = 5.81, s.d. = 2.89) were taken from Barro & Lee (2001). These numbers represent the percentage of the population aged 25 and older who have attended some or all of secondary school, and the average number of years of schooling in the population. Data were used for the most recent years available after 1990. Data that were only available for years prior to 1990 were omitted.

Data of GDP per capita in US dollars was taken from the World factbook (CIA, 2007), and were log-transformed for normality (mean = 3.81, median = 3.85, s.d. = 0.53).

Distance from central Africa, or the human environment of evolutionary adaptedness (EEA), was calculated using the Pythagorean Theorem, as done by Kanazawa (2008). Kanazawa used three points at the corners of sub-Saharan Africa, so theoretically any point within this triangle should be a valid centre point from which to calculate distance. We selected 258 latitude, 2258 longitude, which is in the approximate centre of this area, and calculated distance from this point using the same methods as Kanazawa. Despite our own criticism of this variable and that of others (Wicherts et al., 2010a), we included this variable in the interest of thoroughness. This variable was log-transformed for normality (mean = 4.0, median = 3.97, s.d. = 0.710).

Percentage consanguineous marriages was not used in this study because it was the conclusion of Woodley (2009) that this variable is unlikely to account for the worldwide variation in intelligence. Additionally, consanguineous marriage and associated inbreeding may be a strategy for maintaining coadapted gene complexes that defend against local infectious diseases (Denic & Nicholls, 2007; Fincher & Thornhill, 2008).

All analyses were performed using JMP 8.0.2 statistical software.

3. Results

Log DALY owing to infectious disease and average national IQ correlated at r = -0.82 (n = 107, p < 0.0001) using LVCD, r = -0.82 (n = 184, p < 0.0001; figure A3-1) using LVE and r = -0.76 (n = 184, p < 0.0001; figure A3-1) using WEAM. Zero-order correlations were also performed for each of Murdock's (1949) six world regions (see table A3-2). A hierarchical linear model (HLM) was also performed to determine whether this relationship is consistent across the six regions, finding that it is (LVE: $R^2 = 0.78$, p < 0.0001, n = 184; LVCD: $R^2 = 0.77$, p < 0.0001, n = 107; WEAM: $R^2 = 0.68$, p < 0.0001, n = 184).

Log DALY owing to nutritional deficiencies and IQ correlated at r = -0.72 (n = 184, p < 0.0001). Log DALY owing to infectious disease and log DALY owing to nutritional deficiencies correlated at r = 0.89 (n = 192, p < 0.0001). The partial correlation between IQ and DALY owing to nutritional deficiencies with the effects of DALY owing to infectious disease removed was near zero (r = 0.028; n = 184, p = 0.71), while the partial correlation between IQ and DALY owing to infectious disease with the effects of DALY owing to nutritional deficiencies removed remained strong (r = -0.56; n = 184, p < 0.0001). See table A3-1 for other zero-order correlations. The correlations between these variables and IQ are very similar across the three measures of IQ (see the electronic supplementary material, tables A3-S1 and A3-S2).

To select which, if any, education and wealth variables to include in a multiple regression analysis, partial correlations were performed independently between literacy, enrolment in secondary school, completion of secondary school and AVED, and average national IQ, with the effects of infectious disease removed. If a variable was no longer significant when the effects of infectious disease were removed, it was not included in the multiple regression. Only WEAM

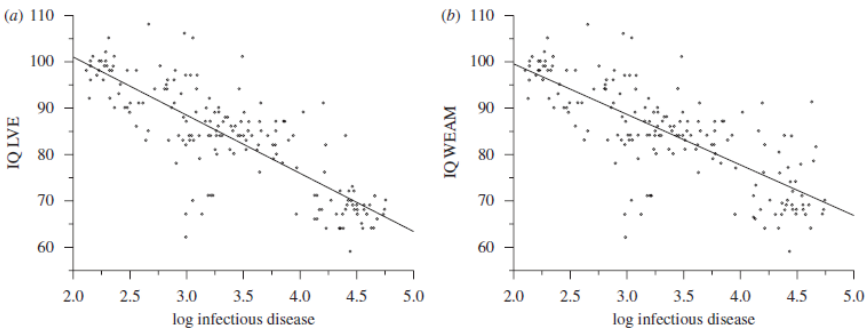

FIGURE A3-1 Log DALY owing to infectious disease and average national IQ correlate (*a*) at *r* = -0.82 (LVE) and (*b*) at *r* = -0.76 (WEAM; n = 184, *p* < 0.0001). The line is the least-squares line through the points.

TABLE A3-1 Zero-order correlations among average national IQ (LVE), log DALY owing to infectious disease, average winter high temperature, distance from EEA, literacy, average years of education (AVED), % enrolling in secondary education, % completing all secondary education and GDP. Values below the diagonal are sample sizes (number of countries), values above the diagonal are correlation coefficients. *$p < 0.05$, **$p < 0.01$, n.s., indicates $p > 0.05$. All others $p < 0.0001$.

	1	2	3	4	5	6	7	8	9
1. average IQ		–0.82	–0.72	0.48	0.61	0.74	0.64	0.36	0.67
2. DALY disease	184		0.71	–0.39	–0.66	–0.79	–0.67	–0.32**	–0.79
3. winter high	124	122		–0.40	–0.57	–0.76	–0.76	–0.25*	–0.52
4. distance from EEA	190	192	124		0.40	0.36	0.25**	0.12 n.s.	0.30
5. literacy	113	113	78	118		0.73	0.91	0.17 n.s.	0.65
6. AVED	130	127	86	131	82		0.86	0.43	0.81
7. some secondary education	123	120	86	123	78	123		0.46	0.67
8. complete secondary education	114	112	73	126	68	95	91		0.37
9. GDP	190	192	124	226	117	130	123	120	

and LVE IQ measures were used for these multivariate analyses in order to have a sample size large enough to make inferences about the individual contributions of each variable. When the effects of log DALY owing to infectious disease were removed, the correlation between IQ and literacy was r = 0.15 (n = 113, p = 0.094) using LVE and r = 0.16 (n = 113, p = 0.1087) using WEAM; IQ and some

TABLE A3-2 Zero-order correlations between average national intelligence and log DALY owing to infectious disease within each of Murdock's (1949) six world regions. Values not in parentheses used LVE, values in parentheses used LVCD and values in square brackets used WEAM.

world area	correlation (*r*)	sample size (countries)	*p*-value
Africa	–0.80 (–0.80) [–0.49]	53 (22) [53]	<0.0001 (<0.0001) [0.0002]
Eastern Eurasia	–0.62 (–0.70)	20 (11)	0.0033 (0.016)
Insular Pacific	–0.85 (–0.83)	17 (12)	<0.0001 (0.0009)
North America	–0.65 (–0.76)	12 (7)	0.022 (0.049)
South America	0.077 (0.043)	23 (16)	0.73 (0.88)
Western Eurasia	–0.65 (–0.73)	59 (39)	<0/0001 (<0.0001)

secondary education was r = 0.093 (n = 120, p = 0.32) using LVE, and r = 0.23 (n = 120, p = 0.049) using WEAM; IQ and completion of secondary education was r = 0.17 (n = 110, p = 0.08) using LVE and r = 0.23 (n = 110, p = 0.030) using WEAM; IQ and AVED was r = 0.23 (n = 127, p = 0.0084) using LVE and r = 0.30 (n = 127, p = 0.0005) using WEAM; and IQ and GDP was r = 0.054 (n = 184, p = 0.46) using LVE and r = 0.036 (n = 184, p = 0.61) using WEAM. AVED was the best predictor of IQ when the effects of infectious disease were removed for both measures of IQ, so this education variable was used in regressions. As such, AVED will have the best chance of all the education variables at being significant in the multiple regression. Although GDP was not a statistically significant predictor of IQ when the effects of infectious disease were removed, and the partial correlation coefficients were well below 0.1, we included this variable in some models at the request of a reviewer (table A3-3).

In a multiple linear regression, average national IQ (LVE and WEAM) was predicted using infectious disease, average winter high temperature, distance from sub-Saharan Africa, AVED and GDP (see table A3-3 for model details). Significant predictors in this model were infectious disease, distance from Africa and winter high temperature. AVED was not significant. When GDP was removed from this model, virtually identical patterns emerged (see the electronic supplementary material, table A3-S3 for model details).

4. Discussion

The negative relationship between infectious disease and IQ was statistically significant at the national level both worldwide and within five of Murdock's (1949) six world regions. All analyses showed that infectious disease was a significant predictor of average national IQ, whether using either of Lynn & Vanhanen's (2006) two datasets or Wicherts et al.'s (2010b) data. The zero-order

TABLE A3-3 Multiple regression analyses predicting average national intelligence using LVE and WEAM (in parentheses where different) by log DALY owing to infectious disease, log distance from EEA, average winter high temperature, average years of education (AVED) and log GDP. Whole model: n = 83 countries, $p < 0.0001$, $R^2 = 0.889$ (0.796).

term	estimate	s.e.	standard beta	VIF	*p*
intercept	95.7 (95.4)	10.9 (13.6)	—	—	<0.0001
DALY disease	–8.30 (–6.50)	1.30 (1.61)	–0.597 (–0.51)	6.03	<0.0001 (0.0001)
Distance from EEA	5.03 (3.91)	0.983 (1.22)	0.231 (0.20)	1.41	<0.0001 (0.0021)
winter high	–0.239 (–0.217)	0.0686 (0.0853)	–0.228 (–0.23)	2.97	0.0008 (0.013)
AVED	–0.0279 (0.394)	0.322 (0.40)	–0.00683 (0.10)	4.30	0.93 (0.33)
GDP	0.265 (–0.262)	0.854 (2.45)	0.0269 (–0.013)	5.22	0.76 (0.92)

correlation between DALY owing to infectious disease and average national IQ was higher than that of any other variable for which there is a previously proposed causal explanation. The world regions analysis showed that the international pattern is repeated within five of the six regions despite a region's generally similar cultural history. The only world region in which this relationship was not significant was South America. This exception may be owing to the presence of several outliers. The group of conspicuous outliers in which IQ was much lower than expected in the worldwide trend (figure A3-1) are all Caribbean countries (St Lucia, Dominica, St Kitts and Nevis, Antigua and Barbuda, Grenada, St Vincent and Grenadines, and Jamaica), which represent 4 of 23 nations in the South America analysis (St Lucia, Dominica, Grenada, and St Vincent and the Grenadines). Because these outliers are in the same geographical location, it is possible that local parasites that are not included in the DALY owing to infectious disease variable are causing these outliers. HLM analysis shows that, despite the nonsignificance of the correlation between IQ and infectious disease within South American nations, this trend is significant overall across Murdock's (1949) six world areas.

Nutritional stress correlated with average national IQ ($r = -0.72$), but this relationship was not significant when the effects of infectious disease were removed. This supports the suggested link between intelligence and nutrition. Given the energetic cost of infectious disease, individuals who are burdened with parasites may be more likely to be affected by nutritional deficiencies. Likewise, individuals who are suffering from nutritional deficiencies may be less able to mount an effective immune response.

Multiple regression shows that, of infectious disease, temperature, evolutionary novelty and AVED, infectious disease is the best predictor of intelligence by a large margin. The effects of years of education are not significant, while temperature and evolutionary novelty seem to have distinct predictive power beyond infectious disease. Although this model cannot rule out the independent effect of distance from central Africa, this effect is difficult to interpret because of the doubt cast on the theory underlying this variable (Wicherts et al., 2010a). Although the effects of education and GDP per capita are not statistically significant when other factors are controlled for, this is not to say that these factors are not involved. A nation of more intelligent individuals is likely to produce a higher GDP, but a wealthier nation is also more able to pay for public education, as well as public medical and sanitation services. An indirect link between education and intelligence may also exist, as a better-educated population may be more interested in public health measures—leading to increased IQ by reducing information about germ theory and hygiene. These sources of endogeneity must be considered when interpreting our findings (and see below). It should also be mentioned that we are not arguing that global variation in intelligence is only caused by parasite stress. Rather, variation in intelligence is probably caused by a variety of factors, including those we have mentioned here as well as factors that are yet unknown.

If the general pathway we propose is correct, there are two plausible mechanisms by which a trade-off in allocation of energy to immune function versus brain development and maintenance may occur. First, parasitic infection may intermittently cause the redirection of energy away from brain development. In this case, during periods of infection, the brain receives fewer energetic resources, but this allocation to brain function will return to pre-infection levels during healthy periods.

During periods of infection, whatever aspects of the brain that are growing and developing will suffer reduced phenotypic quality. Second, exposure to infectious agents may cause a developmental pathway that permanently invests more energy into immune function at the expense of brain growth. In this scenario, large amounts of energy would be allocated into immune function during periods of health, as opposed to only redirecting energy during periods of infection. This could operate through a variety of mechanisms. A plausible mechanism is that higher investment in immune system is triggered by individual exposure to infectious disease at some point during ontogeny. This may include triggering from exposure to maternal antibodies while in utero.

We also propose a complementary hypothesis that may explain some of the effects of infectious disease on intelligence. As we mentioned, it is possible that a conditional developmental pathway exists that invests more energy into the immune system at the expense of brain development. In an environment where there has consistently been a high metabolic cost associated with parasitic infection, selection would not favour the maintenance of a phenotypically plastic trait. That is, the conditional strategy of allocating more energy into brain development during periods of health would be lost, evolutionarily, if periods of health were rare. Peoples living in areas of consistently high prevalence of infectious disease over evolutionary time thus may possess adaptations that favour high obligatory investment in immune function at the expense of other metabolically expensive traits such as intelligence. Data do not currently exist on temporal variation of the severity of infectious disease across the world over human history. For genetically distinct adaptations in intelligence to exist based on this principle, parasite levels must be quite consistent over evolutionary time. If this is not the case, then selection would maintain investment in the immune system and in the brain as a plastic (as opposed to static) trait. The Flynn effect (Flynn, 1987) indicates that conditional developmental causes must be at work at least in part. Large increases in intelligence across a few generations cannot be attributed to genetic differences caused by evolutionary processes. Hence, it does not seem probable that region-specific genetic adaptations are the primary cause of the worldwide variation in intelligence.

Our findings suggest that the heritable variation in intelligence may come from two sources: brain structure and immune system quality. Thus, two individuals may possess identical genes for brain structure, but have different IQ owing

to differences in immune system quality reflecting their personal allocation of energy into brain development versus immunity.

Our findings are consistent with a number of other findings in the literature. In particular, the Flynn effect (Flynn 1987) demands that any hypothesis regarding the worldwide variation and distribution of intelligence must be able to account for some factor that allows for large IQ gains over time spans seemingly too short to be attributed to evolution by natural selection. The parasite-stress hypothesis allows for such a factor in the form of reduced parasitic infection. As societies become modernized, decreased parasite stress may occur through multiple pathways. As national wealth increases, medicine, vaccinations and potable water can be purchased by both the government and by individuals. Moreover, there is cross-national evidence that, as democratization increases, there are corresponding increases in public health legislation and infrastructure. Democratization also increases levels of education, better allowing individuals to seek out and understand information that reduces parasitic infection (Thornhill et al., 2009). This source of endogeneity is not a flaw, but a prediction of our hypothesis.

Mackintosh (2001) presented comprehensive evidence that skin darkness and the associated cellular components (e.g. melanocytes) have an important role in defending against infectious disease. Moreover, Manning et al. (2003) found that, in sub-Saharan Africa, rates of HIV infection were negatively associated with skin darkness. Manning et al. (2003) attributed this relationship in part to lower infection rates of other parasites, especially bacteria and fungi, that lead to tissue damage in the genital tract and hence increased opportunity for contracting HIV. Templer & Arikawa (2006) concluded that, despite the strong negative correlation between skin colour and average national IQ, there must be an unknown mediating factor accounting for both because there is no obvious reason for skin darkness to reduce IQ. Given the previous research linking skin colour to infectious disease (Mackintosh, 2001; Manning et al., 2003), the unknown factor linking skin colour and IQ may be infectious disease.

Several studies have shown a positive relationship between IQ and body symmetry (e.g. Furlow et al., 1997; Prokosch et al., 2005; Bates, 2007; Penke et al., 2009; but see also Johnson et al., 2008). There is evidence that body symmetry is a measure of developmental stability, an important component of which is owing to reduced contact with infectious disease (Thornhill & Møller, 1997). Our study suggests that IQ and body symmetry correlate because they are both affected negatively by exposure to high infectious disease. Individuals who are exposed to infectious disease may have many aspects of their body develop imperfectly, including the brain, negatively affecting both their body symmetry and cognitive ability. Indeed, recent research indicates that there is a positive relationship between body asymmetry and atypical brain asymmetries (Yeo et al., 2007).

The hygiene hypothesis proposes that some autoimmune diseases may be caused by low exposure to pathogens during ontogeny (e.g. Strachan, 1989). Previous studies of individual differences have shown that intelligence corre-

lated positively with the frequency of asthma and allergies (reviewed in Jensen & Sinha, 1993). According to the parasite-stress hypothesis, high intelligence is allowed in part by low exposure to infectious disease. Thus the relationship between intelligence and autoimmune diseases, such as asthma and allergies (reviewed in Gangal & Chowgule, 2009), is probably mediated through exposure to infectious disease. We predict that this positive relationship between IQ and autoimmune diseases will also be robust across nations, and that it will be mediated by infectious disease.

Although our results support our predictions, further studies must be done to establish causation. Longitudinal methods could be used to test this hypothesis on the individual level. Children's IQ could be measured at an early age and remeasured later in life, while monitoring for infectious diseases throughout childhood. This would not only provide another test of our hypothesis, but may be able to determine the effects of individual infectious diseases on cognitive development. Additionally, it could be determined which, if either, trade-off mechanism we discussed is responsible for the detrimental effects of infectious disease on intelligence. Both may operate but with geographical differences based on the consistency of infectious disease over time. As nations develop, they could be monitored for declining rates of parasitic infection to determine (i) whether this corresponds with elevated IQ and (ii) whether any IQ gain is sufficient to account for the Flynn effect.

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Data Supplement

TABLE A3-S-1 Zero-order correlations among average National IQ (LVCD), log DALY infectious disease, average winter high temperature, distance from EEA, literacy, average years of education (AVED), % enrolling in secondary education, % completing all secondary education, and GDP. Values below the diagonal are sample sizes (number of countries), values above the diagonal are correlation coefficients. * indicates $p < 0.05$, ** indicates $p < 0.01$, ns indicates $p > 0.05$. All others $p < 0.0001$.

	1	2	3	4	5	6	7	8	9
1. average IQ		–0.82	–0.72	0.48	0.59	0.75	0.50	0.50	0.73
2. DALY disease	107		0.71	–0.39	–0.66	–0.79	–0.67	–0.32**	–0.79
3. winter high	71	122		–0.40	–0.57	–0.75	–0.76	–0.25*	–0.52
4. distance from EEA	112	192	124		0.40	0.36	0.25**	0.12ns	0.30
5. literacy	66	113	78	118		0.73	0.61	0.17ns	0.65
6. AVED	91	127	91	86	82		0.86	0.43	0.81
7. some 2º education	89	120	86	123	78	123		0.46	0.67
8. complete 2º education	73	112	73	126	68	95	91		0.37
9. GDP		112	192	124	226	117	130	123	120

TABLE A3-S-2 Zero-order correlations among average National (WEAM), log DALY infectious disease, average winter high temperature, distance from EEA, literacy, average years of education (AVED), % enrolling in secondary education, % completing all secondary education, and GDP. Values below the diagonal are sample sizes (number of countries), values above the diagonal are correlation coefficients. * indicates $p < 0.05$, ** indicates $p < 0.01$, ns indicates $p > 0.05$. All others $p < 0.0001$.

	1	2	3	4	5	6	7	8	9
1. average IQ		–0.76	–0.70	0.40	0.57	0.73	0.65	0.38	0.62
2. DALY disease	184		0.71	–0.39	–0.66	–0.79	–0.67	–0.32**	–0.79
3. winter high	124	122		–0.40	–0.57	–0.75	–0.76	–0.25*	–0.52
4. distance from EEA	190	192	124		0.40	0.36	0.25**	0.12ns	0.30
5. literacy	113	113	78	118		0.73	0.61	0.17ns	0.65
6. AVED	130	127	91	86	82		0.86	0.43	0.81
7. some 2º education	123	120	86	123	78	123		0.46	0.67
8. complete 2º education	114	112	73	126	68	95	91		0.37
9. GDP		190	192	124	226	117	130	123	120

TABLE A3-S-3 Multiple regression analyses predicting average national intelligence using LVE and WEAM (in parentheses when different) by log DALY infectious disease, log distance from EEA, average winter high temperature, and average years of education (AVED).

term	estimate	STD error	STD beta	VIF	p
intercept	98.6 (94.2)	5.98 (7.45)	–	–	<0.0001
DALY disease	–8.56 (–6.39)	0.983 (1.22)	–0.616 (–0.50)	3.50	<0.0001
distance from EEA	5.05 (3.90)	1.00 (1.22)	0.232 (0.195)	1.41	<0.0001 (0.0019)
winter high	–0.235 (–0.219)	0.0666 (0.0828)	–0.224 (–0.228)	2.83	0.0007 (0.0099)
AVED	0.0116 (0.377)	0.294 (0.365)	0.00285 (0.10)	3.62	0.97 (0.31)

whole model: n = 83 countries, $p < 0.0001$, $r^2 = 0.889$ (0.796)

A4

THE NEGLECTED TROPICAL DISEASES: CURRENT STATUS OF CONTROL AND THE U.K. CONTRIBUTION

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Introduction

The neglected tropical diseases (NTDs) are an ever-growing list of infections that predominate in the tropics and are neglected in comparison with the "big three": malaria, tuberculosis (TB), and HIV/AIDS (Hotez et al., 2008). The current list includes parasitic helminths, bacteria, protozoa, fungi, ectoparasites, and viruses. One subgroup of the NTDs is the group of seven, which are deemed "tool ready" insofar as they can be treated with safe and effective drugs that must be taken usually just once a year, although frequency may be determined by prevalence and intensity or whether the target of the treatment strategy is control or elimination (Hotez et al., 2006b). Because of drug donations by the pharmaceutical industry, these seven are usually targeted using mass drug admin-

istration (MDA). The target group may be the whole population of a given area or it may be confined to school-age children, again depending on the prevalence and intensity and the aim of the intervention. One or two of the NTDs may soon be eradicated if final efforts are successful. Some of the NTDs are extremely pathogenic, and so new drugs against them are being sought, usually with donor funding. These diseases do not lend themselves to MDA; rather diagnosis and treatment is the strategy. The rest of the NTDs are probably best described as the "even more neglected tropical diseases" because they are either less pathogenic or less frequently encountered. The exception is dengue fever, which is neglected despite an apparent increase in distribution and prevalence. Many of the NTDs will eventually disappear as they have in the developed world when socioeconomic status improves and clean and safe water and sanitation is available to all. Currently, with 1 billion individuals—one-sixth of the human population—living in poverty and often in extremely unhygienic conditions, such development is some way off.

The Seven Tool-Ready NTDs

The seven include six helminths, lymphatic filariasis (LF; elephantiasis), onchocerciasis (river blindness), schistosomiasis (bilharzia), and soil-transmitted helminths (STHs), of which there are three (ascariasis, trichuriasis, and hookworm), and trachoma, which is caused by the bacteria *Chlamydia*.

The Pathology and Need for an MDA Control Strategy (Ottesen, 2006)

Lymphatic filariasis (LF) is caused by two similar species of filariasis worms, *Brugia malayi* and *Wuchereria bancrofti*. They are each transmitted by mosquitoes, and the adult worms inhabit the lymph glands, which they block and therefore restrict lymph drainage. The gross consequence of LF is first a swelling of limbs, and the grosser deformities that occur are usually the result of secondary infections. In females, the breasts and legs are where the swellings typically appear and the extent can be grotesque. In men, legs and the scrotum can be affected, in which case the resulting hydrocele in males may also result in massive scrotal swellings. The definitive numbers of people suffering from these deformities is not known, but an estimate of 40 million is often quoted. The adult worms live for up to 6 years, and the female worms give birth to larvae (microfilariae), which travel around the skin of the human host waiting to be taken up during a mosquito blood meal. Transmission takes place when another human is bitten by an infected and infective mosquito. It has been discovered that an annual dose of either albendazole with Mectizan (ivermectin) or albendazole with diethylcarbamazine (DEC) will not kill the adult worms but will prevent any larvae from circulating in the skin. The theory, therefore, is that if sufficient people in an endemic area can be treated with these combinations of drugs, no larvae will be

available for the biting mosquitoes, and so transmission could be interrupted. If this could be achieved for seven consecutive years—longer than any adult worms will survive in their human host—then elimination of LF might be possible. The distribution of LF globally is widespread, and the Indian subcontinent, the Far East, Africa, and South America are all endemic for LF. The control using MDA is under the umbrella of the Global Alliance for the Elimination of LF (GAELF); however, full control will need significant case management for sufferers with symptoms. Currently, after an exponential increase in coverage from 1998, more than 550 million doses of albendazole are distributed annually—some 80 million with Mectizan and the rest with DEC. The albendazole has all been donated by GlaxoSmithKline (GSK), and more than 2 billion tablets have already been distributed since the start of the programme. Some of the earlier programs have already completed their planned intervention, and transmission has halted in Egypt and Zanzibar. As for case management, washing of swollen limbs regularly with soap has been shown to be very beneficial, and surgery for enlarged scrotal sacs is becoming more available to men with hydroceles.

Funding for GAELF comes from various sources, including the Bill & Melinda Gates Foundation and the British Government Department for International Development (DFID). Other funding for delivery of the donated drugs comes from the U.S. Agency for International Development (USAID), via a contractor and grantees, and a network of nongovernmental organisations (NGOs) also contribute funding and assist with organization of albendazole and Mectizan delivery. The Liverpool School of Tropical Medicine housed the Global Alliance secretariat and now the Centre for Neglected Tropical Diseases, which now works closely with the Schistosomiasis Control Initiative (SCI; see below).

Onchocerciasis (river blindness) is caused by the filarial worm *Onchocerca volvulus*. *Onchocerca volvulus* is transmitted by black fly (*Simulium* species), and the adult worms inhabit nodules in various parts of the body. The adult worms are long lived and, like LF, the female worms give birth to larvae (microfilariae) that travel around the skin of the human host, waiting to be taken up during a *Simulium* blood meal. Transmission takes place when another human is subsequently bitten by an infective fly. Unfortunately, the many microfilariae cause intense itching in their human host and also cause blindness as the traveling microfilariae damage the retina. The very high infection and blindness rates in villages in close proximity to African rivers in which the *Simulium* breed led to an intensive vector control campaign in the middle of the 20th century, when many rivers in 11 countries were sprayed with DDT to control the black fly populations. (The Onchocerciasis Control Project [OCP] was launched in 1974.) In the 1980s it was discovered that an annual dose of Mectizan (ivermectin), although it does not kill the adult worms, prevents any larvae from circulating in the skin. Because the larvae do the damage, an annual dose of Mectizan in an endemic area targeting the whole population should prevent blindness. Indeed since 1985

many millions of people have been treated annually in a campaign of preventive chemotherapy, and, although this campaign is still needed, the prevalence rates and blindness rates have been very significantly reduced. The distribution of onchocerciasis is mainly in Africa, although there are foci in South America. The OCP was closed in 2002, by which time an estimated 600,000 had been saved from blindness. The OCP was replaced by the African Programme for Onchocerciasis Control (APOC), which now targets 19 different countries, concentrating on getting annual Mectizan treatment out to those who live in hypoendemic areas. The Mectizan is provided to the countries who qualify by the Mectizan Donation Programme, which is housed within the Task Force for Global Health in Atlanta. The key to APOC is community-directed treatment with ivermectin (Boatin, 2008; Boatin and Richards, 2006). The donated ivermectin is distributed by trained community volunteers who deliver the ivermectin annually to the community using a dose pole to get the correct dose.

In some areas a new strategy of delivering two treatments of Mectizan per year has been instigated with a view to trying to kill the adult worms rather than merely reducing the microfilaria levels.

Funding for APOC comes from a number of traditional bilateral donors, including DFID, and in fact DFID recently (2009) donated an additional £5 million to APOC. Other funding for delivery of the donated drugs goes to the countries from USAID, via RTI,[4] and a network of NGOs also contributes funding and assists with organization of Mectizan delivery.

Loa loa is another filarial worm with a limited geographical distribution and relative harmless symptoms, whose major significance is the complication it brings to the MDA against onchocerciasis and LF in Africa. Individuals with a heavy *Loa loa* infection may suffer serious side effects when treated with Mectizan and albendazole because of death of *Loa loa* microfilariae.

Schistosomiasis (bilharzia) is caused by species of the genus *Schistosoma*. *S. mansoni* causes intestinal schistosomiasis and is found in Africa and the Middle East and has been exported to South America and the Caribbean; *S. haematobium* causes urinary schistosomiasis—recently renamed urogenital schistosomiasis—and is limited to Africa and the Middle East; *S. japonicum* and *S. mekongi* cause intestinal schistosomiasis in the Far East, and *S. intercalatum* causes schistosomiasis in small foci in central Africa. In all it has been estimated that more than 200 million people may have been infected with schistosomiasis both in 1970 and in 2002 although, because of treatment, other control efforts, population increases, and water resource developments, the distribution of the various species may have changed (Steinmann et al., 2006). The adult schistosome worms are each about one centimetre in length and live in pairs in the blood vessels of the human host; each female worm will lay an estimated 300 eggs per day over a life

[4] Research Triangle Institute (RTI) is better known by its trade name, RTI International.

span of 5–6 years for *S. haematobium* to up to a reported 20 years for *S. mansoni*. The eggs break through the blood vessels into either the bladder or the intestine, causing detectable blood in the urine and less so in the stool. The eggs that do not leave the body via the excreta cause significant damage; *S. mansoni* eggs collect in the liver, where they are trapped, and when they die they cause fibrosis over a period of time, which is shorter in heavier infections. *S. haematobium* eggs cause lesions in the genital areas and also cause fibrosis of the bladder wall. In Egypt, where *S. haematobium* used to be particularly prevalent, bladder cancer was the most prevalent cancer in the country until the year 2000. A concentrated treatment programme throughout the 1990s and a change in water usage after the construction of the Aswan High Dam led to *S. haematobium* being all but eliminated from Egypt, and the associated bladder cancer rates have declined dramatically (Fenwick, 2000, 2006). Five large-scale control programmes were carried out during the period 1970–2000. The first was the Blue Nile Health Project in Sudan, which combined malaria control using indoor residual spraying with praziquantel treatment and mollusiciding. Meanwhile, Brazil embarked on a control programme using treatment of identified cases with first oxamniquin and then praziquantel to reduce the cases of massive liver damage. The others, slightly later, were World Bank–funded programmes in China, the Philippines, and Egypt. The current preferred drug against schistosomiasis is praziquantel, which is available as 600 mg tablets, and a dose of 40 mg/kg is considered curative. Merck donates 20 million tablets a year to the World Health Organization (WHO), and it distributes these to countries looking to initiate programmes. Control of schistosomiasis was initially focused on snail control from 1910 to 1950 because the various treatments for schistosomiasis were unpleasant and relatively ineffective. A few promising agents were tried from 1950 through 1980, but each of them proved to have significant side effects. In 1980, the drug praziquantel was marketed by Bayer after multicentre drug trials were successful, but the price of $1 per tablet was prohibitive. By 1990 a competitive process for manufacture by Shin Poong, a company in South Korea, led to a precipitous reduction in price, and by 2002 the tablets were available at 7 cents per tablet—a 93 percent reduction from the original price (Fenwick, 2008). Despite this reduction, African governments did not rush to buy because the demand for treatment was not high, and yet the numbers requiring treatment represented a very high percentage of the rural population. The leadership for control since 2000 has come from SCI, based at Imperial College London, and was established with a grant awarded by the Bill & Melinda Gates Foundation. Control programmes were established in six countries (Burkina Faso, Mali, Niger, Tanzania, Uganda, and Zambia), and the intention was to lead to national coverage. Programmes focused on MDA to school-age children and in areas of prevalence more than 50 percent of children and then whole populations were targeted. Fishermen and farmers using irrigation were especially targeted. SCI combined the treatment for schistosomiasis with a single pill of albendazole because the prevalence of STHs among people infected

with schistosomiasis was invariably high. By 2008, SCI had delivered more than 40 million treatments to about 20 million people, but this still represented only about 10 percent of the infected population in Africa, so expansion of this programme was essential (Fenwick et al., 2009). Additional support came from three sources. The first was a private equity company (Legatum) that funded SCI to organize implementation in Burundi and Rwanda, and this programme has completed three years of treatment of schistosomiasis and STH. The second was USAID, which through RTI has purchased praziquantel for donation to a number of endemic countries as part of its support for NTD control. The third is DFID, which has allocated £25 million for schistosomiasis and STH, £9.5 million for implementation and management, and £15 million to purchase the drugs. SCI and Liverpool Centre for Neglected Tropical Diseases work together on this award.

The current status of schistosomiasis control is that programmes are going ahead in a number of African countries funded by bilateral donations from USAID and DFID. However, WHO believes that less than 10 percent of the people in need of treatment in Africa were treated in 2009, which means that many areas are in need of treatment (Hotez and Fenwick, 2009).

A constraint is the funding to purchase praziquantel, but even if the funding was available there is a doubt whether production capacity is available beyond 150 million tablets a year. However, another constraint is the lack of capacity of many countries to deliver praziquantel widely, and so scaling up might well be slower than ideal even if funding was made available. Nevertheless, in many countries now the most serious cases of hepatosplenomegaly seem to be on the decrease. One aspect of schistosomiasis that was recently brought to the attention of the medical community is the association between *S. haematobium* and HIV/AIDS, which is why the term urogenital schistosomiasis was recently adopted (Kjetland et al., 2010a, 2010b).

We firmly believe that a stronger case needs to be made for the treatment of young children ages 6–14 with an extra focus on ensuring that young girls, whether in or out of school, are reached with schistosomiasis treatment before genital lesions are developed and therefore the chances of HIV/AIDS are significantly reduced (Hotez et al., 2009).

Soil-transmitted helminths (*Ascaris lumbricoides, Trichuris trichuris, Necator americanus,* and the less common *Ancylostoma duodenale*) The four species of STH, which actually are three diseases—roundworm, whipworm, and hookworm—infect different parts of the digestive tract and have different modes of infection, although none of them use an intermediate host.

Roundworms It is estimated that more than 800 million individuals are infected with roundworm and that most of these are children. It is also likely that most people are not heavily infected and that 10 percent of those infected harbor 90 percent of the worms. However, 10 percent of 800 million means that 80 mil-

lion people have dangerously heavy worm loads. Roundworms live in the small intestine, and their eggs are passed out in the feces. The eggs need to spend time developing in the soil in not-too-hot and not-too-dry conditions, and then they are ready to be ingested. If ingested, the eggs hatch and then migrate through the body until they are coughed up and swallowed. They then pass through to the small intestine where they remain, laying eggs and feeding. In heavy infections, the worms, which are thick and up to 14 inches (35 cm) in length, can cause a serious intestinal blockage.

Whipworms An estimated 600 million people are infected with *Trichuris* worms, which are generally thought to be the least pathogenic of the STHs. They are relatively small (less than 5 cm or 2 inches) and live in the colon. Heavy infections can cause colitis.

Hookworm The two species of hookworm infect almost 600 million people, and their effect on the human host is much greater than the other two types of STH, despite them being the smallest of the STHs at just 1 cm in length. This is because the hookworms attach to the wall of the small intestine and in fact take blood, causing anaemia, which can be severe in heavy infections. Anaemia is the main cause of poor birth outcomes and so hookworms are responsible for a significant number of underweight babies and for anaemia in children and women of childbearing age (Christian et al., 2004). The eggs of the hookworm are passed out in the faeces and then develop in the egg before hatching, releasing a free-living larva. This larva attaches to bare feet or legs and burrows through the skin to reach the bloodstream. Via the heart, they reach the lungs, migrate up the trachea, and are then swallowed.

All three worms are global in distribution, although, thanks to improved sanitation, areas that 100 years ago were heavily infected with hookworm (the classic example being the southern United States) no longer have any hookworm at all.

The worms can be swept from the human digestive system by treatment with a benzimidazole, either albendazole or mebendazole. Neither drug is 100 percent effective, but even if an individual is not completely cleared of worms a high percentage will be swept through the system (Albonico et al., 2004).

Until very recently, the deworming drugs had to be purchased, and, although they were inexpensive (less than 10 cents per dose), few countries organize deworming programmes. From 2008, Johnson and Johnson began a donation program and up to 50 million mebendazole tablets were donated annually to selected countries. From 2010, Johnson and Johnson has reported that it will increase its donation to 200 million tablets a year. Meanwhile, the 2 billion tablets of albendazole that have been donated by GSK for treatment of LF have dewormed millions of individuals annually. In October 2010, GSK announced an increase in its albendazole tablets by 400 million every year to ensure that all school-age children in Africa will be dewormed (Lorenzo Savioli, WHO, personal

communication). Another donor has been "Feed the Children," a programme that has donated many millions of mebendazole tablets for schoolchildren. It can surely be expected that within 5 years children in Africa and the developing world will show improvements in appetite, physical fitness, growth, hemoglobin, school attendance, and cognitive ability (Jukes et al., 2002; Miguel and Kremer, 2004; Nokes et al., 1992). It may be difficult to demonstrate these improvements because of confounding factors, but most parasitologists are convinced of the accuracy of this hypothesis.

Since the millennium, several organizations have increased their deworming activities. SCI has combined deworming with treatment of schistosomiasis. "Children without worms" has handled the Johnson and Johnson donation of mebendazole, "Deworm the World" has accepted Feed the Children mebendazole, and now GSK will donate 400 million tablets per year for Africa, probably through a WHO mechanism. Many NGOs have deworming programs, USAID has included deworming in the integrated NTD treatment programmes, and the United Nations Children's Fund has funded many countries to deworm preschool-age children. In several progressive Asian countries, deworming has been adopted and funded by the state. However, despite all this recent activity, WHO still believes that only 10 percent of people are being dewormed annually.

Trachoma caused by the bacterium *Chlamydia trachomitis* Known as the leading cause of preventable blindess, *Chlamydia* is reported to infect some 80 million people worldwide, and up to 8 million may be visually impaired as a result of their infection. As with all the above, this is an infection in the poorest of the poor, and could be easily prevented by improved water and sanitation. Without better hygiene, the infection is carried from person to person both by physical contact and by flies. As with the other diseases, there has been an initiative to control trachoma. The International Trachoma Initiative (ITI) was started by Dr. J. Cook when he left the Edna McConnell Clark Foundation (EMCF), which for many years funded Dr. Cook's tropical disease research. The EMCF provided startup funding, Pfizer joined in with Zithromax donations, and the Bill & Melinda Gates Foundation also supported the programme. In a slightly different approach, ITI insisted on more than just a treatment program and developed a "SAFE" strategy: S, for incorporating simple surgery to correct eyelid deformities and prevent cornea scarring; A, for antibiotics—three annual doses to control active *Chlamidia*; F, for facial cleanliness to prevent the infection, which leads to conjunctivitis, which will reduce transmission; and finally E, for environmental improvement, including improved water supplies and better sanitation. The first country to eliminate trachoma was Morocco. In 2011 it is estimated that some 70 million doses of Zithromax will be delivered by ITI, which was once independent but is now housed within the Task Force for Global Health.

Integration of Activities Against the Seven Tool-Ready NTDs

WHO, in conjunction with the Global Network for Neglected Tropical Diseases, the Bill & Melinda Gates Foundation, and others, led the drive to bring all the vertical single disease programmes together with a view to integration of the annual MDA programmes. The concept was "sold" to USAID, which resulted in a competitive bid in 2006 for $100 million more than 5 years for integrated MDA, awarded to RTI. This has resulted in 10 countries receiving support for integrated NTD treatments and more than 250 million treatments with the four drugs being delivered.

In 2010, further funding for integrated NTD treatment is on the table again from USAID—and this time up to $450 million may be awarded to several contractors. By November 2010 Family Health International had been awarded $100 million for each of Africa and Asia to take established programmes forward.

Other Neglected Tropical Diseases

Guinea Worm: Dracuncula medinensis

Guinea worm is a nasty worm infection that affects man and water fleas. From more than 3 million infected some 20 years ago, it is estimated that in 2010 only 25,000 cases remain in the world; most of those cases are in South Sudan because of hostilities that have prevented clearance. The latest country to be declared free of Guinea worm was Burkina Faso. The larval worm lives in a water flea and is ingested by anyone drinking unclean, unfiltered water from a pond or lake. The larvae are released in the stomach and over several months make their way to the connective tissue in the leg, where the female becomes gravid with eggs. The female worm produces a blister that burns; when the blister bursts, eggs are released into the water to reinfect the water fleas. The effect on the human host is painful, and secondary infection can be very dangerous. Before control efforts were in place, which depend mostly on health education and providing filters for water, whole villages were likely to be infected. There is no drug to treat this worm, but because there is no animal reservoir the chances are great that it will soon be eradicated. The Carter Center and WHO, with support from the Bill & Melinda Gates Foundation and DFID, have worked tirelessly to reduce the number of infections; with the exceptions of Ghana and Sudan, the target of eradication is getting very close (Hopkins et al., 2005; Ruiz-Tiben and Hopkins, 2006).

The Protozoa: Trypanosomiasis and Leishmaniasis (Croft et al., 2005, 2006)

Sleeping sickness and Chagas disease caused by trypanosomes and visceral leishmaniasis are important diseases that have a high mortality rate, killing over 150,000 per year; they have a poor cure rate even when treated. Cutaneous leishmaniasis does not kill but is disfiguring and also difficult to treat.

Sleeping sickness is transmitted by the bite of the tsetse fly, and once infection has developed to disease, mortality is high. At any one time an estimated 500,000 people may be infected. The drugs available even if cases are diagnosed are old, and there is an urgent need to find new treatments, even though they will never be commercial products. The not-for-profit Drugs for Neglected Diseases initiative (DNDi) based in Geneva is following some promising drug development lines with funding from DFID, the Gates Foundation, and the European Union. Screening for human African trypanosomiasis (HAT) used to be more widespread than it is today because the areas worst affected include current conflict areas in East and Central Africa.

Chagas disease is limited to South America because it is transmitted by a triatoma bug, but still an estimated 9 million are infected and therefore suffer from either an acute stage, which can cause heart failure, or a chronic condition that disturbs the heart, causing palpitations, chest pain, and fainting. Although it is caused by a trypanosome, it is thus very different from HAT. However, this disease should be easily preventable by improving housing conditions or indoor insecticide spraying, which will prevent bedbugs. As with other parasitic infections, it is the poorest people who are infected.

Leishmaniasis affects some 12 million people globally and is transmitted by sandflies. The cutaneous form causes ulcers and can be disfiguring, but the visceral form affects internal organs and is fatal if untreated. However, the treatment often causes side effects and is prohibitively expensive to the poor people who tend to be infected.

The Even More Neglected Tropical Diseases (Hotez et al., 2006a)

Many more diseases occur in the tropics and are even more neglected than those mentioned above. There are helminth infections such as strongyloidiasis, *Toxocariasis* and larva migrans, and loiasis. There are food-borne trematodes,which are very common in the Far East because of the eating of poorly cooked fish. These include opisthorchis, paragonimus, and chlonorchis. The additional Cestodes that affect humans are taeniasis, cysticercosis, and echinococcosis, which include the zoonotic parasitic worms.

Other protozoa include giardiasis and amoebiasis, while bacterial infections include Bartonellosis, bovine tuberculosis, Buruli ulcer, leptospirosis, relapsing fever, rheumatic fever, treponematoses, and syphilis. Two important fungal infections include mycetoma and paracoccidiomycosis; then there are ectoparasitic infections such as scabies, myiasis, and tungiasis. The viral infections include dengue fever, yellow fever, Japanese encephalitis, rabies, and the hemorrhagic fevers.

Thus, although the tool-ready infections can be controlled or eliminated using preventive chemotherapy, there are many more infections that mostly affect the poorest of the poor that are still very neglected. To achieve the Millenium Development Goals, it will be necessary to tackle not only the tool-ready diseases

but also the others mentioned in this paper, because poverty and these diseases are inextricably linked (Gil Gonzalez et al., 2006).

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A5

INTEGRATED IMPLEMENTATION OF PROGRAMS TARGETING NEGLECTED TROPICAL DISEASES THROUGH PREVENTIVE CHEMOTHERAPY: PROVING THE FEASIBILITY AT NATIONAL-SCALE[5]

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Abstract

In 2006, the United States Agency for International Development established the Neglected Tropical Disease (NTD) Control Program to facilitate integration of national programs targeting elimination or control of lymphatic filariasis,

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onchocerciasis, schistosomiasis, soil transmitted helminthiasis and blinding trachoma. By the end of year 3, 12 countries were supported by this program that focused first on disease mapping where needed and then on initiating or expanding disease-specific programs in a coordinated/integrated fashion. The number of persons reached each year increased progressively, with a cumulative total during the first three years of 98 million persons receiving 222 million treatments with donated drugs valued at more than $1.4 billion. Geographic coverage increased substantially for all these infections, and the program has supported training of over 220,000 persons to implement the programs. This current experience of the NTD Control Program demonstrates clearly that an integrated approach to control or eliminate these five neglected diseases can be effective at full national scale.

Introduction

The neglected tropical diseases (NTDs) are a group of conditions causing significant morbidity and mortality worldwide but which until recently received only minimal attention from most of the world, largely because they affect the poorest, most vulnerable and most disenfranchised members of society (Hotez et al., 2009). Afflicting more than one billion persons, one-sixth of the world's population, these diseases cause severe disfigurement, disability, and blindness. The NTDs are among the leading perpetuators of poverty because they significantly diminish economic productivity in affected adults and because they impair the intellectual and physical development of the next generation in disease-endemic areas, setting already vulnerable children on a path to lifelong disability that reinforces a cycle of poverty (Hotez et al., 2009).

Among the 15 most prominent NTDs (Hotez et al., 2006), seven have similar strategies to address their control; namely, single doses of effective treatment , termed preventive chemotherapy (PCT), given once or twice a year to broad segments of the population in disease-endemic areas through mass drug administration (MDA). These seven diseases are lymphatic filariasis (LF), onchocerciasis, schistosomisis, trachoma and three soil-transmitted helminth (STH) infections (ascariasis, hookworm, and trichuriasis) (WHO, 2006). The treatment and diagnostic tools currently available for this group of diseases are sufficiently effective for these NTDs to be targeted either for elimination or for reduction to such low levels that they no longer constitute a significant public health problem.

Most of the drugs used in these single-dose, once- or twice-yearly treatment regimens are donated through large public-private partnerships that bring together public health implementers, public-sector and private-sector donors, and the major pharmaceutical firms producing these drugs (GlaxoSmithKline, Johnson & Johnson, Merck and Co., Inc., Merck-Serono, Pfizer) (Liese et al., 2010).

Historically, many Ministries of Health in disease-endemic countries have supported the control of NTDs through independent, often parallel, programs,

with each maintaining its own planning, funding, drug supply chain, MDA campaign, monitoring, and evaluation. If funding were available for one program, that program might have been able to implement preventive chemotherapy while a sister program could not. However, because there is considerable overlap of these diseases in persons and communities, controlling one of the NTDs and not others that could be managed through a similar strategy is inefficient at best. Furthermore, research has provided sufficient evidence to suggest that co-implementation of the integrated PCT programs is safe for persons and communities in all but a few specific settings (*e.g., Loa loa* co-endemicity with onchocerciasis or LF) (WHO, 2006).

Because of the similarity of their strategic approaches, the epidemiologic overlap among affected populations and the availability of donated drugs, these NTD control programs seemed ideally suited for implementation that could be carried out not in parallel, independent fashion, but, rather, integrated in a way where coordinated treatment interventions for multiple diseases could reduce the duplication of effort expended in treating the diseases separately. Such integration, here considered in the broadest sense as coordination of program activities among different disease-specific programs and as linkages of these activities with other elements of the health care system, should lead to efficiencies of delivery, enhanced effectiveness, increased health benefits, and better use of limited resources that could permit more at-risk people to be reached (Brady et al., 2006). The World Health Organization (WHO) has endorsed such co-implementation of programs as the integrated approach to preventive chemotherapy.

Early pilot studies of NTD program integration generally showed that, despite many practical challenges, such integration was likely to be feasible and to result in at least some of the anticipated efficiencies and cost savings (Garba et al., 2009; Lammie et al., 2006; Richards et al., 2006). While it was clear from these pilot studies that certain elements of program implementation were more amenable to successful integration than others, it was not clear either how successful the scaling up of these integration efforts from pilot studies to national-scale programs could be or just which combinations of activities were most effectively linked.

The opportunity to document the feasibility of integrated approaches to NTD control at full national-scale presented itself when the U.S. Congress in 2006 authorized funds for "the integrated control of neglected tropical diseases" (U.S. Congress, 2006). This authorization led to the establishment of the United States Agency for International Development (USAID) NTD Control Program that envisioned, over a five-year period, facilitating integrated NTD programs in 15 countries. The present report documents the considerable achievements of the first three years of this NTD Control Program towards the development and growth of national integrated NTD programs and in their expansion to full national scale.

Methods

The NTD Control Program

Goals and approach USAID NTD Control Program initiated activities in September 2006. Its defined target was to enable the provision of 160 million preventive chemotherapy treatments to 40 million people in 15 countries through integrated NTD programs over five years. The stated aims of the Program have been 1) to support and empower national governments to develop integrated NTD control programs embedded, where possible, within existing service delivery platforms and to lead these programs in scaling-up activities to full national levels; 2) to provide technical assistance for planning, budgeting, reporting and complying with international standards and guidelines (Table A5-1) to improve program integration; 3) to promote cost-efficiency, improved integration strategies, and effective advocacy; and 4) to assure national ownership, continued commitment, and resource mobilization for sustained support for NTD control.

The prime contractor, RTI International, has provided grants and coordination for a team of non-governmental organizations (NGOs) and implementing partners to support integrated NTD control programs organized and led by the governments of selected countries. The support from the U.S. Government was intended to build on existing commitments by governments and other donors and fill financial and technical gaps that were preventing national programs from reaching full national scale. The Program was mandated to track and report on the additional numbers of persons reached and treatments provided through support of the NTD Control Program (recognizing that in some countries other support also exists for NTD control).

Participating countries and NGOs

The countries currently involved in the USAID-supported, RTI-coordinated NTD Control Program are identified in Table A5-2, along with the lead NGO responsible in each country for interfacing between the national Ministry of Health and RTI. Those five countries which had earlier pilot programs, initiated with support from the Bill and Melinda Gates Foundation (Leading global health organizations, 2006) and aimed at integrating disease-specific NTD control activities, are referred to as the fast-track countries, because they could begin scaling up activities immediately; additional countries have been brought into the program progressively. By the end of year-3, 12 countries were included in the program, of which seven were actively engaged in yearly MDAs. It is from these first 7 implementing countries that the quantitative measures of the NTD Control Program's programmatic achievement during its first 3 years (reported below) are derived.

TABLE A5-1 Disease-Specific Guidelines*

Disease	Diagnostic approach for mapping	Threshold for implementation of pct interventions	Unit of implementation	At-risk population targeted	Drugs	Frequency of intervention†
Lymphatic filariasis (in countries where onchocerciasis is co-endemic)	Antigen detection (ICT) or microfilia detection (microscopy) in whole blood	Prevalence ≥1% in adults in some part of an implementation unit	District or other as defined for ease of operation	≥ 5 years old	IVM and ALB	Once per year (anticipated 4-6 years)
Lymphatic filariasis (in countries where onchocerciasis is *not* co-endemic)				≥ 2 years old	DEC andALB	
Onchocerciasis–APOC	Nodule detection using rapid techniques	Presence of palpable nodules ≥20% in adult men	Meso- or hyper-endemic focus (reflecting river basins)	≥ 5 years old	IVM	Once per year, except in special circumstances
Onchocerciasis–OEPA	Skin snip	Prevalence of infection ≥1% in an implementation unit	Endemic focus	≥ 5 years old	IVM	Twice per year (anticipated 10-14 years)

continued

TABLE A5-1 Continued

Disease	Diagnostic approach for mapping	Threshold for implementation of pct interventions	Unit of implementation	At-risk population targeted	Drugs	Frequency of intervention†
Schistosomiasis	Parasitological methods 1) detecting eggs in urine or stool (microscopy)	High risk: Prevalence of infection ≥50% in SAC	District, Sub-district or Community	SAC and adults	PZQ	Once per year
	2) detecting blood in urine (hemastix or questionnaires)	Moderate-risk: Prevalence of infection ≥10% but <50% in SAC		SAC and at-risk adults		Once every two years
		Low-risk: Prevalence of infection <10% in SAC		SAC presenting at health center		Twice during primary schooling
Soil-transmitted helminthiasis (ascariasis, trichuriasis, hookworm)	Detecting eggs in stool (microscopy)	High-risk: Prevalence of any STH ≥50% in SAC	District, Sub-district or Community	SAC, preschool children, women of childbearing age, pregnant women in second and third trimesters, special adult populations	ALB or MEB	Twice per year
		Low-risk: Prevalence of any STH ≥20% and <50% in SAC				Once per year

Trachoma (blinding)	Eyelid examination for follicular inflammation (TF)	TF prevalence ≥10% in 1-9 year olds	District	Everyone ≥ 6 months old with azithromycin; Children <6 months with tetracycline	AZT and TET	Once per year (AZT); Twice per day for 6 weeks (TET)

* Consistent with established and currently followed WHO recommendations (WHO, 2006), http://whqlibdoc.who.int/publications/2006/9241546. Abbreviations: IVM=Ivermectin; ALB=Albendazole; DEC=Diethylcarbamazine; PZQ=Praziquantel; MBD=Mebendazole; AZITH=Azithromycin; TETRA=tetracycline; SAC=School-aged children; TF=Trachomatous Inflammation.

† Duration of intervention varies for each disease.

TABLE A5-2 Principal Drug Distribution Strategy in Endemic Districts*

NTD control program	Country	Principal drug distribution strategy in endemic districts†					Lead ngo
		LF	Onchocerciasis	Schistosomiasis	STH	Trachoma	
"Fast-Track" Countries	Burkina Faso	Community Household Health center Mobile	Community Household Health center Mobile	Community School-based Household Health center Mobile	Community Household Health center Mobile	Community Household Health center Mobile	Schistosomiasis Control Initiative
	Ghana	Community	Community	School-based	Community	Transmission of blinding trachoma interrupted	World Vision
	Mali	Community School-based Household Mobile	School-based Household	School-based Household Mobile	Community School-based Household Mobile	School-based Household Mobile	Helen Keller International
	Niger	School-based Household	N.A.	School-based Household	School-based Household	School-based Household	Schistosomiasis Control Initiative
	Uganda	Community School-based Household	Community Household	Community School-based Household	Community School-based Household Health center	Community School-based Household Health center	RTI International

Additional Countries	Haiti	School-based Distribution posts	N.A.	N.A.	School-based Distribution posts	N.A.	IMA-World Health
	Sierra Leone	Community Household	Community Household	School-based	Community School-based Household	N.A.	Helen Keller International
	Bangladesh						RTI International
	Cameroon						Helen Keller International
	Nepal						RTI International
	Southern Sudan						Malaria Consortium
	Togo						Health and Development International

* NTD = neglected tropical disease; LF = lymphatic filariasis; STH = soil-transmitted helminths; NGO = nongovernment organizations; NA = not applicable.
† General features of different distribution strategies described by national programs. Community distribution = in the market, mosque, or other busy places, common in urban settings; Schoolbased distribution = in schools, targeting only children in schools; Household distribution = house-to-house, where the drug distributor brings the drugs to persons in their homes; Health center distribution = at a health center, where persons come to the health center to receive the drugs; Mobile distribution = through distributors traveling by vehicle to find households in remote areas.

Drug distribution

All drugs were distributed by the national Ministries of Health whose national NTD control programs determined how best to implement their MDAs (Table A5-2). The drugs were used according to WHO recommendations (Table A5-1). When disease co-endemicity required the use of multiple drugs (including combinations of albendazole, diethylcarbamazine [DEC], ivermectin, mebendazole or praziquantel), these were generally given at the same time, although sometimes the praziquantel treatment was delayed for at least a week after the other drugs were administered. When azithromycin was required, its administration was always at least a week separated from those of the other drugs, as currently recommended.

Albendazole for treatment of LF was donated by GlaxoSmithKline (Gustavsen et al., 2009); when used to treat STH in areas where LF is not endemic, albendazole was obtained from pre-qualified generic manufacturers. Azithromycin (Zithromax) was donated by Pfizer (Knirsch, 2007). Diethylcarbamazine was obtained through WHO from pre-qualified generic manufacturers. Ivermectin (Mectizan) was donated by Merck & Co., Inc. (Thylefors, 2008). Mebendazole was donated by Johnson & Johnson (Liese et al., 2010) to treat persons with STH in countries where its Children Without Worms program operates. Tetracycline eye ointment was obtained from pre-qualified generic manufacturers.

Technical assessments

Mapping. Because knowledge of the distribution of each NTD in a country is absolutely essential for developing any implementation (or integrated-implementation) plan, disease-specific mapping was carried out according to guidelines recommended by WHO and its partners (Table A5-3). Although some of these guidelines are still evolving, for all program assessments, the most up-to-date recommendations were followed.

Program metrics. To document progress toward achieving the program's targets of 40 million additional people treated with 160 million treatments over 5 years, the following indicators were used to track country-specific program progress: 1) number of countries supported by the NTD Control Program; 2) number of additional districts (implementation units) mapped for each endemic disease; 3) number of people treated (i.e., receiving at least one drug or drug package) and recorded in MDA registers for each round of PCT; 4) number of additional treatments (i.e., made possible through support from the NTD Control Program) provided (i.e., number of times a single drug dose is administered) and recorded in MDA registers for each round of PCT; 5) number of additional implementation units reached and reported by national programs for each round of PCT; 6) programmatic coverage: % targeted population reached with appropriate PCT treatment each round of PCT and calculated from register reports as the number

TABLE A5-3 WHO Guidelines for Disease-Specific Mapping

Lymphatic filariasis	
Indicator	Prevalence of *Wucheria bancrofti* antigenemia or *Brugia* microfilaremia
Persons tested	> 15 years old Living > 10 years in the community/village
Diagnostic tool	Immunochromatograpy (ICT) antigen test of finger stick blood or parasitologic examination of night blood films
Sample size	Up to 300 to identify at least 1 antigen- or microfilaremia-positive person (i.e., exceeding threshold of 1%)
Sampling frame	At least 1 village/site in an imlementation unit Convenience sample or otherwise
Onchocerciasis	
Indicator	Prevalence of subcutaneous nodules or *Onchocerca volvulus* microfilariae in the skin
Persons tested	50 adults ≥ 20 years of age and living in the village for > 10 years
Diagnostic tool	Palpation of subcutaneous nodules (also possible: parasitologic examination of skin snip)
Sample size	50 per village; 2-4% of villages in focus
Sampling frame	Convenience or otherwise
Schistosomiasis	
Indicator	Questionnaire; prevalence of microhaematuria or parasite eggs in urine for *Schistosoma haematobium* Prevalence of parasite eggs in stool for *S. mansoni*
Persons tested	School age children (7-14 years of age)
Diagnostic tool	Dipsticks for microhaematuria/urine filtration for S. haematobium Kato-Katz or sedimentation test for *S. mansoni*
Sample size	50 school age children per school or site
Sampling frame	At least 5 villages with expected high prevalence in each ecologic zone In the village: convenience sample
Soil Transmitted Helminths	
Indicator	Prevalence of eggs in stool
Persons tested	School age children (7-14 years of age)
Diagnostic tool	Kato-Katz
Sample size	50 SAC per school or site
Sampling frame	5 villages with expected high prevalence in each ecologic zone In the village: convenience sample
Trachoma	
Indicator	Prevalence of trachomatous inflammation (TF) and trichiasis (TT)
Persons tested	1-9 year-olds for trachomatous inflammation (TF) > 15 year-olds for TT
Diagnostic tool	Clinical examination of eyes
Sample size	50-100 children per cluster
Sampling frame	20 clusters per implementation unit (district or other) Probability Proportional to Estimated Size

treated divided by treatment-eligible populations in the implementation unit (as defined by census reports); 7) geographic coverage: % of endemic districts covered by PCT programs; 8) number of persons trained for integrated NTD control through support from the NTD Control Program.

Program expenditures

Funding levels for each of the program's first three years approximated $13.5 million per year, with the mandate that at least 80% of total annual resources be allocated to country program implementation and that overall management costs by RTI (whose role was to ensure financial accountability of all funds expended and to provide requested technical assistance to national programs) be no more than 20%. Of the 80% allocated for country implementation activities approximately 20% was earmarked for procurement of essential drugs not available through donation programs (*i.e.,* PZQ for schistosomiasis, DEC for LF, and albendazole for childhood de-worming in areas where LF is not co-endemic).

Results

Mapping the geographic distribution of the targeted NTDs

Because knowing the distribution of the targeted NTDs is essential for developing an implementation strategy, the first efforts of the NTD Control Program in the participating countries focused on cataloging the disease-distribution information available and then supporting on-the-ground efforts to map the distribution of infection where sufficient information was not available.

Table A5-4 aggregates the data from all of the districts in the first seven implementing countries (identified in Table A5-2) and indicates the total number of districts that had been mapped for each of the NTDs prior to the initiation of

TABLE A5-4 Mapping of Districts in NTD Control Program Countries*

Disease	Baseline before NTD Control Program Start		Districts Mapped with USAID Support	Districts Mapped with Other Support	No. remaining districts that need mapping-end of year 3
	No. districts already mapped	No. districts needing NTD mapping			
LF	493	33	8	12	13
Onchocerciasis	379	147	0	143	4
Schistosomiasis	346	180	170	0	10
STH	356	170	170	0	0
Trachoma	423	103	68	24	11

* Aggregated total number of districts in the first 7 implementing countries (identified in Table 2).
NTD = neglected tropical disease; USAID = United States Agency for International Development; LF = lymphatic filariasis; STH = soil-transmitted helminths.

the NTD Control Program. It is clear that mapping was already well advanced for LF. For the other diseases, there was still a great need for additional information on the distribution of these infections.

Table A5-4 also shows the progress made by the end of the first three years of support to the participating countries through the NTD Control Program. For each of the targeted diseases, mapping activities progressively defined the extent of the targeted diseases, and as a result of these efforts and those of other partners, only a small number of districts in these countries remained to be mapped for these NTDs at the end of year 3 (now targeted for subsequent years' activities).

Persons treated and number of treatments delivered in Years 1-3

Although programs targeting the individual NTDs were active in many countries prior to the inception of the NTD Control Program, few countries approached these diseases with an integrated control strategy. As seen in Figure A5-1A, after the fast track countries, with earlier support for pilot-scale integration studies by the Bill and Melinda Gates Foundation (Leading global health organizations, 2006), began to receive support for integrated programs from the NTD Control Program, there was a progressive increase in numbers of persons reached each year beginning with 16 million additional individuals in the first year and reaching 27 and 55 million additional persons in each of the second and third years. (These numbers identify only those persons whose treatment was made possible by support to national programs from the NTD Control Program, cumulatively, more than 98 million people over three years.)

Because a treated person in these integrated programs often receives a drug package comprising more than one medication, the metric treatments provided was developed to record the number of individual drug treatments received by the target population. As indicated in Figure A5-1B, 222 million drug treatments were provided during the first three years of support to the 7 implementing countries by the NTD Control Program. The details of these treatments provided (drugs treatments distributed by the seven participating national programs) are found in Table A5-5.

Quantity/value of drugs delivered

As the national programs supported by NTD Control Program funds increased in number and expanded in scope, the number of donated tablets of drug delivered to the national NTD programs has also increased. Table A5-6 shows that *in* year 3 alone more than 300 million drug tablets were donated and delivered to the countries receiving NTD Control Program support. The value of these drugs (as defined by each specific donation program) exceeded $575 million dollars in year 3 and has totaled more than $1.4 billion dollars in the program's first three years.

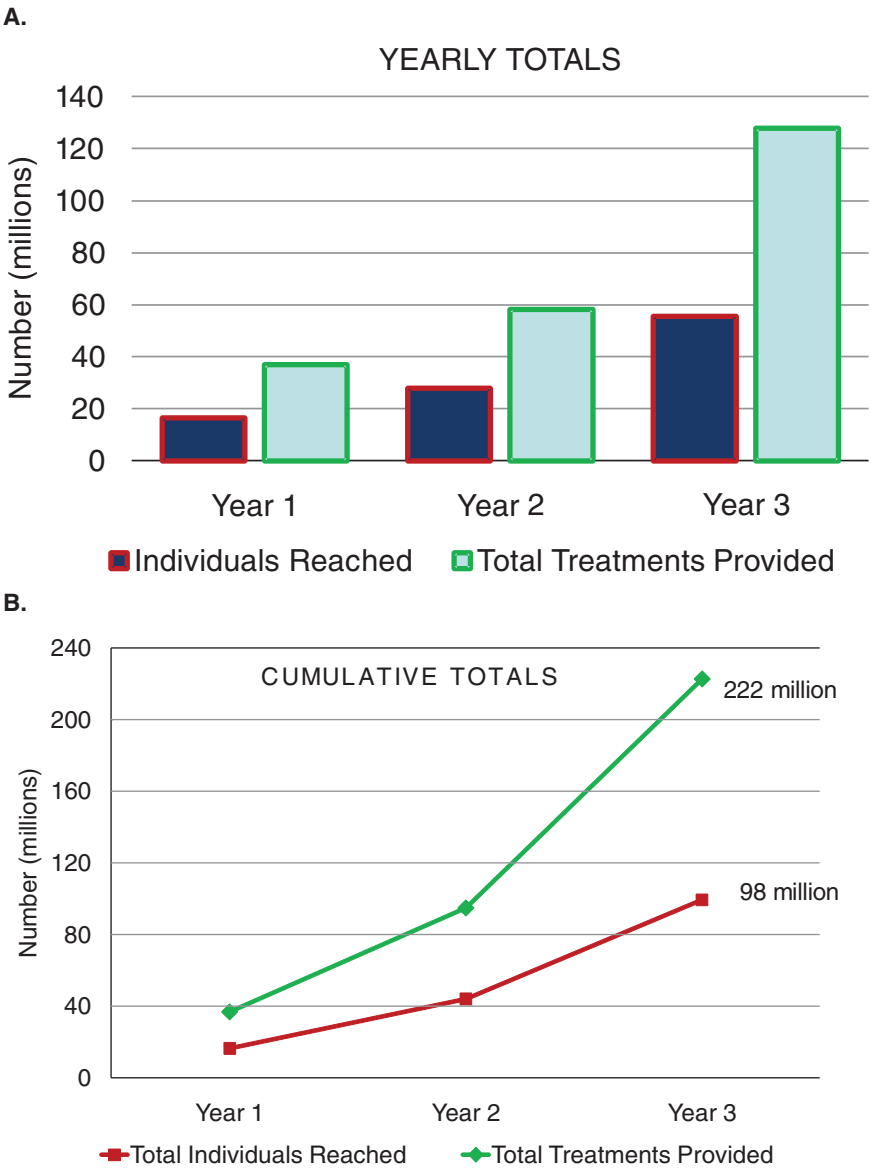

FIGURE A5-1 A. Persons reached (dark blue bars) and treatments provided (light blue bars) during each of the first three years of the Neglected Tropical Disease (NTD) Control Program. **B.** Cumulative totals of persons reached (red line) and treatments provided (green line) over the first three years of the NTD Control Program.

TABLE A5-5 NTD Control Program-Supported Treatments*

Drug	Year 1	Year 2	Year 3
IVM	12,049,342	15,551,089	43,945,901
DEC	0	0	2,111,826
ALB/MBD	13,263,152	20,221,501	51,906,980
PZQ	2,621,978	8,839,281	10,783,581
AZT/TET	8,881,685	13,417,513	19,106,346
Total	36,816,157	58,029,384	127,854,635

* IVM = ivermectin; DEC = diethylcarbamazine; ALB/MBD = albendazole/mebendazole; PZQ = praziquantel; AZT/TET = azithromycin/tetracycline.

Coverage

The *sine qua non* for success of preventive chemotherapy programs is high rates of drug coverage in the disease-endemic populations. Although varying among countries and for specific programs within each country, programmatic coverage (the percentage of targeted persons who actually received the drug) was generally very good (Table A5-7). These values were based on numbers reported by the drug distributors and their supervisors; and when these reported values were subjected to validation studies in coverage surveys, there was generally good agreement between the reported and surveyed coverage values (data not shown).

For successful elimination and large-scale control programs using the preventive chemotherapy strategy it is also necessary to have broad geographic coverage (the percentage of disease-endemic districts covered by PCT programs). Figure A5-2 records the numbers of districts under treatment of each disease during the first 3 years. It shows that for each of the NTDs, the geographic coverage increased progressively during the three years of NTD Control Program activity. Because the program can only expand (*i.e.,* increase geographic coverage) in areas where mapping is complete, those NTDs where mapping is more advanced (*e.g.,* onchocerciasis where the African Programme for Onchocerciasis Control has been a strong and consistent source of funding for mapping and implementation) have the greatest geographic coverage. By the end of year 3, geographic coverage in the 7 implementing countries had increased for each of the NTDs, ranging from a high of 95% for onchocerciasis to a low of 50% for schistosomiasis. The treatment gap remaining for each disease in the first seven countries and targeted in the upcoming years can be appreciated in Figure A5-2.

Training/ national capacity building

At the heart of all PCT programs is the community that is affected by NTDs. Training is designed to empower these communities to treat NTDs within their

TABLE A5-6 Number of Tablets of Donated Drugs Provided* to National NTD Programs in Year 3 of the NTD Control Program

Country	ALB	IVM	PZQ	DEC	Zithromax†	MBD	Tetracycline (tubes)‡	Total Tablets§
Burkina Faso	11,862,300	33,913,000			8,553,600		158,642	54,487,542
Ghana	8,753,500	28,633,500	9,724,000		53,280	3,615,000		50,779,280
Haiti	6,933,600			22,300,000				29,233,600
Mali	4,976,900	14,494,500	3,000,000		8,972,640		198,904	31,642,944
Niger	8,465,000	22,128,500	5,498,500		11,509,920		200,000	47,801,920
Sierra Leone	4,500,000	16,716,850	3,000,000			3,797,498		28,014,348
South Sudan	324,500	9,215,000	3,000,000		505,440		2,400	13,047,340
Uganda	13,947,700	30,286,000			5,598,720	7,000,000		56,832,420
TOTAL	59,763,500	155,387,350	24,222,500	22,300,000	35,193,600	14,412,498	559,946	311,839,394[T•]

* Becase donated drugs are provided to the countries in the year prior to their distribution, the number of drugs delivered (e.g., here in year 3) will not equal the number of treatments provided in the same year. Of the provided drugs, essentially all are utilized for treating the NTDs according to the national strategies (indicated in Table A5-2) and with coverage effectiveness approximated in Table A5-7. Any drugs unused in one year are applied to the requirements for treatment in the following year. NTD = neglected tropical disease; ALB = albendazole; IVM = ivermectin; PZQ = praziquantel; DEC = diethylcarbamazine; MBD = mebendazole.

† In addition, 629,616 bottles of pediatric oral suspension (~3 pediatric doses per bottle) were provided.

‡ Tetracycline ointment tubes are used at the rate of 2 tubes per child for a 6-week course of treatment.

§ Does not include bottles of Zithromax pediatric oral suspension or tubes of tetracycline ointment.

TABLE A5-7 Programmatic Coverage in NTD Control Program Countries*

NTD Control Program	Country	Year 1	Year 2	Year 3
Fast-track countries	Burkina Faso	82-86	79-97	89-100†
	Ghana	78-88		71-92
	Mali	69-100†	58-88	85-89
	Niger	91-99	73-88	78-93
	Uganda		57-97	62-97
Additional countries	Haiti			100**
	Sierra Leone			82-93

* Presented as a range across the different drug packages used in each country.

† 100% values likely reflect incomplete census counts of the targeted population.

own populations. The NTD Control Program has supported the training of over 220,000 persons during its first three years, with the most being community-based health workers/drug distributors (Figure A5-3). Working at levels from the central ministries to the communities, a cascade of training has been facilitated to support social mobilization, community outreach, supply chain organization and management, and technical implementation of PCT. The fundamental content of training courses and refresher training is similar for most programs, but local needs dictate local training and organizational strategies.

NTD control program expenditures

Analysis of expenditures during the first three years shows that the program fulfilled its mandate that at least 80% of program funds be spent on country program implementation. During the first three years, the program received $40,728,320 in funding. Program expenditures by the end of year 3 were $37.9 ($2.8 million remaining to be spent), with 81.3% expended for country program activities and purchase of essential drugs and with 18.7% used for overall management of the program (its grants, monitoring and evaluation, reporting, documentation of best practices, technical and representational meetings, and advocacy activities).

The breakdown of program expenditures reflects the diverse set of activities that must be supported to enable treatment of persons at the community level. Of the 81.3% of funds going directly for country program activities and supplies (Figure A5-4), the largest portion (28%) was spent on the MDAs themselves, including for social mobilization, drug distribution and personnel supervision.

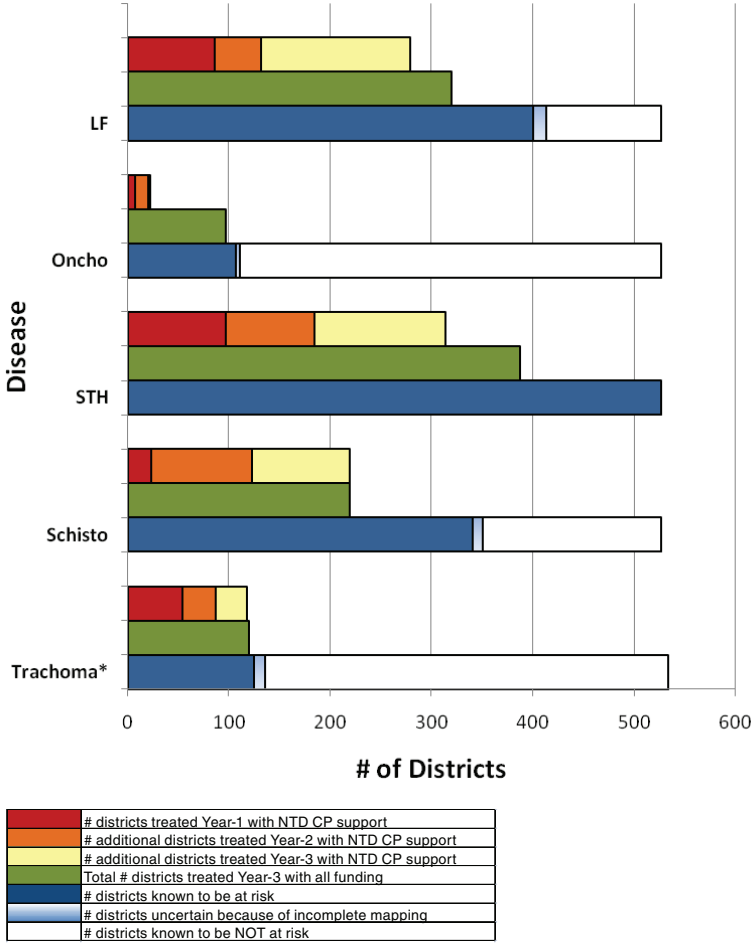

FIGURE A5-2 Number of districts covered by mass drug administration (MDA) treatment during the first three years of the Neglected Tropical Disease (NTD) Control Program in the seven implementing countries (an aggregated total of 526 districts in these countries). For each of the diseases targeted, the bottom bar depicts the number of districts known to be at risk (dark blue bar), the number known not to be at risk (white bar), and those where uncertainty remains because of incomplete mapping (light blue bar). For each of the diseases, the top bar represents the number of districts implementing MDA with the United States Agency for International Development NTD Control Program support (the red bars indicate the number supported in the first year, the orange bar indicates the additional numbers supported in the second year, and the yellow bar indicates the additional supported in the third year). For each disease, the middle bar (green) indicates the total number of districts receiving MDA treatment supported by any funding source. LF = lymphatic filariasis; Oncho = onchocerciasis; STH = soil-transmitted helminths; Schisto = schistosomiasis. *Ghana interrupted transmission of trachoma during year 2 and therefore did not require treatment in year 3.

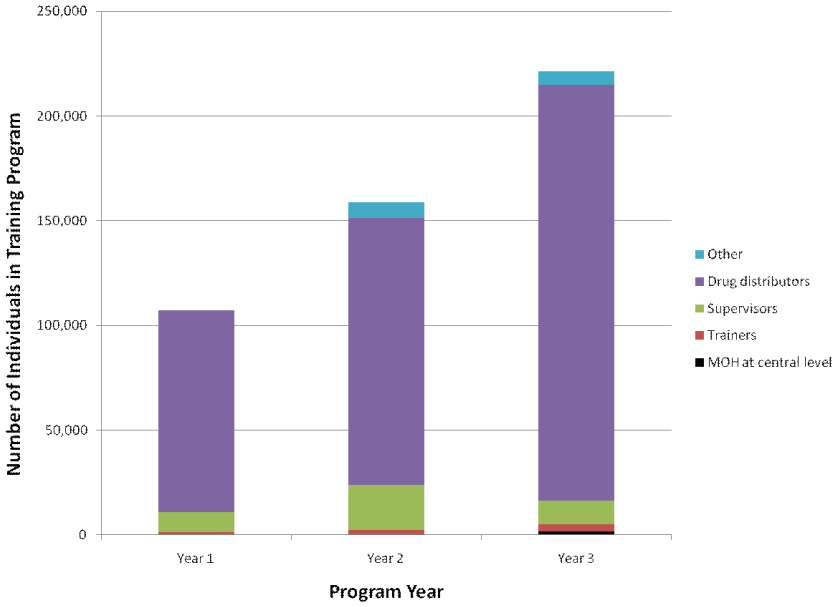

FIGURE A5-3 Number of workers in training programs supported by the Neglected Tropical Disease Control Program. For each of the first three years of the program, the number of persons receiving different types of training are recorded (black indicates training for central-level Ministry of Health [MOH], orange indicates training for trainers, green indicates training for supervisors, purple indicates training for drug distributers, and blue indicates training for others).

Almost equal portions (19-22%) went to drug procurement, capacity building, and country-led management and program monitoring. The remaining 11% was required for the initial mapping to define disease distribution.

Although not yet specifically documented for this program, it should be noted that previous costing studies of programs to control one or more NTDs have shown that in addition to the external support received by disease-endemic countries, the national ministries contribute approximately an equal level of resources in staff salaries and in-kind resources to achieve success (Goldman et al., 2007).

Discussion

The whole concept of program integration is, undeniably, complex and involves, as described by some (Grépin and Reich, 2008), not only the multiple domains of policy, activity and organizational structure, but also multiple levels of integration intensity: coordination, collaboration, and consolidation. To others,

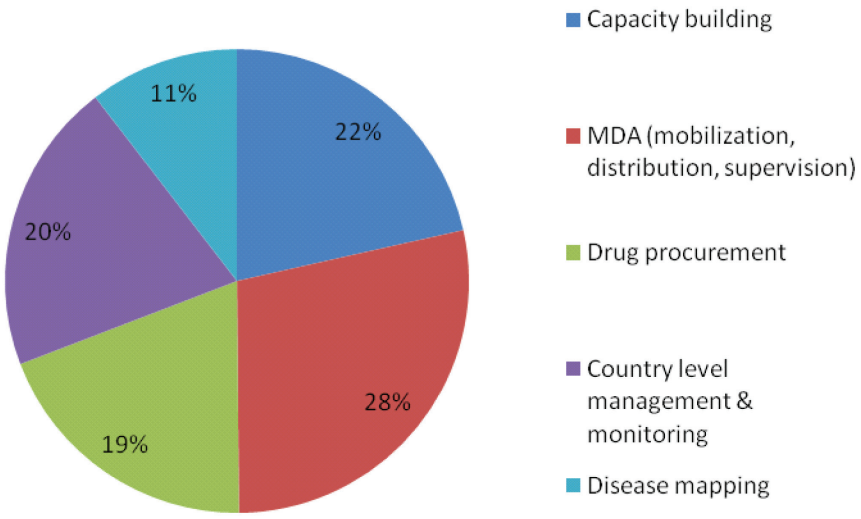

FIGURE A5-4 Distribution of expenditures by the Neglected Tropical Disease Control Program during its first three years. Of the $30.82 million expended on country program implementation during the first 3 years, 22% (dark blue) was spent on capacity building, 28% (red) on mass drug administrations (MDAs) (mobilization, distribution, and supervision), 19% (green) on procurement of non-donated drugs, 20% (purple) on country-level management and monitoring, and 11% (light blue) on disease mapping.

however, integration is more an attitude than a formula – a focus on trying always to find ways to carry out multiple activities with the most efficient and cost-effective use of available resources. From either perspective, the arguments for integrating control programs that target the NTDs remain strong: the populations affected are much the same, the strategic approach (preventive chemotherapy) is essentially identical and the drugs for implementing programs are largely donated, readily available, highly safe and effective. Furthermore, opportunities to embed, or integrate NTD control activities within school-health programs and through other platforms of health service delivery offer the promise of greater efficiency, long-term sustainability and national capacity strengthening.

Early pilot studies confirmed the general feasibility of successful integration of NTD control efforts (Garba et al., 2009; Lammie et al., 2006; Richards et al., 2006), but two major questions have remained. 1) Can the integrated NTD control activities effective in pilot studies be successfully expanded to programs at full national scale? 2) Which elements of individual NTD programs are most successfully integrated and how are they best implemented? The findings in this

present report address the first question, showing clearly that integration of multiple disease-specific NTD control programs can be successfully implemented at full national scale. Assessment and analyses addressing the second question to define the most effective and cost efficient ways of integrating specific program activities are still underway.

From the data in Figure A5-1, it is clear that funds from the USAID support of the NTD Control Program have been effective in facilitating national programs to support, organize, implement, and monitor integrated, formerly disease-specific programs targeting WHO's five 'tool-ready' NTDs (WHO, 2006). In the 7 study countries receiving support during the program's first three years, progressive scaling up resulted in an additional 16 million persons receiving appropriate PCT in the first year, 27 million in the second year, and 55 million in the third year, for a cumulative total of more than 98 million persons reached in three years and quite clearly proving the feasibility for integrated NTD programs to be carried out at full national scale.

Introduction of this funding also effected a major qualitative change in national programs targeting the NTDs. Even though in the year prior to the NTD Control Program, up to 33 million people had received treatment of NTDs in disease-specific programs in the target countries, these national programs were constantly challenged to identify funds, most often on a yearly basis, to support their program activities. With the NTD Control Program, a secure funding source was established, so that these national programs not only could achieve broader disease control in their populations but also could undertake proper planning to address their NTD problems more effectively and cost efficiently.

Different from single-disease programs where each person reached equals one treatment given, in the integrated programs each person reached receives a drug 'package' usually containing more than one drug. Therefore, the metric 'treatments delivered', the number of times a single drug dose is administered, had to be developed to record this programmatic achievement. More than 222 million treatments were provided by national programs during the first three years of the NTD Control Program. It can be predicted with certainty, based on recent studies assessing the impact of disease-specific NTD programs (Chu et al., 2010; Ottesen et al., 2008), that when the program assesses the health benefits from these treatments after 3-5 years of treatment, its impact on personal, societal, and economic well-being will be seen to be enormous.

What even these numbers by themselves fail to impart, however, is an understanding of the magnitude and importance of the public-private partnership between specific pharmaceutical companies and the public sector. It has been the donation of extraordinary amounts of drugs (by GlaxoSmithKline, Johnson & Johnson, Merck & Co., Inc., and Pfizer) that has made possible the successes of these global efforts to control or eliminate the NTDs. In addition, although the drug manufacturers have without question provided most of drugs used in this program, the generic drugs needed for schistosomiasis and STH control and

for LF elimination in countries outside of Africa have also been obtained and provided to national programs in the NTD Control Program by a number of governmental and nongovernmental partner organizations, including the Department for International Development (United Kingdon), the United Nations Children's Fund, University of Notre Dame, WHO, the World Food Program, and World Vision.

In addition to its role in facilitating integrated national MDA programs to provide treatments for their at-risk populations, the NTD Control Program has, of necessity, supported countries in mapping the distribution of infection and developing, in collaboration with WHO, action plans that will enable them to begin or expand implementation of drug delivery in the coming years. Already the empirical experience gained from three years of program activities in the first seven implementing countries has contributed appreciably to the development of new guidelines, norms and regionalized strategies that will facilitate and accelerate program activities in the many countries still needing to begin their integrated NTD control programs.

Major challenges still lie ahead for creating integrated programs targeting NTD control or elimination, not the least of which is the large number of countries requiring these programs. Such a need provides political challenges not just for the national governments which must commit their limited resources and energy to the programs, but also for the bilateral donors to support these national commitments, the drug manufacturers to sustain their long-term pledges, and the various implementing partners necessary to support national programs to carry out their integrated NTD implementation strategies.

In addition to these political challenges, technical challenges also remain, the very first being definition of the geographic scope of each of the NTDs. Mapping the infections must be completed, not just to identify prevalence, but, even more importantly, to define exactly what action must be taken at which level of prevalence and in which geographic area for each of the NTDs. Then, once it is determined what action is required for each of the NTDs, the treatment gaps for specific diseases (*e.g.,* schistosomiasis [Figure A5-2]) must be addressed and the efficiencies of integration (in terms of both cost and impact) identified and quantified so that cost-efficient integrated programs can be established. It does, of course, remain absolutely essential that the specific goals of each individual program being integrated be met, including those program targets that are not MDA-dependent, such as morbidity control (surgical and otherwise) for LF and trachoma, and the water and sanitation goals of the schistosomiasis, STH, and trachoma programs. Sacrificing a program's goals simply for the sake of integration is totally inappropriate. Thus, the elimination targets for LF and blinding trachoma by 2020 (Gustavsen et al., 2009; Knirsch, 2007) must be kept, and for onchocerciasis in the Americas and selected foci in Africa, the elimination targets must also be respected (Diawara et al., 2009; Sauerbrey, 2008).

In just three years, the NTD Control Program has exceeded program expecta-

tions that had been based on previous pilot program activities. This achievement demonstrates not only the feasibility of going to national scale with an integrated approach but also that efficiencies can be achieved through integration. These efficiencies come, in large part, from removing duplication in the operations of specialized disease programs as co-implementation is introduced. They also stem from the ability of the NTD programs to implement PCT through community networks, schools and existing health service delivery platforms, such as child health days. Going forward, even greater gains may accrue as opportunities are pursued strategically to leverage or complement other development-sector efforts, such as water and sanitation improvements, or other health-sector inputs, such as malaria control activities. This type of integration of NTD control within development efforts and on existing health-service delivery platforms holds promise for even greater program efficiency and its positive impact on strengthening national health systems. Although it is clear that not all integrated NTD program activities will have such health system strengthening effects (Utzinger et al., 2009), it is also clear that many of these integrated program activities can very definitely build stronger systems for delivering healthcare and disease prevention to these most underserved populations in NTD-endemic countries (Gyapong et al., 2010).

Although the creation of integrated NTD control programs has brought with it a wide range of political and technical challenges whose importance should not be underestimated (Utzinger et al., 2009), there can be little question but that today's increased attentiveness and support for NTD control provide important opportunities to advance the health of the world's neediest populations towards global health equity in ways never before possible. This current experience of the USAID NTD Control Program has proven already that an integrated approach to these diseases is feasible at full national scale. What still remains now is to draw further on the experiences of this young program to define those elements of disease-specific program integration that can yield the greatest benefits, cost-effectively and cost-efficiently. There appears to be no reason why such integrated NTD programs, following general WHO guidelines and the accumulating experience of a growing number of countries, cannot be replicated in all places where they are needed, so long as necessary political commitment and support can be maintained.

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A6

NEGLECTED TROPICAL DISEASES (NTDs) SLATED FOR ELIMINATION AND ERADICATION

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The Carter Center

More than any of our forebears, our current generation has seen an unprecedented confluence of increased awareness about the needs of neglected populations, thanks to modern communications, modern science's discovery of powerful new tools to help address the terror of neglected diseases, and awesome generosity in cash and in kind to bring those new tools and some old ones to bear on a grand scale, thanks to recent philanthropy and engagement of related industries.

First, some essential definitions: *Eradication* means reducing the incidence of a disease to zero worldwide, such that further control measures are unnecessary. It means total interruption of transmission. Certification of eradication comes later, after a specified period with no cases and adequate surveillance. Eradication will always be a rare phenomenon. *Elimination* should mean stopping transmission of a disease in a limited geographic area, although control measures may still be necessary to combat or prevent reintroduction of the disease from somewhere else. It can also mean reducing manifestations of a disease, such as blinding due to trachoma, to zero. *Control* means reducing incidence or prevalence of a disease, but control measures are still necessary because transmission continues (CDC, 1993).

The World Health Organization (WHO) has established a list of 17 "official" neglected tropical diseases (NTDs): Buruli ulcer, Chagas disease, cysticercosis, dengue, dracunculiasis, echinococcosis, endemic treponematoses, foodborne trematode infections, human African trypanosomiasis, leishmaniasis, leprosy, lymphatic filariasis, onchocerciasis, rabies, schistosomiasis, soil-transmitted helminthiases, and trachoma (WHO, 2010a). Grouping these diseases in one package has been a very effective way to bring attention to these often overlooked causes of much misery. The 17 diseases were chosen because of their adverse impact, relative obscurity, and the availability of tools to combat them.

WHO is the only international body that can legally declare a disease eradi-

cated or eliminated, and WHO's governing body, the World Health Assembly (WHA), or one of the Regional Committees of WHO can officially sanction targeting of a disease for eradication or elimination. Of the 17 NTDs, 1 has been targeted for eradication and 8 have been targeted for elimination by WHO or by a WHO Regional Committee (WHO, 2010a):

- Dracunculiasis (Guinea worm disease) is targeted for eradication.
- Onchocerciasis (river blindness) is targeted for elimination (interrupting transmission) of the parasite in the Americas.
- Lymphatic filariasis is targeted for elimination as a public health problem.
- Trachoma is targeted for elimination of blinding trachoma.
- Leprosy is targeted for elimination as a public health problem.
- Chagas disease is targeted for control and elimination in the Americas.
- Visceral leishmaniasis (kala-azar) is targeted for elimination in Southeast Asia.
- Yaws (an endemic treponematosis) is targeted for elimination in Southeast Asia.
- Human African trypanosomiasis is targeted for elimination as a public health problem.

My more complete thoughts on this aspect of today's topic are spelled out in an article published in *Global Health* magazine in 2009, urging quantitative targets and more precise use of the term "elimination" (Hopkins, 2009). A Senegalese proverb comes to mind when I think of how "elimination" is often invoked so loosely. According to the proverb, "You can hold a log under water as long as you like; it will not turn into a crocodile."

I focus here on four of the NTDs that are targeted for eradication or regional elimination: dracunculiasis, onchocerciasis, lymphatic filariasis, and trachoma, in that order. To varying degrees, progress is being made against each disease.

Dracunculiasis

Dracunculiasis is a painful parasitic infection that people get by drinking contaminated water. The 2- to 3-feet-long (1-meter-long) worms emerge directly through the skin a year later, when they are seeking to deposit hundreds of thousands of larvae back into the water to continue the cycle. People are crippled temporarily for weeks, with severe impact on agricultural productivity and school attendance. There is no cure or vaccine, there is no animal reservoir of the human infection, and recovered patients are not immune to future infection. It can be prevented by teaching people to always filter their drinking water, by not allowing people with emerging worms to enter a water source, by applying ABATE® Larvicide, or by providing safe water from borehole wells, for example (Ruiz-Tiben and Hopkins, 2008). In addition to the severe constraint of a one-year-long

incubation period, *Dracunculus medinensis* has a serious reproductive potential that can magnify the penalty for a missed case: documented surprise explosions of 58, 85, and 91 cases occurred in three separate incidents one year after a single undetected imported case contaminated a village water supply.

The Carter Center has led this eradication campaign since 1986, in close coordination with the endemic countries, the Centers for Disease Control and Prevention (CDC), the United Nations Children's Fund, and WHO. This program has benefited from many very generous donors, including Dupont Coporation, which donated nylon filter material; American Cyanamid (now BASF), which donates ABATE; the Bill & Melinda Gates Foundation and the Conrad N. Hilton Foundation, the U.S. Agency for International Development, and many other bilateral donors, including the federal government of Nigeria; the U.S. Peace Corps volunteers, and other foreign volunteers from Japan, Canada, and a few other nations; and national service volunteers in Ghana and Nigeria.

Tens of thousands of grassroots village volunteers are the bedrock of the Guinea Worm Eradication Program. They were the first to show the utility of village volunteers in Africa as the basis for a surveillance network that provides reliable monthly village-based reports of a disease. They also help educate their neighbors about how to prevent Guinea worm disease, and they distribute cloth filters. In addition to benefiting from the work of former U.S. President Jimmy Carter, the Guinea Worm Eradication Program has benefited from exceptionally strong participation by a former head of state of Ghana, Flt. Lt. Jerry Rawlings, President Amadou Toumani Toure of Mali, and Nigerian former head of state General (Dr.) Yakubu Gowon.

What are the results? As shown in Figure A6-1, as of 2009 we were down to less than 3,200 cases, from an estimated 3.5 million cases in 1986, with 645 endemic villages compared to more than 23,000 villages, and down to 4 countries, all in Africa, instead of 20 countries on two continents. The program will probably report less than 2,000 cases worldwide in 2010, and 1, 2, or 3 of the 4 remaining endemic countries may interrupt or have already interrupted Guinea worm transmission in 2010 (Hopkins et al., 2010; WHO, 2010b).

The final battleground is Southern Sudan, which reported 86 percent of all cases in 2009 and 97 percent so far this year, and which is also approaching a crucial referendum in January 2011 to determine whether it will remain a part of Sudan or separate to form a new nation. Since the Comprehensive Peace Agreement was signed in January 2005 to end the 22-year-long civil war, the Southern Sudan Guinea Worm Eradication Program has made good progress despite the many challenges of large area, little infrastructure, low literacy, and sporadic insecurity that disrupted program operations 32 times in different places in 2009, for example. It has an excellent national program coordinator. We are now aiming to stop transmission in Southern Sudan by the end of 2012, political and security conditions permitting. WHO has certified 187 countries as free of dracunculiasis (Hopkins et al., 2010; WHO, 2010b).

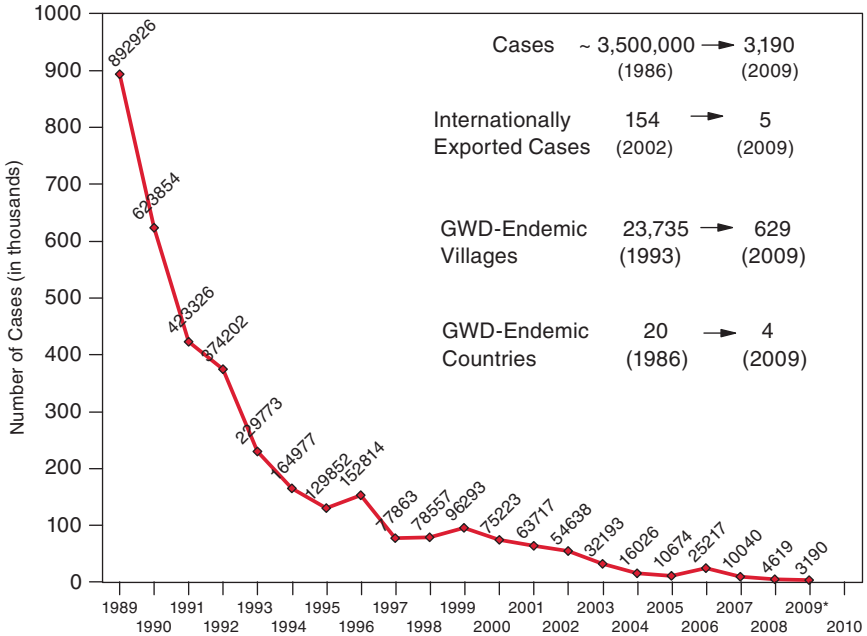

FIGURE A6-1 Number of reported cases of dracunculiasis by year: 1989–2009. SOURCE: The Carter Center.

The global Guinea Worm Eradication Program (GWEP) has progressed over the past 30 years thanks to five key benchmarks: (1) from the outset it had a clear goal; (2) it identified all of the endemic countries; (3) it established effective village-based, active surveillance; (4) it extended interventions throughout the endemic areas; and (5) it monitors and responds to reports of cases and the status of interventions on a monthly basis. When the GWEP succeeds, it will set a precedent as the first parasitic disease of humans to be eradicated, and as the first disease to be eradicated without a vaccine or curative treatment. The GWEP is important evidence of the potential power of health education and community mobilization. Its legacy in endemic areas will include improved health, more productive agriculture, and better school attendance, as well as experienced health workers and village volunteers and changed attitudes.

Onchocerciasis

Onchocerciasis is a potentially blinding parasitic infection spread by repeated bites of black flies, which breed in fast-flowing rivers, rapids, or dams. Increased construction of dams may be increasing suitable habitat for some vector black flies in Africa. Of an estimated 123 million persons at risk in 37 countries, mostly

in Africa, some 37 million persons are actually infected. About a half million people are at risk in six countries in the Americas, and a few thousand in Yemen. The infection may also cause severe itching, but it can be treated or prevented by annual doses of Mectizan® (ivermectin). Because treatment with Mectizan only kills the immature microfilariae and not the adult worms, annual treatments must continue for at least a decade until the adult worms die out. Merck & Company, Inc. set an incredible precedent in 1987, when it announced that it would make its newly discovered Mectizan available to treat populations in poor countries affected by onchocerciasis free of charge, in whatever amounts were needed, for as long as necessary. Three regional programs have waged war on this disease—two in Africa and one in the Americas (Cupp et al., 2010).

In the Americas, the River Blindness Foundation (RBF) launched the Onchocerciasis Elimination Program for the Americas (OEPA) in 1993 in association with CDC, the Pan American Health Organization, and the ministries of health of the six affected countries: Brazil, Colombia, Ecuador, Guatemala, Mexico, and Venezuela. When RBF founder John Moores became a member of the Carter Center's board of trustees, the RBF was absorbed into the Carter Center in 1996 and the Carter Center became OEPA's sponsoring body, providing funding and technical support to assist the national programs. The OEPA strategy is for the national programs to provide mass treatment with Mectizan at least twice per year with a minimum coverage of 85 percent of the eligible population. (Since 2003, some highly endemic communities in Mexico have been treated four times per year.) With one exception, the species of black fly vectors in the Americas are not as efficient transmitters of onchocerciasis as the vectors in Africa, which is part of what makes elimination more feasible in the Americas. The current goal is to stop transmission of onchocerciasis in the Americas by 2012 (WHO, 2010c).

The impact achieved so far in the Americas is summarized in Table A6-1. Two of the six countries (Colombia and Ecuador) and 8 of the 13 endemic foci have interrupted transmission, and two other countries (Guatemala and Mexico) are on the verge of stopping transmission. The main remaining challenge is the small binational focus in the Amazon among the Yanomami population that straddles the border between Brazil and Venezuela. In 2009, the Brazilian side of this focus surpassed the 85 percent coverage goal for the eighth consecutive year, while the Venezuela side achieved the coverage goal for the third consecutive year. So far, Merck's donation accounts for 44 percent of the cumulative expense of this initiative, while the six countries themselves have provided 37 percent, which is a big contrast to the endemic countries in Africa.

The Onchocerciasis Control Program (OCP), which was sponsored by WHO, the World Bank, and others, covered 11 West African countries from 1974 to 2002 and was the first regional African program against onchocerciasis. Using a strategy of vector control that involved aerial spraying of rivers with insecticides to prevent breeding of black flies, to which annual mass drug administration (MDA) of Mectizan was added when that became available in 1987, this program

TABLE A6-1 Current Situation of Ocular Morbidity and Transmission of Onchocerciasis Within the Americas Region, 2010

Focus	Has Blindness Been Eliminated?	Has Ocular Morbidity Disappeared?	Transmission Status
Santa Rosa, GU	Yes	Yes	Eliminated in 2010
Lopez de Micay, CO	Yes	Yes	Interrupted in 2007
Escuintla, GU	Yes	Yes	Eliminated in 2010
North Chiapas, MX	Yes	Yes	Eliminated in 2010
Huehuetenango, GU	Yes	Yes	Interrupted in 2008
Oaxaca, MX	Yes	Yes	Interrupted in 2008
Esmeraldas, EC	Yes	Yes	Interrupted in 2010
Northcentral, VZ	Yes	Yes	Interrupted in 2010
South Chiapas, MX	Yes	Yes	Suspected suppressed
Central, GU	Yes	Yes	Suspected suppressed
Northeast, VZ	Yes	No (1.0%)	Ongoing
Amazonas, BR	Yes	No (6.5%)	Ongoing
South, VZ	Yes	No (16.3%)	Ongoing

SOURCE: The Carter Center.

completely eliminated transmission of onchocerciasis in most of the vast area, except for a few areas of Ghana, Côte d'Ivoire, and Sierra Leone. The OCP proved that vector control could eliminate onchocerciasis in much of West Africa, but this approach was expensive, and vector control was not as feasible in forested endemic areas. Fortunately, MDA with Mectizan is feasible in forested endemic areas, and that is what began to happen after Merck's discovery became available (Cupp et al., 2010).

The African Program for Onchocerciasis Control (APOC), sponsored by WHO and the World Bank with intimate involvement of several international nongovernmental organizations, embraces 19 endemic countries in Africa. It was officially launched in December 1995 and is scheduled to end in 2015. It aims to help constituent countries develop sustainable systems to administer Mectizan annually to at least 65 percent of the eligible population in areas where onchocerciasis was found to be hyperendemic or mesoendemic. This program pioneered the development of "community-directed treatment with ivermectin" (CDTI) using village volunteers selected by the community to distribute Mectizan at locations and times determined by the community. APOC has an ultimate treatment goal (UTG) of about 90 million persons. In 2008, it treated 57 million people, or 63 percent of the total UTG, in 15 of the 19 countries. The prevalence of onchocerciasis was reduced from 46.5 percent in 1995 to 28.5 percent in 2008 (WHO, 2010d). However, studies conducted by the Carter Center in Cameroon and Nigeria have shown that transmission of the parasite persists after 11 years of annual MDA with Mectizan (Katabarwa et al., 2008), that transmission continues in some untreated hypoendemic areas (Katabarwa et al., 2010), and that the

annual MDA with Mectizan is not yet sustainable by several endemic countries without continued external support (Rakers et al., 2009).

In 2002, WHO and the Carter Center co-hosted a Conference on the Eradicability of Onchocerciasis, which concluded that onchocerciasis could not be eliminated in Africa with current tools, but could be eliminated in the Americas. The conference recommended continued research and elimination where possible in certain vulnerable foci in Africa and Yemen, and it underscored the potentially game-changing value of a macrofilaricide to kill the adult worms (Carter Center and WHO, 2002). However, APOC has recently shown that annual or twice per year MDA with Mectizan alone for 15–17 years eliminated onchocerciasis transmission in some hyperendemic foci in Mali and Senegal (Diawara et al., 2009). In 2006, Sudan launched an effort to eliminate onchocerciasis in an isolated focus at Abu Hamad north of Khartoum, and in the next year Uganda launched a nationwide onchocerciasis elimination program, both using twice per year MDA with Mectizan at a desired minimal coverage level of 90 percent, and with technical assistance provided by the Carter Center (Ndyomugyenyi et al., 2007). Uganda's bold decision followed on the heels of its successful elimination of Guinea worm disease, and it had already eliminated onchocerciasis in two foci using focal larviciding and annual MDA with Mectizan. The new offensive by the Government of Uganda takes aim first at 6 more of the 18 endemic foci in the country. Yemen is also conducting MDA twice per year, with the aim of stopping transmission in that relatively minor focus. Unfortunately, Mectizan cannot be used safely in all areas in 10 of the 30 onchocerciasis-endemic African countries where *Loa loa* infections also occur, because of potentially fatal neurological complications.

So onchocerciasis has been eliminated by using vector control and later MDA with Mectizan in most of the OCP area of West Africa. MDA with Mectizan twice or once per year is eliminating transmission in the Americas, and probably in Yemen and perhaps in some parts of the APOC project area. But some endemic areas of countries included in APOC remain inaccessible because of conflict or co-endemic *Loa loa*, or because onchocerciasis is only hypo-endemic and thus not eligible for MDA under APOC. So far, annual MDA with Mectizan alone has not yet been shown to stop transmission in many APOC areas that have had MDA with Mectizan for more than a decade (Katabarwa et al., 2008). Sustaining annual MDA with Mectizan in Africa indefinitely is a daunting prospect (Hopkins et al., 2005). We really need a macrofilaricide to speed interruption of onchocerciasis transmission, and we need a strategy for stopping transmission of onchocerciasis in areas where there is *Loa loa*. Meanwhile, the effort to eliminate lymphatic filariasis is providing some additional help against onchocerciasis.

Lymphatic Filariasis (LF)

Lymphatic filariasis (LF) is a parasitic infection, spread by repeated bites of mosquitoes, that causes extreme swelling of the limbs and genitalia. Of the 1.3

billion people at risk in about 81 countries in Africa, Asia, and the Americas, an estimated 120 million are infected. This disfiguring chronic disease can be prevented by annual MDA with diethylcarbamazine (DEC) and albendazole, or in Africa (where DEC causes unacceptable side effects) with Mectizan and albendazole combined. MDA must continue for at least five to six years until the adult worms that cause LF die. Surgery can reduce disabling hydroceles in men, and palliative care can mitigate secondary infections and swelling of some limbs, thereby also improving people's emotional and social health (Bockarie and Molyneux, 2009).

In a landmark partnership, Merck, which produces Mectizan, and GlaxoSmithKline, which produces albendazole, have both agreed to donate their respective drugs for MDA to help eliminate LF in Africa (Gustavsen et al., 2009). As wonderfully positive secondary effects, both drugs also have deworming qualities against certain intestinal helminths such as *Ascaris* and *Trichuris*, with consequent positive tertiary effects on children's growth, development, nutrition, and cognition. To date, Merck estimates that it has donated 2.5 billion Mectizan tablets for onchocerciasis and LF treatments, with a value of US$3.75 billion (Merck & Company, 2009). GlaxoSmithKline has donated approximately 1.5 billion albendazole treatments to 50 countries, at a value of about $67.5 million. In China, addition of DEC to table salt has been the main tool used to stop LF transmission nationwide.

The International Task Force for Disease Eradication (ITFDE) was the first international body to suggest that LF was potentially eradicable, in a report published in 1993 (CDC, 1993). Soon after WHA adopted the resolution in 1997 calling for LF elimination "as a public health problem," the Global Alliance to Eliminate Lymphatic Filariasis was established in 2000 to help endemic countries achieve annual MDA with the appropriate drugs, aiming for a minimum coverage of 80 percent. Annual treatments to prevent LF have risen from 10 million in 2000 to 385 million, or 29 percent of the population at risk in 53 of the 71 MDA-eligible countries. Thirteen countries have not yet completed mapping for LF as of 2009 (WHO, 2010e). Elimination of LF is progressing, but it needs to be accelerated in order to reach its goal by 2020.

With Carter Center assistance, two Nigerian states have pioneered integrated health education and MDA for onchcocerciasis, LF, and schistosomiasis since 2000 (Njepuome et al., 2009). I believe APOC and the new war on LF should have joined forces immediately to take advantage of synergies. LF is more widespread than onchocerciasis in Africa and so MDA with Mectizan and albendazole for LF not only covers additional villages where onchocerciasis is hypo-endemic and was not being treated, it also adds a second antihelminthic, albendazole, in all onchocerciasis-endemic areas. It is hoped that combined MDA with Mectizan and albendazole for LF will have an enhanced impact on adult onchocercal parasites. Both drugs are contraindicated for mass drug administration in *Loa loa* areas, but bednets can be used there instead to block transmission of LF and malaria. Other

studies in Nigeria by Blackburn et al. (2006) and other colleagues at CDC and the Carter Center have demonstrated the efficacy of using community-based distributors of Mectizan to also distribute bednets. Thus, scaling up integrated MDA and mass distribution of long-lasting insecticidal nets in Africa by mobilizing CDTI-type volunteers could help control or eliminate malaria, LF, onchocerciasis, and schistosomiasis, with significant collateral impact on soil-transmitted helminths. We have the tools and knowledge to do this now; two states in Nigeria are doing it already.

Before turning to trachoma, I want to highlight another initiative proposed by the ITFDE, which is the elimination of LF and malaria from the island of Hispaniola. This island, comprising the Dominican Republic and Haiti, is the main remaining focus of lymphatic filariasis in the Western Hemisphere and the only Caribbean island that is still endemic for malaria (Figure A6-2). It is a source of exported malaria to neighboring countries, including Jamaica, the Bahamas, and the United States. After a 1.5 year-long collaborative project to combat malaria in two adjacent communities on their shared border, in October 2009 the two countries announced a jointly prepared plan to eliminate malaria from the island by 2020 at an estimated cost of $194 million, while Haiti announced a plan to escalate its existing efforts and also eliminate LF by 2020 at a cost of about $49 million. The Dominican Republic expects to stop transmission of LF in 2010. These are expensive plans, but they are put in perspective by knowledge that a single

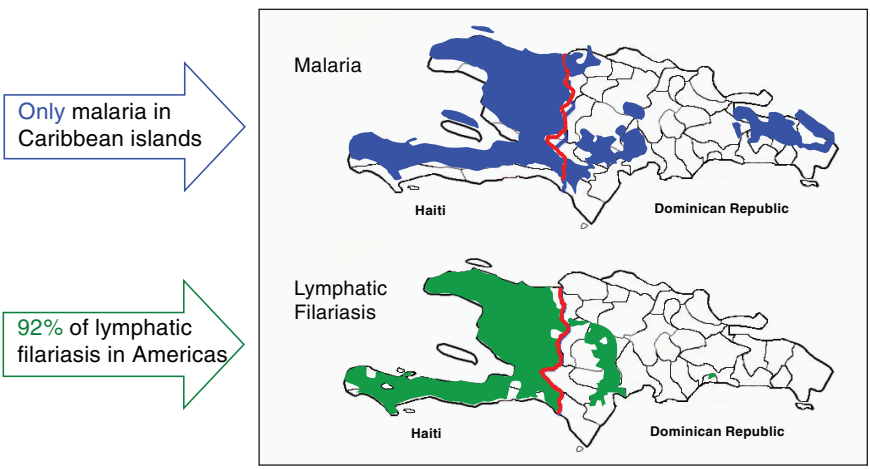

FIGURE A6-2 Geographic distribution of malaria and lymphatic filariasis on the island of Hispaniola in 2006.
SOURCE: The Carter Center.

outbreak of malaria in 2004 cost the Dominican Republic an estimated $200 million in lost tourism revenues alone, apart from loss of life and productivity.

Trachoma

Trachoma is a blinding bacterial infection that is spread by contaminated hands, cloths, and flies. An estimated 540 million persons were at risk and 84 million infected in about 57 countries in 1998, when WHA established a target to eliminate blinding trachoma (not all infections, and not the bacterium) by 2020 (WHO, 2010a). The "SAFE Strategy" for combatting trachoma consists of (S) surgery to prevent progression to blindness, (A) antibiotic administration to treat active infections and prevent spread, (F) facial cleanliness, and (E) environmental improvement, including access to clean water and building household latrines to suppress breeding of vector flies in human feces deposited on the ground. The minimal coverage target for antibiotic administration is 80 percent. The quantified goals are to reduce scarring trachoma, or trichiasis, to less than 1 case per 1,000 population and reduce active trachoma below 5 percent in 1–9-year-old children. Further recommendations for assessing these targets were considered recently at the third Global Scientific Meeting on Trachoma that was convened by WHO in July 2010. Like the three other elimination and eradication efforts considered here, the trachoma program also has significant ancillary benefits, due to improved personal hygiene, expanded use of household latrines, and advocacy for clean water. An explosion of latrine building is under way in the Amhara Region of Ethiopia (Ngondi et al., 2010) as a result of the trachoma program, totaling almost 1.8 million latrines since 2002. Wider use of latrines also prevents other diseases besides trachoma.

Pfizer has donated Zithromax® for use in this mass campaign with a cumulative total of 160 million treatments between 1999 and 2009. As of 2009, this program was reaching about 40 million (33 percent) of the 120 million people thought to be at risk, but the full extent of the problem is not clear. At least eight countries, including Morocco and Ghana, have reduced key indices below prevalence thresholds established by WHO. Overall, the number of countries where trachoma is endemic has been reduced from 57 to somewhere between 38 and 49, the estimated population at risk from 540 million to 120 million, and the number of persons with active disease from 84 million to about 41 million between 1998 and 2009 (Mariotti et al., 2009; WHO, 2010a). It is believed that probably only 10 countries contain 75 percent of the problem. Ethiopia, perhaps the most severely affected country, has begun an aggressive campaign in its worst affected region, Amhara, but needs to extend those efforts nationwide.

But much more remains to be done. Figure A6-3 illustrates the principle that it is best to start intervening in the most highly endemic countries first, because they will take longer to be brought under control. The ITFDE, which I chair, reviewed the status of the global effort to eliminate blinding trachoma by 2020

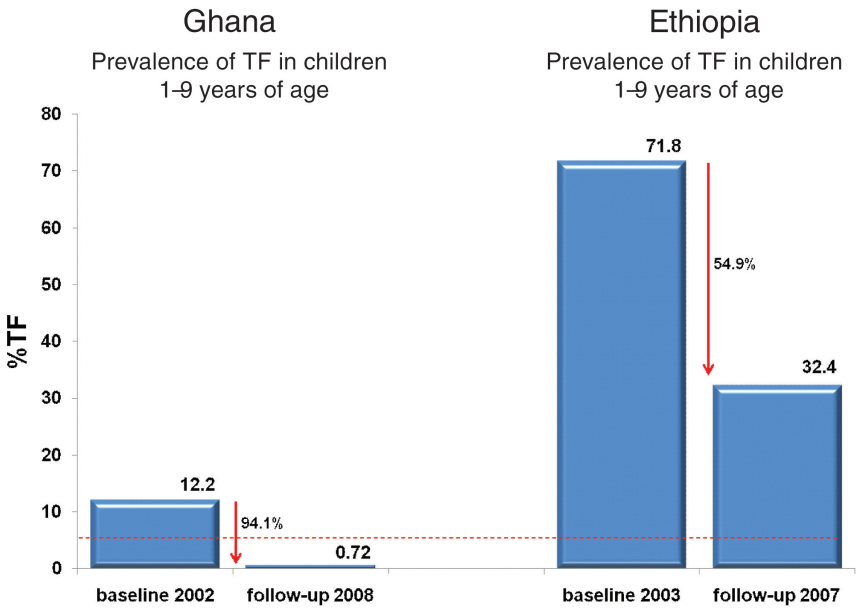

FIGURE A6-3 Prevalence of Trachomatus inflammation-follicular (TF) in children 1–9 years of age in Ghana and Ethiopia, 2007–2008.
SOURCE: The Carter Center.

at its meeting in October 2010. It concluded that it is still possible to reach the thresholds defined by WHO by 2020, but doing so will require significant acceleration of interventions, ascertaining the status of the disease in remaining endemic countries quickly, and implementing the full SAFE strategy in all affected areas of the highest endemic countries within the next two or three years.

Table A6-2 summarizes the current status of elimination efforts against these four NTDs. Dracunculiasis is approaching eradication, onchocerciasis will soon be eliminated in the Americas, and LF is scaling up to possibly become the second parasitic disease to be eradicated. We eagerly await results from the current initiatives against onchocerciasis in Africa, and from scaling up the campaign to eliminate blinding trachoma.

These times of exceptional opportunities and inspiring progress are as exciting for us professionals as they are important to improving the human condition. Most NTDs cannot be eradicated or eliminated, but all can and should be much better controlled. The few NTDs that may be vulnerable to elimination or eradication should be pursued ruthlessly.

More than 2,000 years ago, St. Paul reminded his contemporaries that they were surrounded by a cloud of witnesses as they ran the races (of life) before

TABLE A6-2 Four NTDs Slated for Eradication or "Elimination"

Disease Program	Dracunculiasis	Onchocerciasis		Lymphatic Filariasis	Trachoma
		OEPA	APOC		
Goal	Eradication 2009	Elimination (interrupt transmission) 2012	Control (public health problem) 2015	Elimination (public health problem) 2020	Elimination (blinding trachoma) 2020 (TF <5% in 1–9 y/o)
Endemic Countries Known?	Yes	Yes	Yes	Mostly	Uncertain
Status of Surveillance	Very good	Excellent	Good	Incomplete	Incomplete
Coverage Target for Intervention	100%	>85% × 2	65%	80%	80%
Extent of Intervention	98% filters (2009)	93% (2009) (0.626 m/ 0.672 m)	63% (2008) (57 m/ 90 m)	29% (2009) (385 m/ 1.333 b)	33% (2009) (40 m/ 120 m)
Monitor Disease/ Intervention	Monthly	Monthly	Annually	Annually	No

SOURCE: The Carter Center.

them. And so are we. We should be mindful of what our own witnesses are seeing, and perhaps, of what they will say when we meet them.

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A7

THE NEGLECTED TROPICAL DISEASES AND THE NEGLECTED INFECTIONS OF POVERTY: OVERVIEW OF THEIR COMMON FEATURES, GLOBAL DISEASE BURDEN AND DISTRIBUTION, NEW CONTROL TOOLS, AND PROSPECTS FOR DISEASE ELIMINATION

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Introducing the NTDs and NIoPs

The neglected tropical diseases (NTDs) represent a group of more than a dozen major chronic infectious diseases, most of them parasitic infections, with high endemicity in the developing countries of Africa, Asia, and the Americas. The conceptual framework of the NTDs was formulated in the years following the 2000 launch of the Millennium Declaration (Hotez, 2006, 2008a, 2011; Hotez et al., 2006a, 2007; Molyneux et al., 2005). Both the Millennium Declaration and its eight Millennium Development Goals (MDGs) for sustainable poverty reduction were instrumental in shaping global health policy over the next decade, and they provided a platform and basis for large-scale donor support from both public and private sources. Indeed, MDG 6, "to combat AIDS, malaria, and other diseases," helped to galvanize a new awareness for the impact of HIV/AIDS, malaria, and to some extent tuberculosis and stimulated the establishment of the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), and the U.S. President's Malaria Initiative (Hotez, 2011), in addition to increased research and development support from the National Institutes of Health and the Bill & Melinda Gates Foundation, among others. A new generation of global health celebrities also actively helped to advocate for these important new measures (Hotez, 2008a).

Unfortunately, the excitement generated by the activities outlined above left behind the third and almost forgotten component of MDG 6, namely "the other diseases." In response, a group of concerned scientists and public health experts

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committed to the study of parasitic helminth and protozoan infections began meeting under the auspices of the World Health Organization (WHO) to discuss how global efforts to control these conditions could be scaled and expanded along the lines of PEPFAR and GFATM (Fenwick et al., 2005; Molyneux et al., 2005). A key basis of these discussions involved several decades of experience with programs of mass drug administration to control or eliminate some of the most widespread parasitic helminth infections, especially lymphatic filariasis (LF), onchocerciasis, and to some extent schistosomiasis, in addition to a global campaign to eradicate dracunculiasis (Molyneux, 2004). Most of these interventions relied on global cooperation between WHO and key public–private partnerships and were backed by World Health Assembly resolutions (Brady et al., 2006; Hotez, 2009a; Hotez et al., 2006a, 2006b, 2007; WHO, 2010). From these discussions an informal consensus was created that there are 13 major conditions, which could be targeted for mass drug administration or other large-scale interventions (Hotez et al., 2006b, 2007) (Table A7-1). Provided annually and over a period of several consecutive years, mass drug administration could ultimately lead to the elimination of LF, onchocerciasis, leprosy, and possibly trachoma as public health problems; whereas for schistosomiasis and the three major soil-transmitted helminth infections—ascariasis, trichuriasis, and hookworm infection—annual mass drug administration would lead to important reductions in childhood morbidity (Fenwick et al., 2005; Molyneux, 2004; Molyneux et al., 2005). Moreover, based on the recognition that there is widespread geographic overlap among seven of the NTDs (ascariasis, trichuriasis, hookworm infection, schistosomiasis, LF, onchocerciasis, and trachoma), especially in sub-Saharan Africa, it was possible to target these conditions simultaneously by combining the drugs in an integrated "rapid-impact package" (Hotez et al., 2006a; Molyneux et al., 2005), so named because the drugs can be easily and quickly deployed by a contingent of community drug distributors and would result in rapid reductions in disabilities, improvement in well-being, and ultimately interruption in disease transmission for LF, onchocerciasis, and trachoma (Hotez et al., 2007).

In 2005 and 2006, the first peer-reviewed papers using the term "neglected tropical diseases" as a medical subject heading appeared in PubMed and other scientific literature databases (Brady et al., 2006; Hotez et al., 2006a, 2006b; Lammie et al., 2006; Molyneux et al., 2005; Utzinger and de Savigny, 2006). These publications also coincided with the establishment of a new Department of Neglected Tropical Diseases at WHO (http://www.who.int/neglected_diseases/en/) and, shortly thereafter, the open-access journal *PLoS Neglected Tropical Diseases* (http://www.plosntds.org). A key emphasis of the original list of 13 NTDs was that they exhibited a number of common clinical, epidemiological, and historical features suggesting that the NTDs could be treated as a cohesive group of infections. It was determined that according to some estimates the NTDs exhibited a global burden of disease that was roughly equivalent to that of any of the "big three diseases" targeted by the GFATM (Hotez et al., 2006a, 2007), and

TABLE A7-1 The Neglected Tropical Diseases

The 13 NTDs from Hotez et al. (2006b, 2007)[a]	Approximate Global Prevalence (Hotez et al., 2007, 2009b)	The 17 NTDs from WHO (2010[a]
Helminth Infections		**Helminth Infections**
Soil-transmitted helminth infections: ascariasis, trichuriasis, hookworm	807 million (ascariasis) 604 million (trchuriasis) 576 million (hookworm)	Soil-transmitted helminth infections: ascariasis, trichuriasis, hookworm
Schistosomiasis	207 million	Schistosomiasis
Lymphatic filariasis	120 million	Lymphatic filariasis
Onchocerciasis	37 million	Onchocerciasis
Dracunculiasis	<0.01 million	Dracunculiasis
	20–40 million	Foodborne trematodiases
	ND	Cystic echinococcosis
	ND	Cysticercosis
Protozoan Infections		**Protozoan Infections**
Leishmaniasis	12 million	Leishmaniasis
Chagas disease	8–9 million	Chagas disease
Human African trypanosomiasis	<0.01 million	Human African trypanosomiasis
Bacterial Infections		**Bacterial Infections**
Trachoma	84 million	Trachoma
Leprosy	0.4 million	Leprosy
Buruli ulcer	<0.01 million	Buruli ulcer
	ND	Endemic syphilis (treponematoses)
		Viral Infections
	50 million	Dengue and other arboviral diseases
	0.05 million	Rabies

NOTE: ND, no data.

[a]The list of 13 NTDs from Hotez et al. (2006b, 2007) treats each of the soil-transmitted helminth infections as a separate NTD, whereas the WHO list of 17 combines the three soil-transmitted helminth infections as a single entity.

global efforts could be expanded in order to control or eliminate them through large-scale interventions (Hotez, 2008a, 2011; Hotez et al., 2006a, 2007; Lammie et al., 2006; Molyneux et al., 2005; Utzinger and de Savigny, 2006). Moreover, the concept of the NTDs became critical for purposes of global advocacy and for explaining to health policy makers (and ultimately donors) the opportunity for tackling the NTDs with the same urgency as for HIV/AIDS, tuberculosis, and malaria (Hotez, 2008a).

The major distinguishing features of the 13 NTDs were summarized previ-

ously (Hotez, 2008a, 2010a; Hotez et al., 2006a, 2007, 2009b) and include the following elements:

- The 13 NTDs represent the most common infections of people living in extreme poverty in sub-Saharan Africa, Asia, and Latin America and the Caribbean.
- They disproportionately affect the "bottom billion," which refers to the approximately 1.4 billion people who live below the World Bank poverty figure of US$1.25 per day.
- Among the bottom billion, the NTDs result in chronic infections lasting years or even decades.
- The NTDs produce chronic disability that results in impaired child growth and intellectual and cognitive development, impaired pregnancy outcomes, and decreased worker productivity.
- Through these mechanisms, the NTDs adversely affect not only health but also childhood education and ultimately economic productivity; the NTDs represent an underlying reason why the bottom billion cannot escape poverty.
- Many of the NTDs also cause blindness and disfigurement that are psychologically devastating and result in social stigma.
- This high level of morbidity, economic impairment, and stigma does not necessarily translate into large numbers of deaths; overall, the NTDs cause high-morbidity but low-mortality conditions.
- In contrast to emerging infections such as HIV/AIDS, SARS, and avian influenza, there is a "nonemerging" character about the NTDs. Instead, the NTDs have afflicted humankind for centuries and there are accurate descriptions of some of the NTDs in ancient texts.

In its first report on NTDs published in 2010, WHO listed several additional features (WHO, 2010). In this new document, WHO expands its list of NTDs to also include food-borne trematodiases, cystic echinococcosis, cysticercosis, endemic syphilis and other treponematoses, and selected viral infections, including dengue and other arboviral infections and rabies. In all, WHO considers a total of 17 NTDs by treating the three soil-transmitted helminth infections as a single entity (WHO, 2010). Among the common features that WHO lists for these 17 conditions are the observations that (1) the NTDs are a proxy for poverty and disadvantage; (2) they affect populations with low visibility and little political voice; (3) they do not travel widely; (4) they cause stigma and discrimination, especially of girls and women, and have an important impact on morbidity and mortality; (5) they are relatively neglected by research; and (6) they can be controlled, prevented, and possibly eliminated using effective and feasible solutions (WHO, 2010). Listed in Table A7-2 are diseases that also meet the NTD criteria listed above, but either because they are much less common than the ones in Table A7-1

TABLE A7-2 On the Outside Looking In: NTDs of Global Importance Not Typically Found on Lists of Diseases

Helminth Infections	**Bacterial Infections**
Enterobiasis	Bartonellosis
Loiasis	Bovine tuberculosis
Strongyloidiasis	Brucellosis
Toxocariasis	Cholera
Trichinellosis	Enteric pathogens: Shigella, Salmonella, Escherichia
Protozoan Infections	Leptospirosis
Amoebiasis	Relapsing fever
Cryptosporidiosis	
Giardiasis	**Fungal Infections**
Toxoplasmosis	Mycetoma
Trichomoniasis	Paracoccidiomycosis
Vivax malaria	
	Ectoparasitic Infections
Viral Infections	Myiasis
Viral hemorrhagic fevers	Scabies
	Tungiasis

NOTE: Information about some of these diseases can be found at http://www.plosntds.org/static/scope.action.

or because there are insufficient data about their prevalence and intensity, these NTDs have not been included on conventional lists of the major NTDs. Most of these conditions, however, are considered for review by *PLoS Neglected Tropical Diseases* (http://www.plosntds.org/static/scope.action).

Another important feature about the NTDs is their disproportionate impact on selected populations, especially girls and women (including pregnant women) in part because of their effects on female reproductive health and their ability to exacerbate anemia and promote HIV/AIDS susceptibility (see below; Hotez, 2009b, 2011). In addition, the NTDs disproportionately affect African populations and African Americans who are descendents of the Atlantic slave trade (Hotez, 2009c; Hotez and Kamath, 2009; Lammie et al., 2007); indigenous populations (Hotez, 2010f; WHO, 2010); and populations living under conditions of conflict and postconflict (Beyrer et al., 2007; Hotez and Thompson, 2009).

Finally, there exists a group of infections that are closely related to the NTDs but, because they occur among impoverished people living in the midst of great wealth in the United States, Canada, and Europe, they are referred to as the neglected infections of poverty (NIoPs; see Table A7-3) (Hotez, 2008b, 2009c, 2010f). In the United States, the NIoPs tend to cluster in areas of extreme poverty, such as the Mississippi Delta and post-Katrina Louisiana, the border with Mexico, Appalachia, inner cities, and selected tribal lands. In such areas, the NIoPs disproportionately affect under-represented minorities living in poverty, including African Americans, Hispanics, and Native Americans (Hotez, 2008b), with the

TABLE A7-3 Neglected Infections Amid Wealth: Major Neglected Infections of Poverty in the United States and Europe

United States of America	Europe
Helminth Infections	**Helminth Infections**
Soil-transmitted helminth infections: ascariasis, enterobiasis, trichuriasis, strongyloidiasis	Soil-transmitted helminth infections: ascariasis, enterobiasis, trichuriasis, strongyloidiasis
Toxocariasis	Toxocariasis
Cysticercosis	Trichinellosis
Protozoan Infections	**Protozoan Infections**
Chagas disease	Chagas disease
Cutaneous leishmaniasis	Visceral leishmaniasis
Cryptosporidiosis	Cryptosporidiosis
Giardiasis	Giardiasis
Toxoplasmosis	Toxoplasmosis
Trichomoniasis	Trichomoniasis
Bacterial and Viral Infections	**Bacterial and Viral Infections**
Congenital CMV	Brucellosis
Haemophilus influenzae type A	Leptospirosis
Dengue fever	Nondengue arboviral infections

major NIoPs sometimes referred to as "the 3Cs and the 3Ts"—Chagas disease, cysticercosis, congenital cytomegalovirus infection, toxocariasis, toxoplasmosis, and trichomoniasis. In addition, dengue fever has emerged as an important NIoP in the United States (Hotez, 2008b). Thus, three of the NIoPs are also NTDs listed in Table A7-1. Recently, Congressman Hank Johnson. Jr., of Georgia introduced legislation known as the *Neglected Infections of Impoverished Americans Act of 2010* (H.R. 5986), which calls on the U.S. Department of Health and Human Services to collect additional information about these important yet neglected conditions.

Global Disease Burden

The NTDs are considered high-morbidity but low-mortality infections. Estimates for the number of deaths that result from the 13 NTDs range from 146,000 (Hotez et al., 2006b) to 534,000 (Hotez et al., 2006a) annually. On the basis of deaths alone and in terms of their attention by global health policy makers, the NTDs cannot compete with HIV/AIDS, tuberculosis, or malaria, each of which results in 1 million deaths or more annually. Instead, the adverse health impact of the NTDs is better understood in terms of disability-adjusted life-years (DALYs), that is, the number of healthy life-years lost from premature death or disability. It is the chronic disabling features of the NTDs that provide a more complete

picture of their global health impact. Estimates of the DALYs lost that result from the NTDs range from approximately 20 million DALYs (Hotez et al., 2006b), which would place the NTDs among the top 20 global health conditions, all the way to almost 57 million DALYs (Hotez et al., 2006a, 2007), which would place the NTDs on par with any of the big three conditions. The basis for this wide range in DALY estimates reflects a number of factors, but primarily there is an ongoing scientific debate on whether to incorporate the chronic morbidities associated with long-standing anemia, malnutrition, inflammation, and pain that result from the very high prevalence of soil-transmitted helminth infections and schistosomiasis (King and Dangerfield-Cha, 2008; King et al., 2005).

Still another important feature of the NTD global disease burden is the observation, especially in sub-Saharan Africa, that these conditions geographically overlap with HIV/AIDS and malaria and may affect the susceptibility or clinical progression of these two killer diseases (Hotez et al., 2006a). For example, in the case of malaria there is a high degree of geographic overlap with hookworm infection (Brooker et al., 2006), with evidence to show that co-infections of malaria and hookworm result in severe anemia (Brooker et al., 2007; Hotez and Molyneux, 2008). Similarly, urinary tract schistosomiasis, which occurs in more than 100 million people in sub-Saharan Africa (Van der werf et al., 2003), commonly results in female genital schistosomiasis that is associated with a threefold increased susceptibility to HIV/AIDS (Hotez et al., 2009a; Kjetland et al., 2006). Thus, the NTDs have important collateral effects on the AIDS and malaria epidemics in Africa (Hotez and Molyneux, 2008; Hotez et al., 2006a).

The Geography of the NTDs

The NTDs and NIoPs occur in the setting of extreme poverty, especially in sub-Saharan Africa, South Asia, Southeast Asia, and in tropical regions of the Americas (Hotez, 2011; Hotez et al., 2009b). Sub-Saharan Africa is estimated to account for approximately one-third of the world's soil-transmitted helminth infections, most of the world's cases of schistosomiasis and onchocerciasis, and all of the world's cases of dracunculiasis and human African trypanosomiasis (Hotez and Kamath, 2009). In many areas of sub-Saharan Africa it is not unusual to find seven or more NTDs in one area—the three major soil-transmitted helminth infections, schistosomiasis, LF, onchocerciasis, and trachoma (Molyneux et al., 2005). Latin America and the Caribbean region also exhibit high rates of NTDs, especially in Brazil, where these conditions (with the exception of Chagas disease and possibly trachoma) were imported during the 500 years of the Middle Passage of the African slave trade (Hotez, 2011; Hotez et al., 2008; Lammie et al., 2007). Southeast Asia is also responsible for one-third of the cases of soil-transmitted helminth infections and almost all of the food-borne trematodiases, in addition to high rates of dengue and other arbovirus infections (Hotez, 2011; Hotez and Ehrenberg, 2010). There are no published studies about the overall

prevalence of NTDs in central Asia, but in India, Bangladesh, and Nepal it is believed the rates of these infections (especially LF and the soil-transmitted helminth infections) are extremely high (Hotez, 2011). There are approximately 10 million cases of NIoPs in the United States and an unknown number in Europe and Australia (Hotez, 2008b, 2009c).

There are also a number of interesting geopolitical features about the NTDs (Hotez, 2010b). Among them is the finding that high rates of infection occur in conflict zones (Hotez and Thompson, 2009) as well as in certain Islamic countries, such as Indonesia, Bangaldesh, Sudan, and the west African countries of Mali, Chad, Niger, and Nigeria (Hotez, 2009d). Overall, up to 40 to 50 percent of the world's NTDs occur in the nations that comprise the Organisation of the Islamic Conference (Hotez, 2009d). Similarly, another one-third of the world's NTDs occur in large middle-income countries such as India, China, Pakistan, and Iran, which are also considered nuclear weapons countries (Hotez, 2010c). As shown below, these geopolitical features connect the control of the NTDs with elements of U.S. foreign policy (Hotez, 2010b, 2010c, 2010d, 2010e).

Approaches to Control and Elimination Through Mass Drug Administration

WHO points out that the NTDs can be controlled, prevented, and possibly eliminated using effective and feasible solutions (WHO, 2010). Possibly the most obvious example is the near eradication of dracunculiasis (Guinea worm) through the filtering and treatment of water contaminated with larval-infected copepods, together with case detection and management (Hopkins et al., 2008; Molyneux, 2004; WHO, 2010). Over the next few years it is expected that dracunculiasis would become only the second human infection to ever be eradicated and the first disease eradicated without the requirement of a vaccine. However, in addition to dracunculiasis, there are at least five other NTDs that, through the World Health Assembly or the Pan American Health Organization resolutions, have also been targeted by WHO for elimination as public health problems: LF, onchocerciasis, trachoma, Chagas disease, and leprosy (WHO, 2010). With the exception of Chagas disease (which relies largely on insecticidal spraying and improved housing), these other NTDs would be eliminated primarily through mass drug administration, in which large populations are simultaneously treated with one or two drugs on a once-yearly or twice-yearly basis (LF, onchocerciasis, and blinding trachoma) or through multidrug therapy (leprosy) (Brady et al., 2006; Hotez, 2009a; Lammie et al., 2006; Molyneux, 2004). Over time, this approach would lead to reductions in disease prevalence to the point where transmission of these infections is interrupted (WHO, 2010).

For the most part, mass interventions comprised of population-based drug administration (often together with other allied measures) have been extremely successful in terms of reaching large numbers of affected populations, even in

the most remote areas of Africa, Asia, and the Americas, and in achieving control and elimination targets. In part, these successes have occurred because the medicines used in mass drug administration have an excellent safety profile and can be administered to large populations based on community-wide prevalence assessments (Hotez, 2009b; WHO, 2006). Once a threshold prevalence of a particular NTD has been ascertained, WHO has established algorithms for treating large populations regardless of whether it has been determined if any given individual is currently infected (WHO, 2006). This practice obviates the requirement of bringing in trained microscopists or other skilled workers, as well as expensive equipment, into the field. Also of critical importance, the drugs used in mass administration are either being donated by some of the major multinational pharmaceutical companies or they can be purchased as extremely low-cost generics (WHO, 2010). To date, the number of people who have received mass drug administration is one of the more impressive achievements in global public health over the past century (Hotez et al., 2007; Molyneux, 2004). For instance, more than 500 million people, that is, almost one-half of the more than one billion people at risk for LF, have received either diethylcarbamazine citrate or ivermectin (usually coadministered with albendazole; Ottesen et al., 2008), while more than one-half of the world's people at risk for onchocerciasis have received or are receiving ivermectin (Hotez, 2009a; WHO, 2010). To date, elimination of LF has been achieved in China, Cape Verde, Costa, the Republic of Korea, the Solomon Islands, Suriname, and Trinidad and Tobago (WHO, 2008); onchocerciasis has been eliminated from Mali and Senegal (Diawara et al., 2009); and blinding trachoma has been eliminated from Gambia, Morocco, Iran, Oman, and Mexico (Burton et al., 2010). In addition, leprosy has been eliminated as a public health problem (defined as a prevalence below 1 case per 10,000 populations) in all but 3 of the 122 previously endemic countries (WHO, 2010). The control and elimination programs for these diseases rely on established public–private partnerships that work closely with the disease-endemic countries and WHO (Hotez et al., 2009b).

For other extremely high-prevalence diseases, such as the three major soil-transmitted helminth infections and schistosomiasis, each affecting hundreds of millions of people in low- and middle-income countries, the coverage through mass drug administration has not been nearly as successful (Hotez, 2009a; WHO, 2010). Even though mass drug administration for these conditions has been shown to improve child growth, development, and cognition, currently only about 10 percent of school-aged children in areas affected by soil-transmitted helminth infections receive regular treatments with either albendazole or mebendazole, while fewer than 10 percent of children receive praziquantel for schistosomiasis (Hotez et al., 2010b; WHO, 2010). These helminth infections, but especially hookworm infections, cause important adverse effects in pregnancy and up to one-third of pregnant women in sub-Saharan Africa are affected (Brooker et al., 2008). In order to increase coverage for the seven most common NTDs, includ-

ing the three major soil-transmitted helminth infections, schistosomiasis, LF, onchocerciasis, and blinding trachoma (Table A7-4), it was proposed in 2005 to bundle the drugs in mass drug administration for these conditions in a "rapid impact package," costing as little as US$0.50 per individual (Brady et al., 2006; Hotez, 2009a, 2010a; Hotez et al., 2006a; Lammie et al., 2006; Molyneux et al., 2005; Utzinger and de Savigny, 2006; WHO, 2006). Safety data are now in place to support the coadministration of albendazole, ivermectin, and praziquantel, with studies under way to also examine the addition of azithromycin (Hotez, 2009a).

Today, through support from the U.S. Agency for International Development, national programs of integrated NTD control for the seven most common NTDs in Table A7-4 are under way in the African countries of Burkina Faso, the Democratic Republic of Congo, Ghana, Mali, Niger, Sierra Leone, Southern Sudan, Tanzania, and Uganda, as well as Bangladesh and Nepal in Asia, and Haiti (http://www.neglecteddiseases.gov). In 2010 the U.S. President's Global Health Initiative established targets to reduce the prevalence of the seven NTDs by 50 percent among 70 percent of affected populations and to contribute to the elimination of onchocerciasis in the Americas by 2016, the elimination of LF globally by 2020, and the elimination of leprosy (http://www.neglecteddiseases.gov). In addition, the British Department for International Development (DFID) is supporting national control programs, as is a Global Network for NTDs, which is currently supporting NTD control in Burundi and Rwanda with additional countries planned through funds raised privately (Hotez, 2010a). In all, there are approximately 56 countries with multiple NTDs that should be targeted for rapid

TABLE A7-4 The Seven Major NTDs Targeted for Integrated Control and Elimination with "Rapid Impact Packages"

Seven Major NTDs Targeted by Rapid Impact	Major Drugs Used	Additional NTDs Targeted by Rapid Impact
Soil-transmitted helminth infections: ascariasis, trichuriasis, hookworm	Albendazole or mebendazole	Strongyloidiasis
Schistosomiasis	Praziquantel	Taeniasis Food-borne trematodiases
Lymphatic filariasis	Ivermectin or diethylcarbamazine citrate + albendazole	Strongyloidiasis Scabies
Onchocerciasis	Ivermectin	Strongyloidiasis Scabies
Trachoma	Azithromycin	Other bacterial infections

impact packages (Hotez et al., 2007, 2008a). However, providing global coverage at this scale will require the participation of wealthy nations beyond the United States and the United Kingdom, including other European nations, countries of the Gulf Cooperation Council, and some of the larger emerging economies such as Brazil, China, and India, which have the capacity to control or eliminate some of their indigenous NTDs (Hotez, 2010e).

There are additional NTDs of great public health importance for which mass drug administration approaches are not immediately relevant but which in some cases could still be controlled or eliminated. The example of dracunculiasis was mentioned earlier; in addition, human African trypanosomiasis rates in West Africa caused by *Trypanosoma brucei gambiense* have been greatly curtailed by aggressive case identification and treatment and tsetse control, particularly in postconflict countries such as Angola and the Democratic Republic of Congo, and currently Sudan, which suffered some of the worst epidemics in the 1970s, 1980s, and 1990s (Hotez, 2008a; Jannin et al., 2001). Between 1999 and 2008 the number of new reported cases of this infection fell by 62 percent, to approximately 10,000 cases; similarly, the number of new cases of east African trypanosomiasis caused by *T. brucei rhodesiense* fell by 58 percent to only a few hundred reported reported cases (WHO, 2010). Through insecticide spraying, improved housing, and case detection and treatment, Chagas disease has been eliminated as a public health problem in the Southern Cone countries of Argentina, Brazil, Chile, Paraguay, the Plurinational State of Bolivia, and Uruguay (WHO, 2010), although an estimated 8 to 9 million cases remain in Latin America, with the greatest number of cases in Bolivia. A program to reduce the incidence of visceral leishmaniasis in Bangladesh, India, and Nepal—the three countries with highest disease burden—is under way through a program of early case finding, delivering oral treatment, and vector control (WHO, 2010). Treatments for several of the NIoPs including Chagas disease, cysticercosis, toxocariasis, toxoplasmosis, and trichomoniasis, are available even if the treatments are underused because of their overall neglect by the public health community in the United States (Hotez, 2008b).

Collateral Benefits: Malaria, HIV/AIDS, and Other Co-Infections

Beyond the seven NTDs and leprosy, mass drug administration is expected to have a number of other important collateral effects. For instance, the drugs that comprise the rapid impact package would also target additional high-prevalence NTDs (listed in Tables A7-1 and A7-2) such as strongyloidiasis; taeniasis; the food-borne trematodiases clonorchiasis, opisthorchiasis, and paragonimiasis; and scabies (Hotez et al., 2006a). A recent study conducted in Ethiopia also showed that once-yearly azithromycin used for mass drug administration to combat blinding trachoma resulted in dramatic overall reductions in child mortality (Porco et al., 2009), possibly as a result of reducing bacterial colonization that would otherwise lead to other respiratory or gastrointestinal bacterial infections. It is also

possible that by reducing anemia from hookworm and schistosomiasis the rapid impact package could indirectly reduce severe anemia in sub-Saharan Africa that results from malaria co-infections (Brooker et al., 2007).

Two additional studies suggest that NTD control is of potentially great importance on the HIV/AIDS pandemic, but especially in sub-Saharan Africa. To date, three randomized controlled trials evaluating the effects of deworming on HIV/AIDS progression showed a benefit in reducing plasma viral loads and/or increasing CD4 counts (Walson et al., 2009), while female genital schistosomiasis was shown to result in a threefold increase in horizontal transmission of HIV/AIDS (Kjetland et al., 2006). These studies suggest that widespread administration of praziquantel or the rapid impact package could represent an inexpensive and highly cost-effective intervention to complement widespread AIDS control measures currently being implemented by the GFATM or PEPFAR (Hotez et al., 2006a). In the coming years, an extensive program of operational research and implementation science will be required to maximize use of the rapid impact package and how it can interface with global malaria and HIV/AIDS control efforts.

Access to Innovation

For almost all of the NTDs, there is a desperate need for research and development leading new innovations for control, including improved diagnostics, medicines, or vaccines (Hotez and Pecoul, 2010). The older concept of "tool-ready" versus "tool-deficient" NTDs has been discredited as most of the tool-ready diseases currently targeted by the rapid impact package still require a new generation of improved anthelminthic drugs and vaccines, while tool-deficient diseases such as human African trypanosomiasis, Chagas disease, and leishmaniasis can still be controlled or even eliminated in some areas using currently available insecticides and medicines (Hotez and Pecoul, 2010). Among the diseases now targeted by the rapid impact package, high rates of mebendazole drug failure have been reported for hookworm infection, with a recent meta-analysis reporting only a 15 percent cure rate for single-dose mebendazole (Hotez et al., 2010a; Keiser and Utzinger, 2008). Similarly, single-dose albendazole exhibits a low cure rate for trichuriasis (Keiser and Utzinger, 2008), while high rates of post-treatment re-infection have been described for all of the soil-transmitted helminth infections and schistosomiasis (Hotez et al., 2010a; Keiser and Utzinger, 2008). Several potential backup anthelminthic drugs previously developed for veterinary purposes could potentially be transitioned into human medicines, and there is a need to establish a product development public–private partnership (PD-PPP) for this purpose (Hotez and Pecoul, 2010). Alternatively, the Sabin Vaccine Institute is a PD-PPP developing new vaccines to prevent hookworm infection and schistosomiasis (Hotez et al., 2010a). Such vaccines are sometimes referred to as the "antipoverty vaccines" because of their potential economic impact as well as their

effects on health (Hotez and Ferris, 2006). There is also a need for a new macrofilaricide for onchocerciasis to reduce the number of years for which ivermectin treatments must be provided annually (Hoerauf, 2008). The drug moxidectin is a potential macrofilaricide under development jointly between WHO-TDR (the Special Programme for Research and Training on Tropical Diseases) and Pfizer, as are antimicrobial drugs that target bacterial endosymbionts and also exhibit a macrofilaricidal effect (Hoerauf, 2008; Hotez and Pecoul, 2010). For all seven NTDs targeted for rapid impact packages, there is a pervasive need for new diagnostics (Hotez and Pecoul, 2010).

For human African trypanosomiasis, Chagas disease, and leishmaniasis, there is an urgent need for new and safer drugs to replace the ones now in use, many of which were developed in the early part of the 20th century (Hotez and Pecoul, 2010; McKerrow et al., 2009; Priotto et al., 2009; Yun et al., 2009). Also needed are improved diagnostics, and there is a need for new vaccines, including possibly new therapeutic vaccines for these kinetoplastid diseases (Hotez and Ferris, 2006). Several PD-PPPs are in place for new drugs for kinetoplastid infections, including the Drugs for Neglected Diseases Initiative (DNDi) and the Institute for One World Health (iOWH), while the Infectious Diseases Research Institute (IDRI) is developing a leishmaniasis vaccine, and the Foundation for Innovative Diagnostics (FIND) is investigating new kinetoplastid diagnostics.

For some of the other diseases not yet mentioned, there are also needs to develop new biomarkers to predict the onset of bile duct cancer from the food-borne trematodiases clonorchiasis and opisthorchiasis, in addition to new anticancer vaccines for these helminthiases (Sripa et al., 2010); veterinary transmission blocking vaccines for cysticercosis and echinococcosis (Lightowlers, 2010); and new Buruli ulcer drugs, vaccines, and diagnostics (Hotez and Pecoul, 2010; Portaels et al., 2009). Currently at least five candidate dengue vaccines are under development both by major multinational pharmaceutical companies as well as the International Vaccine Institute (Durbin and Whitehead, 2010). Of interest, today many of the PD-PPPs are partnering with both private- and public-sector manufacturers located in middle-income countries—sometimes referred to as innovative developing countries—such as Brazil, China, Cuba, India, and Indonesia (Morel et al., 2005). For the NIoPs there is an urgent need to develop improved diagnostics, especially for each of the 3C and 3T diseases, and for efforts to accelerate the development of new vaccines combat congenital CMV infection, Chagas disease, and toxoplasmosis (Hotez, 2008b).

Implications for U.S. Foreign Policy

The observation that most of the world's NTDs occur in countries of geopolitical interest to the Untied States has potential foreign policy implications for the U.S. government (Hotez, 2009d, 2010b, 2010c, 2010d). The human right to live in a world free of NTDs has been pointed out previously (Beyrer et al., 2007;

Hotez, 2008a; Hunt, 2006), thereby providing a framework for NTD control as a low-cost yet high-profile U.S. humanitarian intervention (Hotez, 2006). However, the potential for NTDs to actually cause poverty and promote conflicts in the world's Islamic nations and nuclear weapons states (Hotez and Thompson, 2009) provides added urgency for the United States to intervene today through wide-scale interventions with rapid impact packages in all these nations and, ultimately, all of the 56 affected developing countries (Hotez, 2008, 2010b). Finally, there are important opportunities to look to joint research and development cooperation between the United States and some of the world's more advanced Islamic countries and NTD-affected nuclear weapons states in order to develop a new generation of antipoverty vaccines, just as the United States and former Soviet Union cooperated on joint polio and smallpox vaccine development during the middle of the 20th century (Hotez, 2010c, 2010d).

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A8

NEGLECTED INFECTIONS OF POVERTY IN THE UNITED STATES OF AMERICA[7]

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Abstract: In the United States, there is a largely hidden burden of diseases caused by a group of chronic and debilitating parasitic, bacterial, and congenital infections known as the neglected infections of poverty. Like their neglected tropical disease counterparts in developing countries, the neglected infections of poverty in the US disproportionately affect impoverished and under-represented minority populations. The major neglected infections include the helminth infections, toxocariasis, strongyloidiasis, ascariasis, and cysticercosis; the intestinal protozoan infection trichomoniasis; some zoonotic bacterial infections, including leptospirosis; the vector-borne infections Chagas disease, leishmaniasis, trench fever, and dengue fever; and the congenital infections cytomegalovirus (CMV), toxoplasmosis, and syphilis.

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These diseases occur predominantly in people of color living in the Mississippi Delta and elsewhere in the American South, in disadvantaged urban areas, and in the US–Mexico borderlands, as well as in certain immigrant populations and disadvantaged white populations living in Appalachia. Preliminary disease burden estimates of the neglected infections of poverty indicate that tens of thousands, or in some cases, hundreds of thousands of poor Americans harbor these chronic infections, which represent some of the greatest health disparities in the United States. Specific policy recommendations include active surveillance (including newborn screening) to ascertain accurate population-based estimates of disease burden; epidemiological studies to determine the extent of autochthonous transmission of Chagas disease and other infections; mass or targeted treatments; vector control; and research and development for new control tools including improved diagnostics and accelerated development of a vaccine to prevent congenital CMV infection and congenital toxoplasmosis.

Introduction

In the United States of America, the mortality rate resulting from infectious diseases has declined precipitously over the course of the twentieth century (Armstrong et al., 1999), and major scourges such as typhoid fever and malaria are no longer serious public health threats (Humphreys, 2001). However, among the poorest populations living in the US there remains highly prevalent a group of serious parasitic and bacterial diseases such as Chagas disease, cysticercosis, and toxocariasis (Hotez, 2007), which, like the neglected tropical diseases (NTDs), are characterized by their high prevalence, chronic and disabling features, and disproportionate effect on the poor (Hotez, 2007; Hotez et al., 2007). These infections occur outside of tropical regions of Africa, Asia, and Latin America, and I refer to them as *neglected infections of poverty*, because they not well known to the US public-health community, and they promote poverty because of their impact on child development, pregnancy outcomes, and worker productivity (Hotez and Ferris, 2006). In this review I highlight the largely underappreciated burden of the neglected infections of poverty in the US and make policy recommendations for addressing such health disparities.

The Distressed Regions of Poverty in the United States

Demographers and other social scientists measure poverty in a number of ways (Iceland, 2006; Rector and Johnson, 2004), but since the 1960s, the US Census Bureau has used a set of income thresholds that vary by family size and composition (U.S. Census Bureau, 2007a, 2007b). In 2006, there were 36.5 million Americans living in poverty, and the official US poverty rate was 12.3% (Historical poverty tables, 2007; U.S. Census Bureau, 2007b). However, among

under-represented minorities and children, the poverty rate is much higher, particularly in single parent households headed by women (Table A8-1). Poverty in the US is not evenly distributed, but instead it is focally concentrated into several defined geographic regions, each with unique socioeconomic characteristics. Glasmeier has identified six major distressed regions of poverty: Appalachia, the Mississippi Delta, other areas of rural poverty especially in the American South, Native American tribal lands, the borderlands between the United States and Mexico, and highly racially segregated urban areas including mostly black metro areas adjacent to the Great Lakes and in the Northeast (Glasmeier, 2006). Holt has conducted a spatial analysis of the poverty in the United States at the county level and independently identified similar areas of poverty (Figure A8-1) (Holt, 2007).

A robust dataset links poverty to both lower life expectancies from chronic diseases (especially cancer and heart disease) and increased infant and child mortality (Braveman, 2007; Bloche, 2007; Kaplan, 2007; Murray et al., 2005). Partly on this basis, and building on an analysis of mortality by race and ethnicity in 2,077 counties or county clusters, Murray et al. divided the US population into eight groups with different epidemiologic patterns and mortality rates (Murray et al., 2005). Among these eight ''Americas'' were four socioeconomically disadvantaged groups with substantially higher mortality from chronic diseases: America 4 is defined as poor whites living in Appalachia and the Mississippi Valley; America 5, Native Americans living on reservations in the West; America 7, poor blacks living in the rural South; and America 8, blacks living in high-risk urban environments (Murray et al., 2005).

Using a hybrid of these classifications it is possible to identify groups of individuals based on race, ethnicity, and socioeconomic status that are at particular risk for specific neglected infections of poverty. In this paper I review the prevalence of the major neglected diseases of poverty in the US This analy-

TABLE A8-1 Selected US Census Bureau 2006 Poverty Data

Category	Poverty Rate	Reference
Official poverty rate	12.3%	U.S. Census Bureau (2007b)
Non-Hispanic white	8.2%	U.S. Census Bureau (2007b)
Non-Hispanic black	24.3%	U.S. Census Bureau (2007b)
Hispanic	20.6%	U.S. Census Bureau (2007b)
Children under age 18 y	17.4%	U.S. Census Bureau (2007b)
Black female householder, no husband present, with children under age 18 y	43.6%	Historical poverty tables (2007)
Hispanic female householder, no husband present, with children under age 18 y	42.5%	Historical poverty tables (2007)

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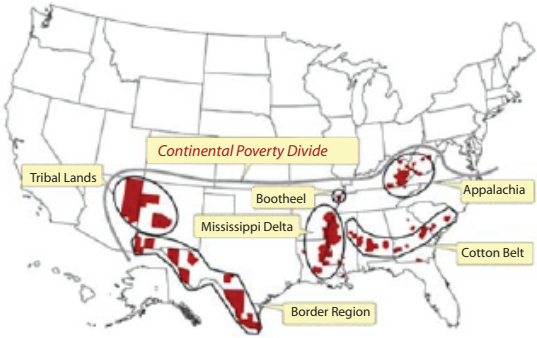
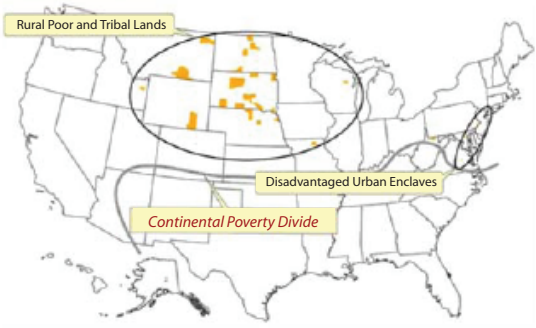


Tribal Lands	Border Region	Mississippi Delta Cotton Belt	Appalachia
Echinococcis	Brucellosis	Ascariasis	Ascariasis
	Cysticercosis	Chagas disease	Strongyloidiasis
	Chagas disease	Congenital CMV	
	Dengue	Congenital toxoplasmosis	
	Leishmaniasis	Toxocariasis	
	Leprosy	Trichomoniasis	



Rural Poor and Tribal Lands	Disadvantaged Urban Enclaves
Echinococcosis	Congenital CMV infection
Toxoplasmosis	Congenital syphilis
Trichinellosis	Congenital toxoplasmosis
	Leptospirosis
	Toxocariasis
	Trench fever
	Trichomoniasis

FIGURE A8-1 Location of counties that represent spatial clusters in which poverty rates are at least two standard deviations higher than the national mean. Top: Counties south of the Continental Divide. Bottom: Counties north of the Continental Divide.
SOURCE: Holt (2007).

sis was conducted in January 2008 using the online database PubMed (U.S. National Library of Medicine, 2008) for 1972–2007 with the Medical Subject Headings (MSHs) ''neglected diseases'', ''poverty'', the specific geographic regions and racial, ethnic, and socioeconomic groups listed above (Glasmeier, 2006; Holt, 2007; Murray et al., 2005), and the specific diseases listed as NTDs on the *PLoS Neglected Tropical Diseases* journal scope page (*PLoS Neglected Tropical Diseases*, 2008), as well as major congenital infections associated with impaired child development including cytomegalovirus (CMV) infection, toxoplasmosis, and syphilis. I also reviewed reference lists of identified articles and hand-searched reviews. I report here either previously published estimates of the number of cases of each neglected infection, or I provide a range of estimates based on reported prevalence rates among selected communities multiplied by published estimates of the population at risk having similar socioeconomic, racial, and ethnic demographics (Table A8-2). For some neglected infections, particularly the soil-transmitted helminth infections, no new surveys have been reported since the 1980s. Some of the regional and national prevalence estimates were modified from a chapter in my recently published book on neglected tropical diseases (Hotez, 2008).

Appalachia

The hilly and mountainous region known as Appalachia comprises parts of 13 states (Figure A8-1) (Glasmeier, 2006). Poverty and isolation is particularly severe in Central Appalachia, which includes parts of West Virginia, Eastern Kentucky and Tennessee, and the southwestern tip of Virginia (Glasmeier, 2006). The plight of the poorest people in this region, typically those working in the coal mining industry, was brought to national attention both during the early 1960s when John F. Kennedy made a presidential campaign swing through the region (Mangum et al., 2003) and with the 1962 publication of Michael Harrington's book, *The Other America: Poverty in the United States* (Harrington, 1962). In 2000, it was estimated that 169,000 housing units in Appalachia, particularly Central Appalachia, had no indoor plumbing (Glasmeier, 2006). Almost 3% of the region overall lacks complete plumbing, although in some counties plumbing is incomplete in upwards of 25% of the housing units (Glasmeier, 2006).

Ascariasis.

The parasitic worm infection ascariasis is one of the world's most common neglected tropical diseases (Hotez et al., 2007), and a leading global cause of impaired child development (Bethony et al., 2006). In very young children, high-intensity *Ascaris lumbricoides* infections also cause intestinal obstruction (Bethony et al., 2006; Blumenthal and Schultz, 1975). During the 1930s, the profound poverty and inadequate sanitation in Appalachia was linked to high rates of

TABLE A8-2 Estimated Prevalence of Neglected Infections of Poverty in the US

Neglected Disease Category	Disease	Estimated Number of Cases	Major Regions or Populations at Risk	References
Soil-transmitted helminth infections	Ascariasis	<4 million	Appalachia, American South	Warren (1974)
	Toxocariasis	1.3-2.8 million	Inner cities, American South, Appalachia	Murray et al. (2005); Sharghi et al. (2000); Wohn et al. (2007)
	Strongyloidiasis	68,000-100,000	Appalachia, African refugees	Murray et al. (2005); Hotez (2008); Walzer et al. (1982) Centers for Disease Control and Prevention (2002)
	Trichenollosis	16 (insufficient data)	Arctic Alaska	Centers for Disease Control and Prevention (2007)
Platyhelminth Infections	Cysticercosis	41,400-169,000	US-Mexico borderlands	Hotez (2008); Pew Hispanic Center (2008); DeGiorgio et al. (2005)
	Schistosomiasis	8,000	African refugees	Franco-Paredes et al. (2007); Posey et al. (2007
	Echonococcis	Insufficient data	Tribal Lands and Arctic Alaska	—
Protozoan Infections	Giardiasis	2.0-2.5 million	All regions	Mead et al. (1999); Yoder et al. (2007)
	Trichomoniasis	880,000 (black women)	American South, Inner cities	Murray et al. (2005); Sutton et al. (2007)
	Cryptosporidiosis	300,000	All regions	Mead et al. (1999)
	Chagas disease	3,000 to >1 million	US-Mexico borderlands, American South	Glasmeier (2006); Hanford et al. (2007); Leiby et al. (2002); Milei et al. (1992); Tobler et al. (2007)
	Cyclosporiasis	16,624	All regions	Mead et al. (1999)

TABLE A8-2 Continued

Neglected Disease Category	Disease	Estimated Number of Cases	Major Regions or Populations at Risk	References
	Congenital toxoplasmosis	≤4,000 annually	American South, inner cities, US-Mexico borderlands, Arctic Alaska	Jones et al. (2007)
	Leishmaniasis	Insufficient data	US-Mexico borderlands	—
	Amebiasis	Insufficient data	US-Mexico borderlands	—
Bacterial Infections	Congenital syphilis	1,528 between 2000 and 2002	American South, Inner cities	Centers for Disease Control and Prevention (2002)
	Brucellosis	1,554	US-Mexico borderlands	Troy et al. (2005); Mead et al. (1999)
	Bovine tuberculosis	129 cases between 1994 and 2000	US-Mexico borderlands	LoBue et al. (2003)
	Leprosy	166	US-Mexico borderlands	Truman et al. (2005)
	Trench fever	Insufficient data	Inner cities	—
	Leptospirosis	Insufficient data	Inner cities	—
Viral Infections	Dengue fever	110,000-200,000 new infections annually	US-Mexico borderlands, American South	Glasmeier (2006); Brunkard et al. (2007); Pew Hispanic Center (2008)
	Congenital CMV	27,002 annually; 6,652 in blacks; 4,196 in Hispanics	American south, Inner cities	Colugnati et al. (2007)
	Human rabies	2	All regions	Centers for Disease Control and Prevention (2007)

ascariasis (Otto and Cort, 1934). For instance, it was noted that among children aged 5–14 y, the prevalence in Breathitt County in Eastern Kentucky was 75%, higher than in many developing countries (Otto and Cort, 1934). During the late 1970s Walzer et al. reported that approximately 14% of schoolchildren in Clay County (Eastern Kentucky) were infected with *A. lumbricoides* and almost 13% were also infected with the whipworm *Trichuris trichiura* (Walzer et al., 1982), while other investigators also reported that ascariasis was still highly endemic in the region (Blumenthal, 1977; Dauer et al., 1968; Jones, 1983). Warren previously estimated that four million people are infected with *A. lumbricoides* in the US (Table A8-2) (Warren, 1974): however, no surveys for ascariasis have since been conducted.

Strongyloidiasis.

Strongyloidiasis, caused by the threadworm *Strongyloides stercoralis*, is another important soiltransmitted helminth infection, associated with chronic enteritis, impaired child development, eosinophilia, and hyperinfection in immunocompromised hosts (Dada-Adegbola and Bakare, 2004; Milder et al., 1981; Siddiqui and Berk, 2001). The disease is underreported partly because of the difficulty of diagnosing the infection by fecal examination (Kithcne et al., 2000; Siddiqui and Berk, 2001). A review of several studies conducted during the 1960s, 70s, and 80s and determined that the prevalence in Central Appalachia ranged from 0.4% (Charleston, West Virginia) to 4.0% (Harlan County, Kentucky, and Johnson City, Tennessee) (Siddiqui and Berk, 2001). Based on 3,271 fecal examinations in Kentucky, Walzer et al. estimated that the overall prevalence was approximately 1% (Walzer et al., 1982). A high percentage of the patients with strongyloidiasis were found to be older white males, most of whom had underlying chronic illnesses including chronic obstructive pulmonary disease (Berk et al., 1987; Kitchen et al., 2000; Milder et al., 1981; Walzer et al., 1982). These infections may have been acquired in coal mines. Murray et al. determined that 11 million people compose the poor white Appalachians in America 4 (Murray et al., 2005), while the Centers for Disease Control and Prevention (CDC) reported that the population of rural Appalachia is approximately 6.8 million (Centers for Disease Control and Prevention, 2002). Based on Walzer's prevalence determination of 1%, I estimate there are approximately 68,000 (Hotez, 2008) to 110,000 Appalachians infected with *S. stercoralis* (Table A8-2).

Mississippi Delta and the American South

Throughout the twentieth century and continuing today, the Mississippi Delta (''the Delta,'' composed predominantly of the Delta regions of Mississippi, Louisiana, Arkansas, and Tennessee, but also including the adjacent ''boot-heel'' of Missouri) and the areas of the former Cotton Belt in the American South, have re-

mained among the poorest regions in the nation (Figure A8-1) (Glasmeier, 2006). High rural poverty rates, inadequate housing, and poor health are the hallmarks of poverty in the Delta and adjacent regions (Felix and Stewart, 2005; Glasmeier, 2006). More than one-half of the population is black (McKinnon, 2001), and over one third of the total Delta black population lives in poverty, as does almost one-half of the rural black Delta population (Glasmeier, 2006). Overall, 5.8 million people live in America 7, the poor blacks of the rural American South (Murray et al., 2005).

In the first half of the twentieth century as many as 42% of black schoolchildren in the Delta had splenomegaly indicative of active malaria infection, and almost twice as many blacks died from malaria as whites (Humphreys, 2001). The high rates of malaria among blacks were attributed to exposure to *Anopheles* mosquitoes as a result of crowding and inadequate housing located next to swampy land, and diminished host resistance because of malnourishment and overwork (Humphreys, 2001). Throughout the American South during the early twentieth century, malaria combined with hookworm infection and pellagra to produce a generation of anemic, weak, and unproductive children and adults (Bleakley, 2007; Hotez, 2008; Humphreys, 2001; Martin and Humphreys, 2006). By the 1960s these infections were no longer endemic in the Delta, but the health status (as measured by cancer and heart disease mortality rates and infant mortality rates) of the eight states that make up the this region still consistently ranks at the bottom among all the United States (Felix and Stewart, 2005). Tuberculosis rates among southern blacks are also considerably higher than whites (Acevedo-Garcia, 2000; Centers for Disease Control and Prevention, 2004; Richardus and Kunst, 2001). Poverty is a major determinant but not the only one (Centers for Disease Control and Prevention, 2004), as incarceration and other involuntary social forces also account for high rates of tuberculosis and some sexually transmitted infections (Centers for Disease Control and Prevention, 2004; Richardus and Kunst, 2001; Thomas, 2006; Thomas and Torrone, 2006). For the blacks living in the Delta and elsewhere in the American South, several parasitic and congenital infections rank among the most important neglected infections of poverty, especially in post-Katrina Louisiana.

Neglected infections in pre- and post-Katrina Louisiana.

Despite the apparent eradication of malaria and hookworm infection from the American South (Hotez, 2008; Humphreys, 2001; Martin, 1972; Martin and Humphreys, 2006), other important parasitic infections remain, particularly in Louisiana. Even before Hurricane Katrina, the Delta region of Louisiana exhibited some of the highest poverty rates in the nation—in 2000, approximately 36% of blacks lived below the poverty level in this area (Glasmeier, 2006). It was previously determined that, outside of Appalachia, Louisiana exhibited some of the highest rates of ascariasis in the US [24], and during the 1970s and

1980s considerable numbers of the rural residents of Louisiana and elsewhere in the American South were infected (Adams and Perkin, 1985; Blumenthal and Schultz, 1975, 1976; Miller et al., 1978; Morgan et al., 1972; Schultz, 1982). Some children exhibited parasite intensities high enough to produce acute intestinal obstruction (Blumenthal, 1977; Blumenthal and Schultz, 1975). Although *A. lumbricoides* infections were highest in rural Louisiana, they were also prevalent among kindergarten children living in New Orleans (Hubbard et al., 1974). In addition, during the 1970s and 1980s Louisiana children were at risk for infection with the dog roundworm, *Toxocara canis* (Smith et al., 1984), and up to 30% of rural black children, mostly in the South, were seropositive for this infection (toxocariasis will be discussed in the section on inner cities) (Herrmann et al., 1985). Unfortunately, no surveys for either ascariasis or toxocariasis in Louisiana have been published since the 1980s.

Following the devastation of Hurricane Katrina in 2005, prolonged flooding combined with poverty to create conditions that could promote the emergence of additional neglected infections, including vector-borne viral diseases such as dengue fever (Gubler et al., 2001; Moore et al., 1988; Morens and Fauci, 2008) and Chagas disease (Diaz, 2007; Dorn et al., 2007). Chagas disease is of particular concern, because of the noted rise in domestic triatomines, especially *Triatoma sanguisuga*, which transmits the causative American trypanosome *Trypanosoma cruzi* (Diaz, 2007; Dorn et al., 2007). In Louisiana, almost 30% of the armadillos and 38% of the opossums are infected with *T. cruzi*, and a case of Chagas disease was recently reported in post-Katrina New Orleans (Dorn et al., 2007). Therefore, many of the requirements for autochthonous Chagas disease transmission are in place in Louisiana (Diaz, 2007), with an established case already present. In the coming decade, global warming and increased flooding in the region could combine to promote dengue and Chagas disease epidemics among the poor in Louisiana (Gubler et al., 2001).

The feminization of poverty.

The term ''feminization of poverty'' refers to the observation that in the US and elsewhere women often have fewer economic resources than do men and are more likely to be heads of single-parent families (Starrels et al., 1994). Poverty is particularly feminized among black women (Starrels et al., 1994). As shown in Table A8-1, almost one-half of black female heads of single-parent households live below the poverty level, and black mothers are twice as likely to have premature or low birth weight infants or to have infants that die in infancy than white mothers (Braveman, 2007). Congenital infections, typically the result of primary cytomegalovirus (CMV) infection, toxoplasmosis, or syphilis during pregnancy, are important factors underlying these high rates of poor birth outcome. These congenital infections cause devastating long-term neurological

dysfunction including cognitive impairments, intellectual retardation, and hearing and vision loss (Centers for Disease Control and Prevention, 2002; McLeod et al., 2006; Prober and Enright, 2003). In this way, the major congenital infections are also important poverty-promoting factors causing billions of dollars in economic losses (Prober and Enright, 2003). In the US, black children and their mothers bear a disproportionate congenital disease burden (Staras et al., 2006). With respect to congenital CMV, black women exhibit a 4-fold increase in primary infection during pregnancy compared to white women, and when stratified for women between the ages of 12 and 19 there is almost a 50-fold increase (Colugnati et al., 2007). Of the estimated 27,002 primary CMV infections in pregnancy in the US estimated to occur annually, 6,652 of them occur in black women (Table A8-2) (Colugnati et al., 2007). Similarly, almost 55% of the cases of congenital syphilis occur among blacks (Centers for Disease Control and Prevention, 2002), and blacks suffer from higher rates of toxoplasmosis than do whites (Table A8-2) (Jones et al., 2007). In addition to primary infections during pregnancy and congenital infections, black women also exhibit an approximately 10-fold higher prevalence of trichomoniasis (13.3%) than white (1.3%) women (Sutton et al., 2007). Based on Murray's estimate that 13.3 million blacks live either in America 7 (rural South) and in America 8 (high-risk urban environments; Murray et al., 2005), I estimate that approximately 880,000 black women in the US are infected with the protozoan parasite *Trichomonas vaginalis* (Table A8-2).

Disadvantaged Urban Enclaves (Inner Cities)

High-poverty areas in American inner cities are sometimes defined as neighborhoods where more than 40% of the population is poor (Jargowsky, 1997). Jargowsky described such neighborhoods as ones that ''tend to have a threatening appearance marked by dilapidated housing, vacant units with broken or boarded up windows, abandoned or burned out cars, and men 'hanging out' on street corners'' (Jargowsky, 1997). One measure of inner city poverty used by sociologists and economists is a dissimilarity index, which measures the degree of segregation by race and income, with blacks living in the poorest neighborhoods (Glasmeier, 2006). The cities with the highest dissimilarity index are the Northeastern cities and the Midwestern cities near the Great Lakes (Figure A8-1) (Glasmeier, 2006). Several neglected infections are present in these and other disadvantaged urban enclaves.

Rat-borne and louse-borne bacterial infections.

Over the last two decades, outbreaks of leptospirosis, a bacterial infection transmitted through rat urine and responsible for a serious hemorrhagic complication known as Weil's disease, have been reported among the poor living in

Baltimore (Vinetz et al., 1996) and Detroit (Demers et al., 1985; Thiermann and Frank, 1980). Similarly, bartonellosis, caused by the gram-negative bacterium *Bartonella quintana*, has emerged among the homeless (Brouqui and Raoult, 2006; Jackson et al., 1996; Spach et al., 1995). *B. quintana* is the cause of louse-borne trench fever, so named because it was common among soldiers living under extreme conditions in the trenches during World War I (Jackson et al., 1996; Spach et al., 1995). Beginning in the 1990s, small outbreaks of *B. quintana* bacteremia and endocarditis was noted among the homeless living in Seattle, Washington, and elsewhere (Brouqui and Raoult, 2006; Jackson et al., 1996; Spach et al., 1995). With global warming and increased flooding such rat- and louse-borne infections may increase among the homeless (Gubler et al., 2001).

Toxocariasis.

Toxocariasis is an important neglected infection of poverty among socio-economically disadvantaged black children (Despommier, 2003; Herrmann et al., 1985; Sharghi et al., 2000). Playgrounds and sandboxes in poor urban neighborhoods are often contaminated with eggs of the dog roundworm, *Toxocara canis* (Chorazy and Richardson, 2005; Sharghi et al., 2000). When children accidentally ingest these roundworms eggs the released larvae migrate through tissues to cause visceral larval migrans and eosinophilic granuloma of the liver (Despommier, 2003; Kaplan et al., 2001; Sharghi et al., 2000) or ocular larva migrans (Despommier, 2003; Stewart et al., 2005). Another form of the disease, covert toxocariasis, has been associated with asthma (Buijs et al., 1997; Sharghi et al., 2000, 2001), and may possibly be linked to the rise in asthma observed in inner city children (Busse and Mitchell, 2007), as well as impaired cognitive development and lower intelligence (Marmor et al., 1987; Nelson et al., 1996; Sharghi et al., 2000). Based on serologic studies that measure antibody to *T. canis* antigens, the prevalence rate of toxocariasis among inner city blacks living in Connecticut cities was found to be 10% and even higher among inner city Hispanics (Sharghi et al., 2001). As noted previously, the prevalence among socio-economically disadvantaged blacks in the American South was as high as 30% (Herrmann et al., 1985). In an unpublished study from the CDC it was recently estimated that approximately 21% of blacks are seropositive (Won et al., 2007; Peter Schantz, personal communication), indicating exposure to the parasite. I previously estimated that approximately 500,000 blacks are seropositive for *T. canis* antibody (Hotez, 2008). However, based on the estimate that 13.3 million impoverished blacks live in America 7 and 8 (Murray et al., 2005) and prevalence estimates between 10% and 21%, as many as 1.3 million to 2.8 million individuals may be exposed or infected (Table A8-2).

African Refugees and Other Special Immigrant Groups

Since the 1980s, the US has relocated and successfully treated populations of refugees from Southeast Asia and other developing regions with high prevalence rates of helminth infections—especially hookworm infection, filarial infections, and strongyloidiasis (Garg et al., 2005; Nutman et al., 1987; Seybolt et al., 2006)—tuberculosis, and hepatitis B (Barnett, 2004). Beginning in 2000, the immigration of refugees from sub-Saharan Africa markedly increased (Franco-Paredes et al., 2007), and today the US settles an estimated 70,000 refugees annually, including 25,000 refugees from Africa (Posey et al., 2007). Notable among the refugees are the ''Lost Boys and Girls of Sudan,'' raised initially in poor Ethiopian refugee camps before relocating to Kenya (Franco-Paredes et al., 2007). Since 2000, almost 4,000 Lost Boys and Girls have been settled in the US. By serologic testing it was determined that almost one-half of these special immigrants are seropositive for both schistosomiasis (mostly *Schistosoma mansoni* infection) and strongyloidiasis (Posey et al., 2007). In addition, an estimated 8,000 Somali Bantu have been relocated to the US, with up to three-fourths of them seropositive for schistosomiasis (most likely *Schistosoma haematobium* infection) and one-fourth positive for strongyloidiasis (Posey et al., 2007). It is generally accepted that seropositivity for these two parasitic infections is a result of chronic and persistent untreated infections (Franco-Paredes et al., 2007). Therefore, of the roughly 4,000 Sudanese immigrants and 8,000 Somali immigrants there are approximately 8,000 cases of schistosomiasis and 3,000 cases of strongyloidiasis (Table 8-2). Accordingly, the CDC now recommends presumptive treatment for these special immigrant populations with anthelminthics (Franco-Paredes et al., 2007; Miller et al., 2000; Posey et al., 2007).

The Borderlands of Mexico

An estimated 10 million people live in the border region between the US and Mexico, many of whom are of Hispanic heritage (the majority American citizens) (Figure A8-1) (Glasmeier, 2006). These border communities are among the poorest in the US, and substandard or inadequate housing is common to the region (Glasmeier, 2006). Several important neglected infections of poverty occur in this setting, including vector-borne diseases, helminth infections, and other zoonoses. A related at-risk population is the estimated 750,000 to 12 million migrant farm laborers from Mexico and Central America (Holmes, 2006).

Vector-borne diseases: Dengue, Chagas disease, and leishmaniasis.

Poor housing without plumbing, air conditioning, or window screens is a key factor in promoting vector-borne diseases (Reiter et al., 2003). It has been estimated that this situation describes more than 30,000 border households, in addition to large numbers of mobile homes in the region (Glasmeier, 2006). Over

the 20-y period between 1980 and 1999 there were 65,514 cases of dengue fever reported from the Mexico side of the border, compared to only 64 cases in the US (Brunkard et al., 2007; Gubler et al., 2001; Reiter, 2001). An earlier assessment suggested that the higher-quality dwellings on the US side accounted for this disparity (Gubler et al., 2001); however, more recent studies indicate that dengue is under-reported in the US near the Mexican border (Brunkard et al., 2007). A cross-sectional survey in Brownsville, Texas and Matamoros Tamaulipas, Mexico detected 2% and 7.3% recent infections, respectively, with evidence of past infection in 40% of Brownsville residents (Brunkard et al., 2007). Risk factors and predictors of dengue among the Brownsville residents include low weekly family income, absence of air conditioning, and inadequate street drainage (Brunkard et al., 2007). Assuming that 10 million people live in the US–Mexico borderlands, a 2% prevalence of recent infections (Brunkard et al., 2007) translates to approximately 200,000 people with recent dengue fever (Table A8-2). Alternatively, the Pew Hispanic Center estimates that there are 26,784,268 Mexican Americans living in the US (Pew Hispanic Center, 2008). At an overall poverty rate of 20.6% for Hispanics in the US (Table A8-1), there are almost six million impoverished Mexican Americans in the US. If 2% of this population suffers from a recent dengue infection, I estimate there are 110,000 recent dengue infections in the US (Table A8-2).

In addition to evidence for Chagas disease in post-Katrina Louisiana as described above, the US borderlands with Mexico have also emerged as an endemic region (Beard et al., 2003; Bern et al., 2007; Centers for Disease Control and Prevention, 2006, 2007; Dodd and Leiby, 2004; Hanford et al., 2007; Leiby et al., 2000, 2002; Milei et al., 1992; Navin et al., 1985; Rassi et al., 2000; Tarleton et al., 2007; Tobler et al., 2007). Because of concerns about the risk of new contamination of the national blood supply with *T. cruzi* (Bern et al., 2003; Centers for Disease Control and Prevention, 2007; Dodd and Leiby, 2004; Leiby et al., 2002), with a recent estimate that between 1 in 4,655 and 1 in 25,000 US blood donors are seropositive for *T. cruzi* antibodies and presumed infected (Centers for Disease Control and Prevention, 2007; Tobler et al., 2007), there is great interest in expanding current blood screening efforts (Bern et al., 2007). In 2006, the US Food and Drug Administration approved a new commercial ELISA test for blood donation screening that utilizes parasite lysate antigens for detection of antibodies (Bern et al., 2007; Centers for Disease Control and Prevention, 2007). Estimates of the prevalence of Chagas disease along the Mexico border and in the US vary widely. Previously, it was estimated that 50,000 to 100,000 Latin American immigrants in the US are infected (Leiby et al., 2002), but more recently it was found that of 10,192 blood specimens from El Paso, Texas, of which 73% were from donors of Hispanic origin, three donors were positive (Tobler et al., 2007). With an overall prevalence of 0.03% (Tobler et al., 2007) and 10 million people living in the US–Mexico borderlands (Glasmeier, 2006), I estimate that approximately 3,000 people have Chagas disease in the region. Other estimates are considerably

higher. Milei et al. argued that there are 370,000 *T. cruzi*–infected individuals in the US during the 1990s (Milei et al., 1992), while Hanford et al. revised these estimates to suggest that over one million Hispanics in the US have Chagas disease (with almost 270,000 in Texas alone) and that at least 150,000 Latin America–born immigrants are expected to develop clinically apparent chronic Chagas disease (Hanford et al., 2007). Congenital Chagas disease may also occur (Bern et al., 2007; Muñoz et al., 2007). Of particular concern is the possibility that *T. cruzi* transmission to humans today occurs in the US–Mexico borderlands. In South Texas and elsewhere along the US–Mexico borderlands, dogs and coyotes are seropositive and there is a domestic canine transmission cycle (Beard et al., 2003). In addition, wood rats are common hosts, and the infection occurs among domestic cattle, horses, and sheep (Hanford et al., 2007). Infected vectors or hosts are present in 64 of the 254 counties in Texas (Hanford et al., 2007), so people living in the estimated 30,000 poor-quality dwellings in the borderlands region are at high risk for transmission.

Another vector-borne neglected disease, cutaneous leishmaniasis, is transmitted by sandflies and is endemic in Mexico and Central America. Infection with *Leishmania mexicana* has been reported from South Texas, including among individuals with no travel history (Enserink, 2000; Maloney et al., 2002); wood rats or other rodents may also serve as reservoir hosts.

Cysticercosis and other zoonoses.

Cysticercosis results when humans accidentally ingest eggs of the pork tapeworm, *Taenia solium*, which are shed or excreted by close household or family contacts. This condition is now a leading cause of epilepsy, seizures, and other neurological sequelae in the US–Mexico borderlands (DeGiorgio et al., 2005a, 2005b; del la Garza et al., 2005; Ong et al., 2002; Shandera et al., 1994; Sorvillo et al., 2007; Wallin and Kurtzke, 2004; White and Atmar, 2002), accounting for approximately 10% of seizures presenting to emergency rooms in Los Angeles and, presumably, other border cities as well (Ong et al., 2002). With an incidence rate of 8 to 10 per 100,000 per year among Hispanic populations (Shandera et al., 1994; Wallin and Kurtzke, 2004), I previously estimated that up to 3,500 new cases of cysticercosis occur annually (Hotez, 2008). In a seroprevalence study of rural Ventura County, California, it was found that 1.8% of that population have cysticercosis (DeGiorgio et al., 2005a, 2005b). I previously reported that there are 41,400 Hispanics in the US with cysticercosis (Hotez, 2008), but based on the observation that 9.4 million Hispanics live in poverty in the US (Pew Hispanic Center, 2008), the number of people with cysticercosis may be substantially higher. If 1.8% of this population is also infected, there may be as many as 169,000 cases of cysticercosis among Hispanics in the US (Table A8-2).

There are two other zoonoses of medical importance in the US–Mexico borderlands. Brucellosis is one of the most common zoonosis worldwide and a

leading cause of disability (Pappas et al., 2006). Goat and cow dairy products are an important source of infection from Mexico (Troy et al., 2005), with 1,056 cases of brucellosis reported between 1993 and 2002 (although Mead et al. (1999) estimated that 1,554 cases occur annually, of which almost 80% of the cases occur among individuals of Hispanic origin; Troy et al., 2005). Between 1994 and 2000, 129 cases of bovine tuberculosis (*Mycobacterium bovis*) were reported, nearly all among patients of Hispanic origin, particularly children (LoBue et al., 2003).

Neglected infections among migrant farm workers.

Approximately 95% of the several million migrant agricultural workers in the US were born in Mexico, and almost all of them live below the poverty line (Holmes, 2006). They have significant health disparities, with case fatality rates more than five times the US average. In addition to very high rates of HIV, tuberculosis, and chronic diseases (Centers for Disease Control and Prevention, 1992; Holmes, 2006; Poss, 1998; Villarejo, 2003), the Mexican-born migrant workers living in the US often suffer from high rates of parasitic infection, including ascariasis and hookworm infection (Bechtel, 1998; Ciesielski et al., 1992; Holmes, 2006; Ortiz, 1980) (for which there is evidence of autochthonous transmission on US farms; Ciesielski et al., 1993), cysticercosis and Chagas disease (Ciesielski et al., 1993; Villarejo, 2003), and other neglected infections (Centers for Disease Control and Prevention, 1992; Holmes, 2006).

Tribal Lands and Arctic Native Americans

Approximately 4 million Native Americans are distributed among 500 tribes in the United States, with approximately one fourth living on tribal lands or lands specifically designated as Native American lands (Figure A8-1) (Glasmeier, 2006). Almost 30% of those living on tribal lands live in poverty, where the child poverty rates are more than 40% (Glasmeier, 2006).

Neglected infections in continental US tribal lands.

Across the US, Native Americans are highly susceptible to diabetes mellitus and obesity, and almost one-third of Native Americans die before the age of 45 (Glasmeier, 2006). Up to 40% of Native Americans also live in overcrowded conditions (Glasmeier, 2006), and because of this and for additional reasons of genetic susceptibility and low vaccine coverage, high rates of invasive bacterial and viral respiratory infections occur among Native Americans, especially the Navajo and Apache (Benin et al., 2005; Bockova et al., 2002; Millar et al., 2005; Watt et al., 2007). On some reservations up to one in five homes lack complete

in-house plumbing, a rate that is 20 times the national average (Glasmeier, 2006). In this setting, certain neglected infections of poverty are common. Over the last twenty years in the American Southwest, trachoma has been common among the Navajo (Ludlam, 1978; Rearwin et al., 1997), while cystic echinococcosis has been endemic among the Navajo, Zuni, and Santo Domingo Indians because of an enzootic dog–sheep cycle on tribal lands and elsewhere in the region (Katz et al., 1980; Pappaioanou et al., 1977; Schantz et al., 1977).

Neglected infections among the Inuit.

Because of their dietary reliance on meat from sea mammals and polar bear the Inuit living in Alaska and the Canadian Arctic are at risk of foodborne parasitic diseases, including echinococcosis, toxoplasmosis and congenital toxoplasmosis, and trichinellosis (Hotez, 2008). Cystic echinococcosis in the Arctic is due to an enzootic cycle involving moose, reindeer, and elk (Rausch, 2003), while trichinellosis caused by *Trichinella spiralis nativa* is prevalent because of high rates of infection among walruses and polar bear (Proulx et al., 2002). Toxoplasmosis and congenital toxoplasmosis are also extremely common among the Inuit, and are due to consumption of infected seal and caribou meat (McDonald et al., 1990).

Other Regions

The most diagnosed parasitic in the infection in the US is giardiasis (Kappus et al., 1994; Yoder et al., 2007), with as many as 2.0–2.5 million cases occurring annually (Furness et al., 2000; Mead et al., 1999). The greatest number of cases occurs between June and October and among children aged 1–4 and 5–9 y and adults aged 35–39 y (Yoder et al., 2007). An estimated 300,000 cases of cryptosporidiosis also occur annually (Mead et al., 1999), and this infection has emerged as a leading cause of recreational water outbreaks of diarrhea in the US and among patients with HIV/AIDS (Yoder et al., 2007). A 10-fold increase in cryptosporidiosis transmission occurs during the summer and early fall (Yoder et al., 2007). Although both giardiasis and cryptosporidiosis are common, there is no evidence to suggest that they disproportionately affect poor and underrepresented minority populations. In contrast, the intestinal protozoan disease amebiasis does disproportionately affect the poor, but no US prevalence data are available for this disease. Among the notifiable neglected infections of poverty there were 166 cases of leprosy (with most of the cases in Texas, California, New York and Louisiana; Truman et al., 2005), 16 cases of trichinellosis, and two cases of human rabies reported in 2005 (Table A8-2) (Centers for Disease Control and Prevention, 2007).

Policy Recommendations

Based on my estimates of prevalence (Table A8-2) and other health and socioeconomic impacts, the most important neglected helminth infections of poverty in the US are the helminth diseases toxocariasis (inner cities and the American South), ascariasis (Appalachia and the American South), strongyloidiasis (Appalachia), and cysticercosis (US–Mexico borderlands). Among the important vector-borne neglected infections are dengue and Chagas disease in the US–Mexico borderlands and in post-Katrina Louisiana. Congenital infections such as congenital CMV and congenital syphilis stand out as health disparities in inner cities and the American South. Trench fever and leptospirosis are important among the homeless and other disadvantaged urban populations.

Among the common features of these neglected infections are (1) their highly disproportionate health impact on people of color and people living in poverty; (2) their chronic, largely insidious, and disabling features; and (3) their ability to promote poverty because of their impact on child development, pregnancy outcome, and productive capacity. It is important to note that, while some of these neglected infections occur exclusively among recent immigrant populations, most do not. Instead, poverty is the single most important determinant. Control of these neglected infections needs to be prioritized by policy makers and public health experts because it is both a highly cost-effective mechanism for lifting disadvantaged populations out of poverty and consistent with our shared American values of equity and equality (Putsch and Pololi, 2004). The World Health Organization also recognizes that control of neglected diseases represents a fundamental human right (Hunt, 2006).

An important obstacle to the control or elimination of the neglected infections of poverty in the US is the absence of reliable population-based estimates of prevalence and disease burden data about these conditions (Hotez, 2007, 2008). These neglected infections are underdiagnosed and most are not reportable to the CDC. The estimates I provide here are preliminary and based on very few active surveillance studies, including some obtained by analyses of sera collected from National Health and Examination Surveys. For some of the neglected infections of poverty, seropositivity may be equated with active infection (Brunkard et al., 2007; DeGiorgio et al., 2005a; Franco-Paredes et al., 2007; Posey et al., 2007; Tobler et al., 2007), whereas for others it may reflect both current and past infections (Despommier, 2003; Herrmann et al., 1985). For infections such as Chagas disease estimates reported here vary widely. We also lack a system for the national collection of fecal samples for intestinal parasitic infections. Expanded measures are urgently needed to implement active surveillance and obtain population-based estimates of the neglected infections (Table A8-3). An added measure would be to expand newborn screening for toxoplasmosis (Hotez, 2007; Kim, 2006), and possibly congenital Chagas disease. Screening for congenital toxoplamosis would also likely benefit persons of all socioeconomic circumstances (McLeod et al.,

2006). Such efforts would create opportunities to determine the extent and true disease burden of these neglected infections.

There is also an urgent need to better define the transmission dynamics of some of the neglected diseases (Table A8-3). For Chagas disease, and to some extent, dengue and leishmaniasis, the full extent of authochthonous transmission in Louisiana and the US–Mexico borderlands is poorly understood. A full appreciation of Chagas disease transmission mechanisms would include molecular genotyping of the parasite to determine whether different strains or demes are endemic, and a complete characterization of the different vectors and animal reservoir hosts. Similarly, the extent of autochthonous cysticercosis transmission in the US is largely unstudied, as it is for many of the bacterial zoonoses including urban foci of leptospirosis and trench fever. For toxocariasis, the contribution of feral versus domesticated animal reservoirs to transmission is also not well understood.

Following enhanced surveillance and improved understanding of transmission dynamics, there are several opportunities to treat or prevent neglected infections of poverty in the US using existing drugs or other control tools (Table A8-3). Through either populationbased drug administration or case identification and treatment, the soil-transmitted helminths could be controlled by administration of albendazole and ivermectin (Bethony et al., 2006), while expanded use of praziquantel would treat schistosomiasis among selected immigrant populations (Posey et al., 2007) and prevent transmission of *T. solium* eggs and possibly reduce the incidence of cysticercosis (Garcia et al., 2007). Metronidazole and tinidazole are available for the treatment of trichomoniasis and giardiasis (Nailor and Sobel, 2007; Tinidazole, 2004), and nitazoxanide is available for cryptosporidiosis and giardiasis (Nitazoxanide, 2003; Yoder et al., 2007). Pyrimethamine plus sulfadiazine is used for the treatment of toxoplasmosis, and the optimal length of treatment and its impact on child development and neurological sequelae need to be determined (McLeod et al., 2006). Antibiotics are available for the treatment of leptospirosis and other bacterial zoonoses (Griffith et al., 2006). An important role also exists for veterinary public health interventions to prevent zoonotic transmission to humans, possibly including the mass treatment of *Toxocara*-infected dogs, *Toxoplasma*-infected cats, and other measures (Jones et al., 2008). The control of almost all of the neglected infections of poverty would also benefit from improvements in environmental sanitation, piped clean water, and improvements in housing in some of the poorest endemic areas. For Chagas disease, dengue, and leishmaniasis, consideration of expanded vector control approaches is warranted (Gubler et al., 2001; Yamagata and Nakagawa, 2006).

Development of new control and prevention tools is needed (Table A8-3). Currently, the serologic-based diagnostic tests for most of the parasitic infections rely on extracts or crude preparations of parasite antigens and would benefit from the development of improved and widely available diagnostic kits that utilize standardized and purified recombinant antigens. For Chagas disease there is a

TABLE A8-3 Priority Needs for Enhanced Surveillance, Treatment, and Prevention Efforts for the High Priority Neglected Infections of Poverty

Disease Category	Disease	Expanded Active Surveillance and Treatment	Newborn Screening and Treatment	Epidemiological Transmission Studies	New Diagnostics	New Drugs	New Vaccines
Helminth Infections	Ascariasis	+		+			
	Toxocariasis	+		+	+		
	Strongyloidiasis	+		+	+		
	Cysticercosis	+		+	+	+	
Protozoan Infections	Giardiasis	+					
	Cryptosporidiosis	+		+		+	
	Trichomoniasis	+					
	Chagas disease	+	+	+	+	+	+
	Leishmaniasis	+		+	+	+	+
	Congenital toxoplasmosis	+	+	+	+	+	+
Bacterial Infections	Congenital syphilis		+	+			
	Brucellosis	+		+			
	Bovine tuberculosis	+		+			
	Trench fever	+		+			
	Leptospirosis	+		+			
Viral Infections	Dengue fever	+		+		+	+
	Congenital CMV	+	+	+		+	+

particularly urgent need for rapid diagnostic tests and polymerase chain reaction-based assays for detection of acute and congenital infections. Furthermore, no drugs adequately and reliably treat Chagas disease (Rocha et al., 2007), dengue (Keller et al., 2006), or congenital CMV infection (DeVries, 2007). Although vaccines for dengue (Pediatric Dengue Vaccine Initiative, 2008) and CMV infection (Schleiss and Heineman, 2005) are under development, progress has been slow because of inadequate resources and commercial incentives (Hotez and Ferris, 2006). A pediatric dengue vaccine initiative was recently established through support by the Gates Foundation (Pediatric Dengue Vaccine Initiative, 2008). For CMV infection, both a live attenuated vaccine and a recombinant vaccine have been developed (Schleiss and Heineman, 2005), but clinical testing in pregnant women to determine the impact of these vaccines on vertical transmission has been severely lagging because of inadequate support—a tragedy, given that more than 10,000 congenital CMV infections occur among infants of color annually (Colugnati et al., 2007).

In 2006, the annual budget of the National Institute of Allergy and Infectious Diseases (NIAID) was $4.4 billion, with approximately $1.6 billion of this amount spent on biodefense (U.S. Department of Health and Human Services, 2008). Of the selected disease-specific areas targeted for funding by the NIAID in their published annual report, none specifically mentions a neglected infection of poverty (U.S. Department of Health and Human Services, 2008). A consequence of this lack of targeted funding for neglected diseases is that the development of critically needed new tools for these conditions has lagged behind those for biodefense. The Global Forum on Health Research has coined the term ‘‘the 10/90 gap’’ to describe how only 10% of resources are devoted to 90% of the global burden of disease, i.e., that represented by disease disproportionately occurring in developing countries (Bell, 2005). The absence of development of new tools for neglected infections of poverty, such as those outlined above, highlights a unique American 10/90 gap for poor people and people of color in the US.

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A9

DEVELOPING VACCINES TO COMBAT HOOKWORM INFECTION AND INTESTINAL SCHISTOSOMIASIS[9]

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Abstract: Hookworm infection and schistosomiasis rank among the most important health problems in developing countries. Both cause anaemia and malnutrition, and schistosomiasis also results in substantial intestinal, liver and genitourinary pathology. In sub-Saharan Africa and Brazil, co-infections with the hookworm, *Necator americanus*, and the intestinal schistosome, *Schistosoma mansoni*, are common. The development of vaccines for these infections could substantially reduce the global disability associated with these helminthiases. New genomic, proteomic, immunological and X-ray crystallographic data have led to the discovery of several promising candidate vaccine antigens. Here, we describe recent progress in this field and the rationale for vaccine development.

In terms of their global health impact on children and pregnant women, as well as on adults engaged in subsistence farming, human hookworm infection (known as 'hookworm') and schistosomiasis are two of the most common and important human infections (Hotez et al., 2008a, 2008b). Together, their disease burdens exceed those of all other neglected tropical diseases (Hotez et al., 2006; King and Dangerfield-Cha, 2008; King et al., 2005; WHO Expert Committee, 2002). They also trap the world's poorest people in poverty because of their deleterious effects on child development and economic productivity (Bleakley, 2007; Hotez et al., 2009; King, 2010). Until recently, the importance of these conditions as global health and economic problems had been underappreciated. Even the United Nations Millennium Development Goals for sustainable poverty reduction did not specifically mention these two conditions (Hotez et al., 2007). An important reason for this 'neglect' is that hookworm and schistosomiasis typically affect health without resulting in mortality, with infections such as HIV or malaria causing tenfold more deaths (Table A9-1). However, when the chronic morbidities of these two infections are fully considered according to disability-adjusted life years (DALYs; years of life lost owing to disability, ill health or death), hookworm and schistosomiasis combined rank among the most important diseases in developing countries, resulting in 4.5–92 million DALYs annually, the upper limit of which is greater than the DALYs due to malaria or HIV/AIDS (Hotez et al., 2006; King and Dangerfield-Cha, 2008; King et al., 2005). Current efforts to control hookworm and schistosomiasis are inadequate and new tools that combat hookworm and schistosomiasis, with an emphasis on disease caused by *Necator americanus*, the major hookworm of humans, and *Schistosoma mansoni*, the primary cause of intestinal schistosomiasis.

Global Distribution and Pathobiology

Hookworms are roundworm parasites that belong to the phylum Nematoda. They share phylogenetic similarities with the free-living nematode *Caenorhabditis elegans* and with the parasitic nematodes *Nippostrongylus brasiliensis* and

TABLE A9-1 Impact of hookworm, schistosomiasis, HIV/AIDS, and malaria.

Disease	Main causative agents	Infections	DALYs*	Deaths (annual)	Refs
Hookworm	*Necator americanus* and *Ancyostoma duodenale*	576-740 million	1.5-22.1 million	65,000	Bethony et al. (2006)
Schistosomiasis	*Schistosoma haematobium*, *Schistosoma mansoni*, and *Schistosoma japonicum*	207 million	3-70 million	280,000	King and Dangerfield-Cha (2008); Steinmann et al. (2006)
HIV/AIDS	HIV-1 and HIV-2	33.2 million	84.5 million	2.1 million	Cohen et al. (2008); WHO, 2004
Malaria	*Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium knowlesi*	515 million	46.5 million	1 million	Greenwood et al. (2008); Rowe et al. (2006); Snow et al. (2005); WHO, 2004

*The wide range of disability-affected life year (DALY) estimates for hookworm infection and schistosomiasis reflects alternative disability weights assigned by different investigators. Such differences are expected to be resolved in the coming years through an initiative of the Institute of Health Metrics and Evaluation at the University of Washington, Seattle, USA.

Heligmosomoides polygyrus, which are often used by immunologists to study T helper 2 (TH2) cell and related responses in mice (Finkelman et al., 2004) (Box A9-1). Schistosomes are platyhelminths (flatworms) that belong to the order Trematoda (commonly called the trematodes or flukes). Human infections with hookworms and schistosomes occur predominantly in areas of rural poverty in sub-Saharan Africa, Southeast Asia and tropical regions of the Americas. The epidemiology and pathobiology of both hookworm and schistosomiasis have been extensively reviewed recently (Bethony et al., 2006; Brooker et al., 2004; Gryseels et al., 2006; Hotez et al., 2004, 2005; Steinmann et al., 2006) and are only briefly discussed here.

Hookworm

The global distribution and life cycle of hookworms are shown in Figure A9-1. An estimated 600 million to 700 million people are infected worldwide, with the most infections occurring in the Asian countries of Indonesia, Bangladesh and India (60 million to 70 million people in each), followed by Nigeria and the Democratic republic of the Congo in Africa, and Brazil (30 million to 40 million people in each) (Bethony et al., 2006; de Silva et al., 2003; Hotez and Kamath,

BOX A9-1
Immune Evasion and Regulation of Helminth Infections

- Vaccination against hookworm and schistosomiasis requires more than the discovery of target antigens. An understanding of the immunology of the host–parasite relationship is necessary to avoid inducing ineffective immune mechanisms or amplifying a dangerous immunopathogenic response (Maizels et al., 1999, 2004).
- Infection with these helminths occurs in childhood and (in the case of hookworms) sometimes plateaus or increases in intensity as adults age (Bethony et al., 2002); in addition, infected individuals can tolerate the presence of the parasite for years and even decades.
- Both infections are typically overdispersed in endemic areas, with a minority (5–10%) of infected individuals harbouring most (80%) of the parasites (Bethony et al., 2002, 2006). Severe immunopathological complications such as granulomatous disease and organ failure are also highly overdispersed, occurring in only 10% of people with these infections (Andrade, 2009).
- Helminths have an elaborate life cycle in the human host, with a succession of developmental stages that occupy a range of exposed extracellular locations, such as the skin, vasculature, bloodstream and gastrointestinal tract (Hotez et al., 2004; Maizel et al., 1999).
- Helminth infection leads to a strong T helper 2 (T_H2)-type response, a phenomenon that is important for immunology as a whole (Maizels et al., 1999, 2004). The T_H2-type response is characterized by elevated levels of total and parasite-specific immunoglobulin E (IgE), as well as by increased levels of interleukin-4 (IL-4), IL-5 and IL-13, with concomitant expansion and mobilization of specific effector cells such as mast cells, eosinophils and basophils (Maizels et al., 1999, 2004). The high levels of total and specific IgE associated with hookworm are comparable to levels seen in allergic diseases in non-endemic countries (Erb, 2007).
- The T_H2 response is induced against a background of potent, parasite-induced immunoregulation, thought to be mediated by alternatively activated macrophages, CD4+CD25+ forkhead box P3+ regulatory T cells and CD4+CD25+ IL-10-producing T regulatory 1 cells (Erb, 2007; Maizels et al., 1999, 2004).
- This response creates an immune environment so extensively downregulated that it not only protects the host from the strong inflammatory effects of helminth infection (especially in *Schistosoma mansoni* infection), but may also partially reduce the effects of other IgE-mediated disorders such as atopy, asthma and anaphylaxis (Erb, 2007; Maizels et al., 2004).
- Convincing proof-of-concept evidence that vaccines may be realistic goals comes from the successful immunization of laboratory animals (for *S. mansoni*) and canines (for *Ancylostoma caninum*) with radiation-attenuated, live larval parasites, or thevaccination of livestock with adult-stage antigens (linked with parasite blood feeding) to protect against blood-feeding nematode parasites that cause haemonchiasis.

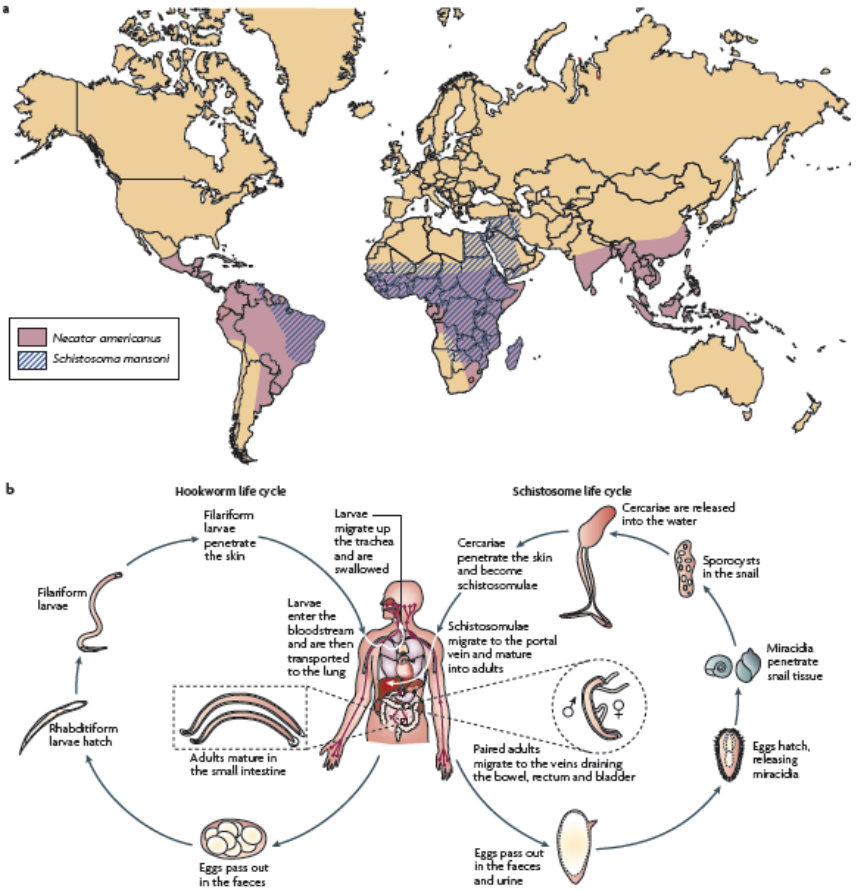

FIGURE A9-1 Global distributions and life cycles of hookworms and schistosomes. **a|** The distribution of *Schistosoma mansoni*, which causes intestinal schitosomiasis and *Necator americanus*, a hookworm, are shown (deSilva et al., 2003; Hotez et al., 2004, 2005). **b|** The life cycles of hookworms and schistosomes.

2009; Hotez et al., 2008c). Approximately 85% of hookworm infections are caused by *N. americanus*, and the remainder are caused by *Ancylostoma duodenale*. Microscopic infective larvae (third-stage larvae, or L3) live as non-feeding, non-replicating, developmentally arrested environmental stages in the soil, where they survive for a few days to weeks, depending on the temperature and the level of moisture. Hookworm L3 phenotypically resemble the developmentally arrested dauer larvae of *C. elegans* (Tissenbaum et al., 2000). Human infection occurs when L3 come into contact with the skin. Larvae actively penetrate skin and

migrate in the afferent vasculature to the lungs, where they ascend the pulmonary tree to the pharynx, are swallowed and moult to become adult male and female hookworms ~1 cm long. Adult hookworms burrow deep into the mucosa and submucosa of the small intestine, eventually rupturing capillaries and arterioles (Brooker et al., 2004; Hotez et al., 2004). Blood ingestion ensues, followed by the lysis of erythrocytes, an ordered enzymatic digestion of host haemoglobin (Ranjit et al., 2009; Williamson et al., 2004) and haeme detoxification (Zhan et al., 2005, 2010). Almost all of the pathology and morbidity owing to hookworm is the result of intestinal blood loss (Hotez et al., 2004). Female and male hookworms mate in the small intestine, and the females release microscopic eggs that exit the body in host faeces. The eggs hatch in the soil, resulting in a new generation of first-stage larvae, which feed on bacteria and other organic debris in the soil before they moult twice to the L3 stage and continue the life cycle.

Schistosomiasis

Approximately 90% of the world's 207 million cases of schistosomiasis occur in sub-Saharan Africa, with the most in Nigeria, Tanzania, the Democratic republic of the Congo and Ghana (Steinmann et al., 2006). In Africa, *Schistosoma haematobium* is the cause of urinary tract schistosomiasis (accounting for approximately two-thirds of the world's cases of schistosomiasis), whereas *S. mansoni* is the main cause of intestinal schistosomiasis (approximately one-third of total cases) (Figure A9-1). *S. mansoni* also causes intestinal schistosomiasis in Latin America, with most of the cases occurring in Brazil, whereas *Schistosoma japonicum* and *Schistosoma mekongi* cause fewer than one million cases of intestinal schistosomiasis in Asia (Steinmann et al., 2006). Schistosomiasis is a fresh-water-borne disease, and humans become infected when free-swimming microscopic cercariae penetrate the skin. These larvae shed their tails to become schistosomulae, which enter the vasculature and lungs before relocating to the venous system, where they become sexually mature adults that pair and mate (Gryseels et al., 2006). Adult *S. haematobium* schistosomes migrate to the venous plexus, which drains the bladder and reproductive organs, whereas *S. mansoni* and *S. japonicum* go to the mesenteric veins draining the intestine (Gryseels et al., 2006). Female schistosomes produce eggs that are equipped with a spine to facilitate penetration through blood vessels and into the urinary tract and genitals (*S. haematobium*) or into the intestine and liver (*S. mansoni* and *S. japonicum*). During chronic infection, which can last 5–7 years, much of the pathology from schistosome infection is a product of the immune response to parasite eggs in host tissues, and the resulting granulomatous lesions lead to fibrosis, which, in turn, can cause severe circulatory impairment of the affected organs (Gryseels et al., 2006; King and Dangerfield-Cha, 2008; Steinmann et al., 2006).

Hookworms, Schistosomes and Anaemia

Both hookworm and schistosomiasis cause chronic anaemia that, over the long term, can manifest as impaired neurological and cognitive functioning in children, diminished work capacity in adults, and adverse outcomes of pregnancy in both mother and child (Tolentino and Friedman, 2007). The WHO defines anaemia as a blood haemoglobin concentration of below 11–13 g per 100 ml, depending on age, sex and pregnancy status; severe anaemia in pregnancy is defined as a haemoglobin concentration of below 7 g per 100 ml (WHO, 2001). Approximately 50% of anaemia cases result from iron deficiency (iron deficiency anaemia (IDA)), with nearly three-quarters of the morbidity from IDA occurring in the poorest regions of Africa, Asia and the Americas (Stoltzfus, 2003). IDA is associated with ~841,000 deaths and ~35 million DALYs annually, mostly by contributing to both maternal and perinatal mortality and through adverse effects on childhood development and cognition (Larocque et al., 2005; Stoltzfus, 2003). Young children are particularly susceptible to IDA, because of their increased iron requirements during growth periods, as are women of reproductive age, because of menstrual losses and the high iron demands of a growing fetus during pregnancy (Tolentino and Friedman, 2007).

Hookworm-associated anaemia

IDA is the hallmark of hookworm and results from intestinal blood loss caused by the feeding of adult worms at the site of parasite attachment in the intestine (Crompton, 2000; Hotez et al., 2004). Infection with 25–30 adult *N. americanus* hookworms results in at least 1 ml of blood loss per day, a volume containing an amount of iron roughly equivalent to the daily requirement of an adolescent boy or girl and slightly more than the daily requirement of a younger child in order for them to grow (Crompton, 2000; FAO and WHO, 2002). As well as causing IDA, intestinal blood loss can result in protein malnutrition (Brooker et al., 2004; Hotez et al., 2004). Numerous epidemiological studies confirm the substantial contribution of hookworm to the global burden of IDA (Stoltzfus et al., 1997). Among school-aged children in Zanzibar, Tanzania, 41% of IDA and 57% of moderate to severe anaemia is attributable to hookworm (Stoltzfus et al., 1997). Hookworm has been shown to be an important risk factor for anaemia in Brazilian schoolchildren (Brooker et al., 2007), and it has been identified as a key determinant of IDA in preschool children in Kenya (Brooker et al., 1999), Tanzania (Sousa-Figueiredo et al., 2008) and Malawi (Calis et al., 2008). Similarly, studies have identified hookworm as an important cause of IDA in non-pregnant women in Zanzibar and Vietnam (Nguyen et al., 2006; Stoltzfus et al., 1997), whereas it accounts for 41–54% of the moderate to severe anaemia in pregnant women in Nepal (Dreyfuss et al., 2000; Stoltzfus et al., 1997). The positive association between intensity of the hookworm infection and anaemia in children and during pregnancy was confirmed in recent meta-analyses (Brooker

et al., 2008; Smith and Brooker, 2010). For both children and women, anaemia is far more likely to be present in those with moderate to heavy hookworm infections (Brooker et al., 2008; Stoltzfus et al., 1997), which are defined on the basis of quantitative faecal egg counts exceeding 1,999 eggs per gram (epg) of faeces compared with counts of individuals with no or light infection (<2,000 epg of faeces) (WHO Expert Committee, 2002).

Schistosomiasis-associated anaemia

All of the major forms of human schistosomiasis are associated with anaemia (Friedman et al., 2005a, 2005b; King and Dangerfield-Cha, 2008; King et al., 2005; Koukounari et al., 2006, 2007, 2008; Stephenson, 1993; Sturrock et al., 1996; Tohon et al., 2008). As found for hookworm, children and pregnant women infected with schistosomes are especially susceptible to anaemia (Ajanga et al., 2006; Friedman et al., 2005a, 2005b, 2007; Koukounari et al., 2006, 2007, 2008; Prual et al., 1992; Stephenson, 1993; Sturrock et al., 1996; Tohon et al., 2008) and reduced haemoglobin concentrations in both have been associated with moderate to high faecal or urine schistosome egg counts (Friedman et al., 2005a; Koukounari et al., 2006, 2007, 2008; Prual et al., 1992; Sturrock et al., 1996; Tolentino and Friedman, 2007). The anaemia associated with schistosomiasis has been attributed to several mechanisms, including iron deficiency due to blood loss in the intestine or urine, splenic sequestration and destruction of erythrocytes, autoimmune haemolysis, and the chronic inflammatory response to schistosome eggs deposited in host tissues (Friedman et al., 2005b; Tolentino and Friedman, 2007).

Co-infections

In Africa and South America, co-infections with hookworm and schistosomes are common, and there are at least a dozen countries with more than five million cases of each helminth infection (Hotez et al., 2008b). It has been proposed that co-infection with *N. americanus* and *S. mansoni* is synergistic with respect to worm burdens and the resulting pathologic sequelae, including anaemia (Brito et al., 2006; Brooker et al., 2007; Ezeamama et al., 2008; Fleming et al., 2006; Friis et al., 2003; Guyatt et al., 2001; King, 2010; Lwambo et al., 1999; Raso et al., 2006; Stephenson, 1994; Stephenson et al., 1985). A similar relationship has been suggested between hookworm and *S. japonicum* infection in East Asia (Ezeamama et al., 2008). In sub-Saharan Africa, there is also extensive geographical overlap among areas of hookworm, schistosomiasis, and malaria transmission resulting from infection with *Plasmodium falciparum*, another notable cause of anaemia (Brooker et al., 2007; Demissie et al., 2009). In Kenya and Tanzania, the anaemias resulting from hookworm and *P. falciparum* co-infections have been shown to be additive (Brooker et al., 2007). There are

conflicting data on whether hookworm or schistosomiasis increase host susceptibility to malaria or adversely affect the clinical course of the disease (Hotez et al., 2006). In Africa, female genital schistosomiasis caused by *S. haematobium* was shown to increase the odds ratio of acquiring HIV/AIDS threefold (Kjetland et al., 2006), and it has been suggested that *S. mansoni* may also affect susceptibility to HIV (Chenine et al., 2008; Da'dara and Harn, 2010). Hookworm and other intestinal nematode infections are immuno modulatory and may increase viral loads and the progression of HIV/AIDS (Bentwich et al., 2008), but larger studies are needed to confirm this relationship. Anaemia itself may adversely affect the course of HIV/AIDS (Moore, 2000), so hookworm and schistosomiasis may indirectly impact the progression of this disease. The global public health impact of anaemia and other pathological sequelae resulting from hookworm and schistosomiasis have stimulated efforts to develop more effective control strategies for these conditions. Such measures include the development of new control tools, foremost among these being anthelmintic vaccines. The current status of the development of vaccines is outlined below, first for hookworm and then for schistosomiasis.

Rationale For a Human Hookworm Vaccine

Hookworm and other common intestinal helminth infections such as ascariasis and trichuriasis are strongly associated with poverty and poor sanitation. However, improvements in sanitation or other environmental and personal protective control measures (such as footwear) frequently have a minimal impact on parasite prevalence or the intensity of infection, especially without accompanying programmes of health education and economic development (Asaolu and Ofoezie, 2003; Moraes et al., 2004). The WHO has proposed annual mass treatment (that is, deworming of an entire population or age stratum in an endemic area) with a benzimidazole such as albendazole or mebendazole as the most cost-effective means of reducing the childhood morbidity related to chronic intestinal helminth infection (although the impact on improving childhood cognition is variable) (Hotez, 2009; Olsen, 2007; Smith and Brooker, 2010; WHO, 2006, 2008). There is evidence that both albendazole and mebendazole interfere with invertebrate tubulin and microtubules and reduce the number of adult worms in the intestine (Geary et al., 2010). In 2001, the 54th World Health Assembly committed to providing annual deworming for school-aged children wherever the prevalence in this age group exceeds 50% (Hotez, 2009; Olsen, 2007; Smith and Brooker, 2010; WHO, 2006, 2008), although as of 2008 only 9% of school-aged children and 21% of preschool-aged children at risk of acquiring intestinal helminth infections have benefited from this intervention (Hotez, 2009; WHO, 2008).

New information indicates that annual deworming may be less effective for hookworm than other intestinal helminth infections. For example, single-dose

albendazole or mebendazole typically achieves either cure or substantial reductions in worm burdens and faecal egg counts for ascariasis (Hotez, 2009; Keiser and Utzinger, 2008). However, for hookworm high rates of drug failure have been reported for mebendazole, with an average cure rate of only 15% (Keiser and Utzinger, 2008). Furthermore, after repeated administration in the same population, the efficacy of mebendazole has been reported to diminish over time (Albonico et al., 2003), raising concerns about possible drug resistance. Indeed, drug failures have been shown to occur with benzimidazoles when used ubiquitously in livestock and have been associated with specific point mutations in the parasite gene encoding β-tubulin (Geerts and Gryseels, 2000). Although the same mutations have not yet been associated with drug failure in humans, efforts are underway to determine whether benzimidazole failures for hookworm and other helminth infections result from similar resistance mechanisms (Geerts and Gryseels, 2000).

Evidence of widespread mebendazole drug failure indicates that the global control of human hookworm depends solely on the continued efficacy of albendazole. However, although treatment with albendazole cures existing infections, it does not confer protection from reinfection, which often occurs as early as 6 months after treatment in areas of high transmission (Albonico et al., 1995). Concerns about mebendazole drug failure, possible emerging resistance to the benzimidazoles and the rapid reinfection after treatment provided the impetus for establishing the Human Hookworm Vaccine Initiative, a non-profit product development partnership based at the Sabin Vaccine Institute (Washington DC, USA) that was established in 2000 to develop and test new vaccines for hookworm (Bethony et al., 2006; Bottazzi and Brown, 2008; Brooker et al., 2004; Diemert et al., 2008; Hotez and Brown, 2008; Hotez and Ferris, 2006; Hotez et al., 2008a, 2008b; Loukas et al., 2006). Prior efforts to develop human hookworm vaccines were limited to basic research conducted in university laboratories, although a live attenuated canine hookworm vaccine was developed by industry and briefly marketed for pet owners in the early 1970s (Bethony et al., 2006; Loukas et al., 2006; Miller, 1978). The HHVI is the only partnership in the world that is currently working on vaccine development for hookworm and consists of investigators from the Sabin Vaccine Institute, the George Washington University (Washington DC, USA), The Fundacao oswaldo Cruz (FIoCrUZ; Brazil), the Instituto Butantan (Sao Paulo, Brazil), James Cook University (Cairns, Australia) and the London School of Hygiene and Tropical Medicine (UK). The ultimate aim of vaccine development efforts is to prevent moderate and heavy hookworm infections (that is, infections associated with faecal egg counts exceeding 1,999 epg of faeces), which are associated with substantial intestinal blood loss. Such a vaccine could be administered to very young preschool-aged children in a programme of 'vaccine-linked chemotherapy' (Bergquist et al., 2008) before their exposure to infective larvae in the environment, or to both preschool-aged and school-aged children who may have already been exposed and even infected.

Targeting Hookworm Blood Feeding

The vaccines that are currently under development by the HHVI target the nutritional and metabolic requirements of the adult hookworm. The main approach has been to identify the essential components involved in parasite blood feeding, to genetically engineer these components as recombinant proteins and then to combine the recombinant components with one or more adjuvants to elicit protective antibodies on vaccination (Loukas et al., 2006). These protective antibodies would either directly neutralize the parasite macromolecules required for blood feeding and nutrition or indirectly damage important parasite structures. Protective immunity in vaccinated individuals would manifest as diminished hookwormrelated blood loss and reduced numbers of hookworms in the intestine compared with levels in unvaccinated people. Based on prior experiences with live attenuated helminth vaccines for veterinary use, including those for canine hookworm and bovine lungworm, sterilizing immunity is not considered an attainable — or necessary — goal for anthelmintic vaccines (Bethony et al., 2006; Miller, 1978; Urquhart, 1985) (Table A9-2). However, as the morbidity associated with hookworm is proportional to the number of worms harboured by individuals, a vaccine that prevents most moderate and heavy infections would be sufficient to have a major impact on the worldwide burden of hookworm and the associated anaemia.

Over the past decade, the molecular basis by which hookworms ingest and derive nutrition from host blood has been elucidated. As with all haematophagous parasites, *N. americanus* depends on host haemoglobin and serum proteins for survival. Adult hookworms ingest blood, lyse erythrocytes, degrade haemoglobin and serum proteins, and then absorb the digested peptides and amino acids (Ranjit et al., 2009; Williamson et al., 2004) (Figure A9-2). Following haemolysis, adult *N. americanus* hookworms use a hierarchical cascade of haemoglobinases (haemoglobin-degrading proteases), beginning with the cleavage of intact haemoglobin by an aspartic protease, APr1, followed by further proteolysis through the action of several cysteine proteases and metalloproteinases, all of which are expressed in the brush border membrane of the parasite's digestive tract (Ranjit et al., 2009). The resultant small peptides and free amino acids are possibly absorbed through the parasite gut through a homologue of the membrane-spanning amino acid transporter of the free-living nematode *C. elegans* (Meissner et al., 2004). After their cleavage from digested globin, both iron-containing haeme and iron-containing haematin are potentially toxic to hookworms, because these compounds can generate oxygen radicals that may damage parasite structures (Brophy and Pritchard, 1992). Therefore, in addition to haemoglobinases, all blood-feeding parasites such as hookworms and *P. falciparum* have evolved mechanisms to detoxify and transport haeme (Deponte and Becker, 2005; Jani et al., 2008; Zhan et al., 2002, 2005). In the case of *N. americanus* and other hookworms, one putative mechanism for neutralizing these toxic moieties involves the pairing of glutathione *S*-transferase 1 (GST1) molecules as homodimers to create

TABLE A9-2 Successful* vaccines against helminth infections

Parasite	Host		Treatment	Vaccine		Application	Status as of 2010
	Definitive	Intermediate		Target	Type		
Dictyocaulus spp. (McKeand, 2000; Ploeger, 2002; Vercruysse et al., 2004)	Cattle	NA	Benzimidazoles‡	L3	X-irradiated L3	Veterinary	Dictol and Bovilis (Intervet)
Ancylostoma caninum (Miller, 1998; Steves et al., 1973)	Canines	NA	Benzimidazoles‡	L3	X-irradiated L3	Veterinary	Discontinued (1974)
Haemonchus contortus (Bethony et al., 2006; Knox et al., 2003)	Runimants	NA	Benzimidazoles‡	H11. H-Gal-GP and TSBP	Excretory or secretory fractions	Veterinary	Experimental
Taenia ovis (Lightowlers, 2006)	Canines	Sheep	Praziquantel	TO45	Recombinant	Veterinary	Experimental
Taenia saginata (Lightowlers, 2006)	Humans	Cattle	Praziquantel	TSA9 and TSA18	Recombinant	Veterinary (transmission blocking)	Experimental
Taenia solium (Lightowlers, 2006)	Humans	Swine	Praziquantel	TSOL18	Recombinant	Veterinary (transmission blocking)	Experimental
Echinococcus granulosus (Lightowlers, 2006)	Canines	Sheep§	Benzimidazoles‡	EG95	Recombinant	Veterinary	Licensed‖

H11, membrane glycoprotein H11 (also known as aminopeptidase N); H-Gal-GP, gut membrane-associated protein complex of adult *H. contortus*; L3, third-stage larvae; NA, not applicable; TSBP, thiol sepharose-binding fraction of adult *H. contortus*. *Defined as an efficacy of greater than 90% in field trials. ‡Fenbendazole, oxfendazole or albendazole. §Humans are accidental hosts. ‖Licensed by the University of Melbourne, Australia, and AgResearch, New Zealand, with manufacture in China (Lightowlers, 2006).

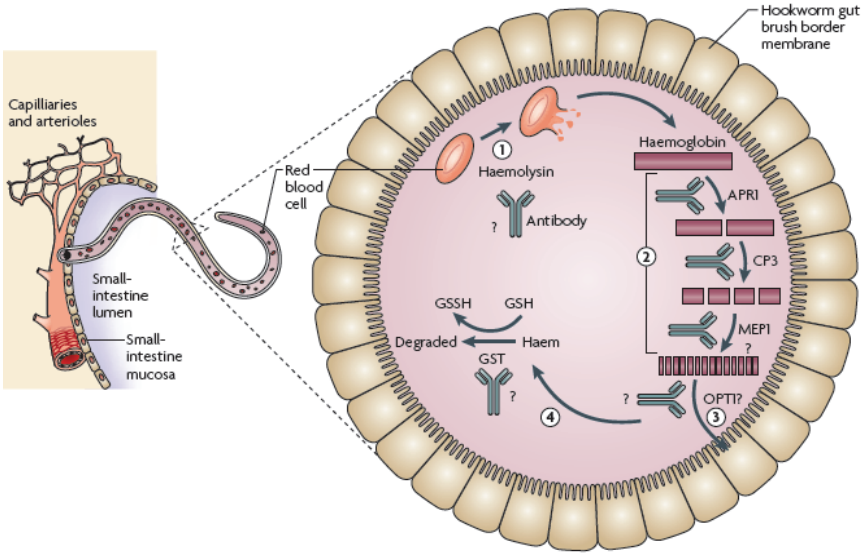

FIGURE A9-2 *Necator americanus* degradation of host blood components and potential vaccine targets. Adult worlms in the gut ingest blood, and parasite haemolysins drill pores into the erythrocytes, releasing haemoglobin into the parasite gut lumen (step 1). Haemoglobin is digested by the hierarchichal and ordered cascade of haemoglobinases (APR1, and aspartic protease. CP3, a cysteine protease, and MEP1, a metalloproteinase) lining the brush border membrane of the parasite gut (step 2). The globin peptides and free amino acids that are released following heamoglobin digestion are absorbed into the gut cells, putatively being transported by OPT1 (step 3). Free haeme is detoxified by the action of glutathione S-transferase (GST) (step 4). Antibodies that could be induced by vaccination to neutralize the function of target proteins and interrupt blood feeding are shown. Question marks indicate steps that have not been experimentally confirmed. GSH, glutathione; GSSH, glutathione disulphide.

specific pockets capable of binding haeme and haematin (Asojo et al., 2007; Zhan et al., 2002, 2005) (Figure A9-2).

Antigens of the Human Hookworm Vaccine

From approximately two-dozen proteins that are putatively involved in the hookworm blood-feeding process (Brooker et al., 2004; Loukas et al., 2006), two lead candidate antigens have been selected for clinical development. The antigen selection programme of the HHVI is based on a ranking system that includes several key criteria, such as efficacy in animal trials, immuno-epidemiological observations in individuals resident in endemic areas, and the feasibility of protein expression and scaled-up manufacture using low-cost expression systems such as yeast, bacteria, or plants (Loukas et al., 2006) (Table A9-3). In addition,

TABLE A9-3 Ranking of Lead Candidate *Necator americanus* Vaccine Antigens

Necator americanus antigen	Target of IgE*	Measure of efficacy in animal model				Ease of manufacture#	Known function or structure**	Final score‡‡
		Reduced adult worm counts (dog)‡	Reduced adult worm counts (hamster)§	Prevention of blood loss‖	Reduced faecal egg counts¶			
ASP2	Yes§§	2	3	1	3	3	2	14/23 (61%)
APR1	No	2	2	3	3	2	2	14/23 (61%)
GST1	No	2	3	1	1	3	2	12/23 (52%)
CP2	ND	1	2	ND	3	2	2	10/19 (53%)

GST1, glutathione *S*-transferase 1; IgE, immunoglobulin E; ND, not determined. *If individuals naturally infected with hookworm develop IgE to the protein, the antigen is immediately down-selected. ‡Reflects quintiles (represented by a score out of 5) of the reduced worm burdens of vaccinated dogs challenged with infective larvae compared with the burden of controls. §Reflects quintiles (represented by a score out of 5) of the reduced worm burdens of vaccinated hamsters challenged with infective larvae compared with the burden of controls. ‖Each level (from 1 to 3) represents an increment of 0.5 g per ml in the haemoglobin concentration of vaccinated and challenged animals (with 0 representing the concentration in a control group). ¶Reflects quartiles (represented by a score out of 4) of reduced faecal egg counts in vaccinated animals challenged with infective larvae, compared with controls. #A major impediment to the success of efficacious vaccine antigens is the ease and cost-effectiveness with which their production can be scaled up for synthesis according to good manufacturing practices: 0 means it is not feasible; 1 means it is difficult but potentially feasible; 2 means it will give modest yields and a relatively stable protein but substantial process development is required; 3 means it will give high yields of soluble, stable protein with a straightforward scale up for synthesis according to good manufacturing practices. **Known protein function and/or structure assists in determining the mechanism of protection and aids process development: 0 means that the function and/or structure are unknown; 1 means that the function or structure is known; 2 means that the function and structure are known. ‡‡Tally of scores for each category; if a category score was not obtained because the experiment was not carried out, the category is not counted for the final score. §§Recognition that naturally infected individuals develop *N. americanus* ASP2-specific IgE antibodies occurred late in the development process.

antigens are prioritized if there is a plausible mechanism of protection associated with them, such as triggering the production of antibodies that inhibit crucial parasite enzymes or target important surface antigens. Both GST1 and APr1 are involved in parasite blood feeding, and it is thought that each antigen induces antibodies that interfere with the function of the respective protein and impair worm survival. Both antigens are therefore being considered for eventual combination in a human hookworm vaccine.

GST1 is a 24 kDa polypeptide that is expressed as a recombinant protein in the yeast *Pichia pastoris* to generate the antigen used for vaccines. Both GST1 from *N. americanus* and its orthologue from the canine hookworm *Ancylostoma caninum* have peroxidase activity that catalyses the conjugation of reduced glutathione to various electrophiles (Asojo et al., 2007; Zhan et al., 2002, 2005). Both proteins belong to the Nu class of nematode GSTs, which is characterized by a reduced peroxidase activity relative to other classes of GSTs but an increased binding capacity for haeme and related products (Asojo et al., 2007; Schuller et al., 2005; van Rossum et al., 2004; Zhan et al., 2002, 2005). According to X-ray crystallography studies, *N. americanus* GST1 forms homodimers in solution to create atypically large binding cavities that are accessible to a diversity of ligands, including haeme (Asojo et al., 2007), to which GST1 from both *A. caninum* and *N. americanus* binds with high affinity *in vitro* (Zhan et al., 2002, 2005). Both haeme and haematin contain oxidative iron that can result in the formation of oxygen radicals, which damage helminth structures. *In vivo*, GSTs may protect hookworms by binding and detoxifying haeme and the haematin byproducts that are generated during the blood digestion process (Zhan et al., 2002, 2005).

On the basis of their putative roles in hookworm blood feeding, GST1 from both *N. americanus* and *A. caninum* were tested in laboratory animal models of hookworm. In dogs, vaccination with recombinant *A. caninum* GST1 resulted in high levels of antibodies; following challenge with infective *A. caninum* larvae, the worm burdens and faecal egg counts of these vaccinated dogs were substantially lower than those observed in controls (Zhan et al., 2005). In hamsters, vaccination with recombinant *A. caninum* GST1 also resulted in cross-protection, with substantially lower worm burdens (less than half) following heterologous challenge with infective *N. americanus* larvae than those seen in controls (Xiao et al., 2008; Zhan et al., 2005), as did vaccination with *N. americanus* GST1 followed by homologous larval challenge (Zhan et al., 2002). A recombinant GST from the nematode parasite *Wuchereria bancrofti* is also showing promise in a jird model as a protective antigen against lymphatic filariasis (Veerapathran et al., 2009). Because of these encouraging results, recombinant *N. americanus* GST1 (formulated with Alhydrogel [aluminium hydroxide]) has been produced according to current good manufacturing practices in preparation for clinical trials.

N. americanus APr1 is a 45 kDa protein. For stability and safety reasons, including concerns about injecting humans with an active proteolytic enzyme, the version of this aspartic protease used for vaccination has been inactivated by

substituting alanines for the catalytic aspartic acid residues (Pearson et al., 2009). The recombinant protein has been expressed in multiple systems, with *Escherichia coli* (Pearson et al., 2009) and tobacco plants (Yusibov and Rabindran, 2008) producing the highest yields. The rationale for selecting *N. americanus* APr1 for development was based on successful laboratory animal trials. In dogs vaccinated with either *N. americanus* APr1 or *A. caninum* APr1, high levels of antibody were induced that inhibited protease activity *in vitro*; this was associated with substantially diminished blood loss (measured by haemoglobin levels) and worm burdens following challenge with *A. caninum* larvae compared with those seen in controls (Loukas et al., 2005; Pearson et al., 2009). Vaccination with *A. caninum* APr1 also resulted in a substantial reduction in the worm burdens of hamsters challenged with *N. americanus* compared with burdens of controls (Xiao et al., 2008). These findings also suggest that cross-reactive immunity between *Necator* spp. and *Ancylostoma* spp. hookworms may occur. Following vaccination, APr1-specific antibodies are ingested by the parasite during blood feeding and localize to the parasite gut, where they can inhibit parasite feeding by neutralizing enzyme activity (Loukas et al., 2005; Xiao et al., 2008) (Figure A9-2). Efforts to optimize both the yield and the solubility of *N. americanus* APr1 are in progress. A chimeric protein consisting of *N. americanus* GST1 fused to epitopes of *N. americanus* APr1, to generate neutralizing antibodies and inhibit parasite blood digestion, is already under development (Pearson et al., 2010). Additional key molecules involved in hookworm blood feeding have been identified from proteomic and transcriptomic analyses of the hookworm gut (Ranjit et al., 2006). These molecules include a putative hookworm orthologue of a prolylcarboxypeptidase ('contortin') that protects sheep against *Haemonchus contortus* infection (Geldhof and Knox, 2008), and the extracellular domain of an intestinal peptide transporter that is essential for nutrient uptake and growth in *C. elegans* (Meissner et al., 2004).

Previous vaccine antigens

ASP2 from *N. americanus* infective larvae was previously under consideration as a candidate vaccine antigen (Bethony et al., 2005; Fujiwara et al., 2005, 2008; Goud et al., 2005). The canine hookworm orthologue of this molecule was determined to be a major immunogen associated with an effective vaccine consisting of live attenuated *A. caninum* L3 larvae (Bethony et al., 2005; Fujiwara et al., 2006). In a Phase I trial conducted in healthy volunteers in the United States, ASP2 adjuvanted with Alhydrogel was shown to be safe and immunogenic (Goud et al., 2005). However, in a second Phase I trial conducted at a hookworm endemic site in Brazil, some of the adult volunteers experienced generalized urticaria immediately after vaccination (D.J.D., unpublished observations). The study was halted, and it was found that individuals who developed urticaria had high levels of immunoglobulin E (IgE) against ASP2. This finding has led to

testing for the levels of IgE specific for candidate vaccine antigens using sera from individuals resident in hookworm-endemic areas. No detectable levels of IgE specific to *N. americanus* GST1 (J.M.B. and D.J.D., unpublished observations) or *N. americanus* APr1 (REF. 100) have been found in individuals living in hookworm-endemic areas of Brazil, thus permitting their continued development as candidate vaccine antigens. The reason neither recombinant adult hookworm protein induces IgE during natural infection is unknown, but it may be related to antigen structure or presentation to the immune system.

Vaccinating Against Schistosomiasis

In both Brazil and most of sub-Saharan Africa, *N. americanus* hookworm infections are co-endemic with intestinal schistosomiasis caused by *S. mansoni* (Hotez et al., 2008b). Vaccines to combat each of these helminth infections are being developed because both diseases are associated with anaemia and malnutrition, especially in children. Ultimately, the two vaccines may be co-administered or combined in a multivalent anthelmintic vaccine (see below) (Hotez et al., 2008b). The justification for developing vaccines against schistosomiasis has been reviewed recently (Bergquist et al., 2008; McManus and Loukas, 2008) and includes the high disease burden (King and Dangerfield-Cha, 2008; King et al., 2005), the high rates of post-treatment re infection, the inability of chemotherapy-based morbidity control to interrupt transmission (King et al., 2006), the exclusive reliance on praziquantel for control and concerns about emerging drug resistance without new drugs in the development pipeline (Bergquist et al., 2008; McManus and Loukas, 2008). An important additional stimulus to develop new preventive approaches to schistosomiasis is the observation of so-called ‘rebound morbidity’: up to 80% of children living in high-transmission areas can suffer recurrent aggressive inflammation following interrupted annual chemotherapy because of reinfection. The feasibility of developing vaccines for schistosomiasis has been extensively reviewed (Bergquist et al., 2008; McManus and Loukas, 2008; Oliviera et al., 2008). Humans living in endemic areas can become resistant or partially immune to reinfection over time (Correa-Oliviera et al., 2000). Furthermore, irradiated cercariae can elicit high levels of protective immunity in laboratory animals, and several recombinant-protein vaccines have been shown to elicit comparable levels of protective immunity in immunized animals that were subsequently challenged with cercariae (McManus and Loukas, 2008).

Schistosome Antigens Under Development

To date, one vaccine for urinary schistosomiasis has entered clinical trials. The Institut Pasteur and the French Institut National de la Sante et de la recherché Medicale have taken a recombinant 28 kDa GST cloned from *S. haematobium* through both Phase I and Phase II clinical trials in Europe and

West Africa (Capron et al., 2005; McManus and Loukas, 2008) (see also Le Project Bilhvax 3). Known as Bilhvax, this GST formulated with an aluminium hydroxide adjuvant has been reported to be immunogenic and safe after testing in healthy adults (Capron et al., 2005). However, further information regarding its efficacy, the duration of protection and the progress towards licensure are not available in the published literature. In addition, other vaccine candidates for intestinal schistosomiasis caused by *S. mansoni* will soon be ready for clinical testing (Oliviera et al., 2008). One candidate is a 14 kDa fatty acid-binding protein known as Sm14 (Moser et al., 1991), which in experimental animals (mice and rabbits) elicits protection against *S. mansoni* as well as against *Fasciola hepatica*, another trematode fluke (Tendler and Simpson, 2008). Recently, the group developing this vaccine reported success in stabilizing Sm14 by replacing a crucial cysteine residue in order to prevent dimerization (Ramos et al., 2009). Recombinant Sm14 is being developed as an anthelmintic vaccine by a partnership between private and government organizations in Brazil for use against both fascioliasis of livestock and human schistosomiasis caused by *S. mansoni* (Tendler and Simpson, 2008). Another *S. mansoni* vaccine potentially moving into clinical development is Sm-p80, which is a DNA vaccine encoding the large subunit of a calcium-dependent neutral protease, providing levels of protection in baboons that are comparable to irradiated cercariae (Zhang et al., 2010). Finally, the schistosome molecule paramyosin is undergoing pilot-scale production in Asia for use against *S. japonicum* infection, possibly as a transmission-blocking vaccine, administered to water buffaloes (Jiz et al., 2008).

The Sabin Vaccine Institute, in partnership with FIoCrUZ and the Instituto Butantan, is also working to transition a *S. mansoni* vaccine into clinical testing in Brazil (J.M.B., D.J.D. and P.J.H., unpublished observations). The primary targets of this vaccine development programme are schistosome membrane proteins identified by combined genomic, post-genomic and proteomic analyses of the adult *S. mansoni* outer surface, or tegument (Loukas et al., 2007) (Table A9-4). The tegument of adult schistosomes is a single syncytium covering the body wall and is thought to be a dynamic layer involved in several key physiological processes, including parasite nutrition, osmoregulation and evasion of host immunity (Loukas et al., 2007). Hence, the schistosome tegument is a potentially vulnerable target for immunological attack by host antibodies. However, analysis of the schistosome proteome predicts that surprisingly few membrane-spanning proteins of the tegument are accessible to the host immune response (Braschi and Wilson, 2006; Loukas et al., 2007). They include a family of tetraspanin integral membrane proteins (Tran et al., 2006) and several outer-membrane proteins of unknown function, such as Sm29 (Cardoso et al., 2006, 2008). The tetraspanins are so named because they contain four transmembrane domains, with two extracellular loops that are predicted to interact with exogenous proteins or ligands (Figure A9-3). The second extracellular domain fragment of a schistosome tetraspanin known as TSP2, from *S. mansoni*, has been selected for development as

TABLE A9-4 Ranking of Lead Candidate *Schistosoma mansoni* Vaccine Antigens

Schistosoma mansoni antigen	Target of IgE*	Reduced adult worm counts (nice)‡	Reduced egg counts (mice)§	Preferential recognition by resistant humans‖	Intramammalian stage targeted¶	Ease of manufacture	Known function or structure#	RNAi phenotype**	Final score‡‡
TSP2	No	4	4	3	3	3	1	2	20/23 (87%)
Sm29	ND	4	3	1	2	1	0	Nd	11/21 (52%)
Tsp1	ND	3	3	0	2	3	1	2	14/23 (56%)

Ig, immunoglobulin; ND, not determined. *If individuals naturally infected with *S. mansoni* develop IgE specific to the protein, the antigen is immediately down-selected. ‡Reflects quintiles (represented by a score out of 5) of the reduced worm burdens of vaccinated mice challenged with infective larvae compared with the burdens of controls. Vaccines used antigen formulated with an adjuvant that has been approved (or is under assessment) for human use. §Reflects quintiles (represented by a score out of 5) of the reduced liver egg and/or fecal egg burdens of vaccinated mice challenged with infective larvae compared with the burdens of controls. ‖Reflects tertiles (represented by a score out of 3) of the difference in the mean levels of IgG1 or IgG3 units between resistant (naturally resistant or drug-induced resistant) and chronically infected groups (McManus and Loukas, 2008). ¶Protein accessible to the immune system in intramammalian developmental stages: 1 means it can be detected on the surface of the fixed schistosomulum or adult; 2 means it can be detected on the surface of the live schistosomulum or adult; 3 means it can be detected on the surface of the live schistosomulum and adult. #Known protein function and/or structure assists in determining the mechanism of protection and aids process development: 0 means that the function and/or structure is unknown; 1 means that the function or structure is known; 2 means that the function and structure are known. **Reflects the essential nature of the target protein for parasite survival, based on RNA interference (RNAi) experiments. 0 means that RNAi results in no effect; 1 means that RNAi results in a deleterious *in vitro* phenotype; 2 means that RNAi results in a deleterious *in vitro* phenotype and affects survival *in vivo* (in animal models) after the transfer of parasites treated with double-stranded RNA into mice. ‡‡Tally of scores for each category; if a category score was not obtained because the experiment was not carried out, the category is not counted for the final score.

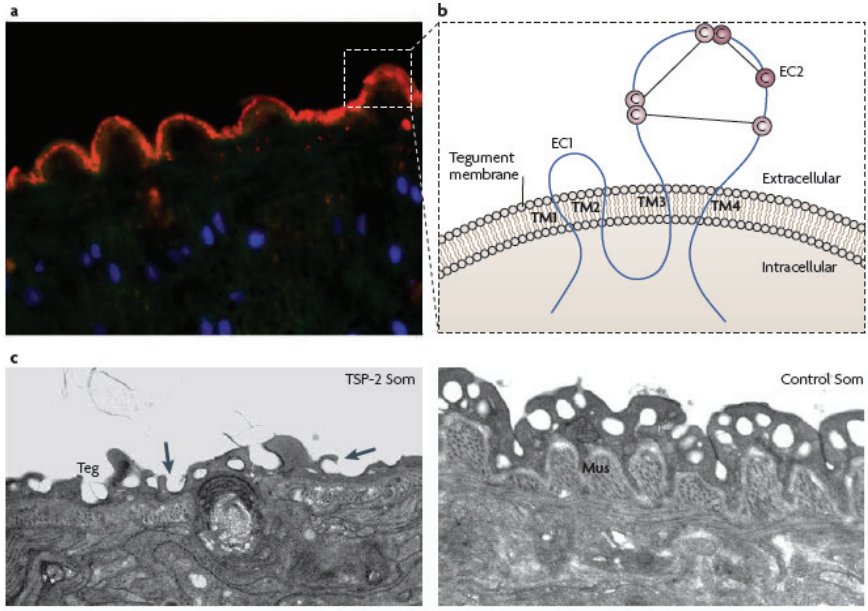

FIGURE A9-3 *Schistosoma mansoni* tegument. **a|** A fluorescence micrograph of the tegument of an adult male *Schistosoma mansoni* probed with a mouse antibody raised recombinant TSP2 (red), a tetraspinin. Nuclei. Stained with 4',6-diamidino-2-phenylindole (DAPI), are blue. **b|** A schematic representation of *S. mansoni* TSP2 in the tegument plasma membrane. Extracellular loops (ECs) are indicated, and cysteine residues are shown (the lines between them denote the disulphide bond pairing); transmembrane domains (TMs) are shown numbered from amino terminus to carboxyl terminus. **c|** The tegument of an *S. mansoni* schistosomula incubated for 7 days with *S. mansoni tsp*2 (left) or luciferase (control; right) double-stranded RNAs. Digitate extensions (arrows) are more abundant on the surface of the tegument incubated with *tsp*2 double-stranded RNAs. Mus, muscle; Som, schistosoma; Teg. Surface layer of the tegument. Part **a** image is reproduced, with permission, from Loukas et al., 2007 ©Elsevier. Part **c** image is reproduced from Tran et al. (2010).

a human vaccine antigen. When this 9 kDa extracellular domain was expressed in either *P. pastoris* or *E. coli* and formulated with several adjuvants (including Freund's complete adjuvant (Tran et al., 2006), aluminium hydroxide, or aluminium hydroxide with CpGs) it provided high levels of protection in mice vaccinated with the antigen and then challenged with *S. mansoni* cercariae (A.L. and M.S.P., unpublished observations). In addition, evidence from human epidemiological studies indicates that putatively resistant individuals living in endemic areas of Brazil have elevated antibody responses to this protein compared with the responses of chronically infected individuals from the same endemic areas

(Tran et al., 2006). recently, the *S. japonicum* orthologue of *S. mansoni* TSP2 was described and resulted in protection in mice that was similar to that described for *S. mansoni* TSP2, suggesting that this molecule may be effective against multiple human schistosome species (Yuan et al., 2010).

S. mansoni TSP2 is thought to have a crucial role in tegument development and maturation (Tran et al., 2010). The ultrastructural morphology of adult worms and schisto somula treated *in vitro* with *S. mansoni tsp2* double-stranded rNA (dsrNA) displays a distinctly vacuolated and thinner tegument compared with that of controls, suggestive of impaired closure of tegumentary invaginations (Tran et al., 2010). Moreover, injection of mice with schistosomulae that had been pre-treated with *S. mansoni tsp2* dsrNA resulted in 83% fewer parasites being recovered from the mesenteric veins 4 weeks later when compared with recovery from mice injected with untreated schistosomulae (Tran et al., 2010). These results suggest that tetraspanins have important structural roles in tegument development, maturation or stability. other tegument tetraspanins are attractive vaccine candidates; for example, *S. mansoni tsp3* is the most highly upregulated mrNA in maturing schistosomula, a developmental stage that is widely accepted as being susceptible to damage by the human immune system (Fitzpatrick et al., 2009; Gobert et al., 2010). In addition, Sj23 (23 kDa integral membrane protein of *S. japonicum*) is a tegument tetra spanin that is showing promise as a DNA vaccine for water buffaloes, which are an important reservoir host for *S. japonicum* in China (Da'dara et al., 2008).

Future Directions

By targeting both hookworms and schistosomes, human helminth vaccines are being developed to reduce parasiteinduced morbidity, the symptoms of which include intestinal blood loss and inflammation (Hotez et al., 2008b). Administered in early childhood, such vaccines could prevent the major paediatric sequelae of these infections, including anaemia, malnutrition, growth failure and impaired cognitive development.

The human hookworm vaccine is being developed as a bivalent product consisting of two co-formulated recombinant proteins (GST1 and APr1 from *N. americanus*) to prevent moderate and heavy hookworm infections caused by *N. americanus*. The vaccine is intended primarily for preschool- and school-aged children (<10 years of age) living in *N. americanus*-endemic regions. Similarly, TSP2 from *S. mansoni* is being developed as a recombinant-protein vaccine for the prevention of heavy-intensity infections of *S. mansoni*, the leading cause of intestinal schistosomiasis. A paediatric population will be targeted for both vaccines because this age group is at the greatest risk of developing the severe developmental, growth and cognitive impairments associated with these chronic infections (Bethony et al., 2006; Brooker et al., 2004; Hotez et al., 2004, 2005, 2008a). Initially, vaccines containing the hookworm and schistosome antigens

are being formulated with Alhydrogel; however, they will also be evaluated with an additional immunostimulant such as a lipid A derivative. The vaccines will be delivered by intramuscular injection, and the goal is to achieve the desired protection after one or two doses, depending on the number of doses required to achieve a protective response. The desired result is the prevention of moderate and heavy helminth infections, which would have a major impact on the anaemia, malnutrition and end-organ pathology associated with these parasitic infections in children (King and Dangerfield-Cha, 2008; Stoltzfus et al., 1997). The extension of protection into adulthood would also prevent the severe anaemia that is related to infection with these parasites during pregnancy, and reduce transmission. Such vaccines may also have an important impact on poverty reduction because of their anticipated effect on improving child and maternal health and development (Hotez and Ferris, 2006).

Both vaccines are being developed with the ultimate goal that even the most impoverished populations will have access to them as soon as they are available. As such, a strategic road map is being followed to ensure that lowcost manufacturing processes are used and that vaccine manufacturers in middle-income disease-endemic countries are involved from the start. In the Americas, Brazil is the furthest advanced, with two major vaccine manufacturers — FIoCrUZ/Bio-Manguinhos and the Instituto Butantan — actively engaged in development (Morel et al., 2005). Accurate forecasting of the eventual demand for licensed vaccines is essential: for hookworm, it is estimated that there are approximately one billion children at risk globally, so that covering a global birth cohort would require the vaccination of 100 million children annually (WHO, 2008). Demand forecasting is underway for an intestinal schistosomiasis vaccine.

Substantial hurdles must be overcome during clinical development of hookworm and schistosomiasis vaccines, not least of which is securing adequate funding to conduct the clinical trials required for licensure. Additional obstacles include obtaining access to the novel adjuvants that may be required to induce an adequate immune response and the difficulty of conducting large-scale efficacy studies in endemic areas. As hookworm and schistosomiasis are prevalent in resourcelimited, rural areas of the tropics and subtropics, this is where Phase III clinical trials must be conducted, which can be logistically challenging. Furthermore, because the clinical effects of these parasitic infections are chronic, with sequelae such as IDA often appearing only after months or years of infection, efficacy trials will be necessarily long.

Combining hookworm and schistosomiasis vaccines

In the future, vaccines for hookworm and intestinal schistosomiasis could be combined in a multivalent anthelmintic vaccine (Hotez et al., 2008b), which may increase vaccine efficiency and reduce the timeframe for widespread distribution in affected areas of Africa and Latin America. The Sabin Vaccine Institute

is currently working with the WHO to build consensus on the use of hookworm and schistosomiasis vaccines in resourcepoor settings (WHO, 2005). Health systems established through the integrated control of mass drug administration for neglected tropical diseases and expanded global deworming efforts for preschool- and school-aged children (Hotez et al., 2007, 2009) could ultimately provide an infrastructure for linking newly developed vaccines with anthelmintic chemotherapy.

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Competing Interests Statement

The authors declare no competing financial interests.

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A10

THE BILL & MELINDA GATES FOUNDATION APPROACH AND STRATEGY TO THE NEGLECTED TROPICAL DISEASES 1998–2010

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Introduction

The Global Health Program at the Bill & Melinda Gates Foundation (BMGF) has over the past decade developed a portfolio of 14 diseases that have been put into a single foundation strategic program around the theme "neglected and other infectious diseases" (NOIDs). As a group, the NOIDs represent one segment of a larger group of global health diseases (as many as 47 different infectious diseases according to some) that share several common characteristics: their impact is overrepresented in tropical areas; they affect the poorest, disenfranchised popu-

[13] Acknowledgements to the Neglected and Other Infectious Diseases Team who have contributed to this strategy over the past 12 years including David Brandling Bennett, Jan Agosti, Thomas Kanyok, Kathryn Aultman, Anastasia Pantelias, Erin Shutes, Ken Duncan, and Guy Stallworthy.

lations; and they have been underrepresented in terms of attention—including resources for research and development (R&D) of drugs, vaccines, diagnostics, and vector tools, both in the North and in the South.[14] These diseases are unified neither by their biology nor by their clinical manifestation in humans (which are extremely diverse), but rather by the populations that they affect and the fact that the world has now chosen to collectively address them.

Over the past decade, parallel to the creation of the BMGF Global Health Program, an increasingly cohesive community has emerged, with strong leadership at the World Health Organization (WHO) and from the scientific community. In his "manifesto" for the control and elimination of neglected tropical diseases (NTDs), Dr. Peter Hotez characterized NTDs as "the most common infections of the world's poorest people and the leading causes of chronic disability and poverty in low and middle-income countries (Hotez and Pecoul, 2010)." The first WHO report on NTDs, published in 2010, identified additional common features of this group of diseases, including their limited geographic focus, unique impact on morbidity as well as mortality, and the public health goal of control, prevention, and elimination using feasible solutions (WHO, 2010). Another criterion has been the relationship to stigma and discrimination, particularly in women. The Global Network for Neglected Tropical Diseases likewise characterizes these diseases as "diseases of poverty, afflicting the world's poorest and trapping them in a cycle of poverty."[15]

There are weaknesses to applying any single criterion to the NTD framework. Some diseases that are not included in the NTD category fit the WHO criteria. Malaria and deaths due to pneumonia and diarrhea are also associated with poverty and with excess risk in tropical areas. AIDS also causes stigma and discrimination. Conversely, some diseases proposed as part of the NTD category do not appear to fit the WHO criteria. Effective and feasible solutions are not currently available for dengue and are not optimized to achieve impact goals for human papillomavirus (HPV). With respect to the "poorest of the poor" definition, there are again exceptions (dengue also affects wealthy populations within endemic countries), and there is a lack of robust data (distribution of disease burden by quintile, for example) to substantiate this claim.

Nevertheless, the NTD framework has resonated within the foundation, the donor community, and the disease advocates. As a group, the NTD framework is today viewed by the global health community as a distinct category of diseases. However, prioritization of diseases and approach within that framework varies by organization.

[14] The Global Health Program encompasses the following strategy programs: Diarrhea and Enteric Diseases, Malaria, Pneumonia, Tuberculosis, HIV, Reproductive Health, Nutrition, and Maternal, Neonatal, and Child Health.

[15] Global Network for Neglected Tropical Diseases website, globalnetwork.org.

Origin of the BMGF Portfolio

The foundation's investments in these diseases were not originally conceived as a cohesive portfolio. Instead, investment decisions were made on a disease-by-disease basis and classified as "other ID" for record-keeping purposes. Strategy assessments were written for individual diseases. In this manner, investments were made in 13 diseases between 1998 and 2007. In late 2007, the Global Health Program reorganized and strategic program teams were formed, along with the creation of a single NOIDs team. In 2008, the first strategy was developed that provided an aggregate view of the foundation's investments in these diseases.

The foundation's unique terminology for this space—neglected and other infectious diseases, or NOIDs—was coined as part of the 2007–2008 strategy development process. "Neglected" reflected that most of these diseases were part of the group of diseases defined as neglected tropical diseases by the global community. "Other" was retained because there was not a 100 percent overlap between the diseases in the foundation's portfolio and the various definitions from the global NTD community.

The priority diseases over the past decade include onchocerciasis, lymphatic filariasis (LF), schistosomiasis, trachoma, human African trypanosomiasis (HAT), visceral leishmaniasis (VL), soil-transmitted helminths (STHs; hookworm, *Ascaris*, and *Trichuris*), rabies, HPV, Japanese encephalitis (JE), and dengue. Our investments across the NOIDs portfolio are summarized by disease in Figure A10-1. The distribution of these investments by tool and approach is seen in Figure A10-2, which shows the balance of what our investments have been irrespective of disease.

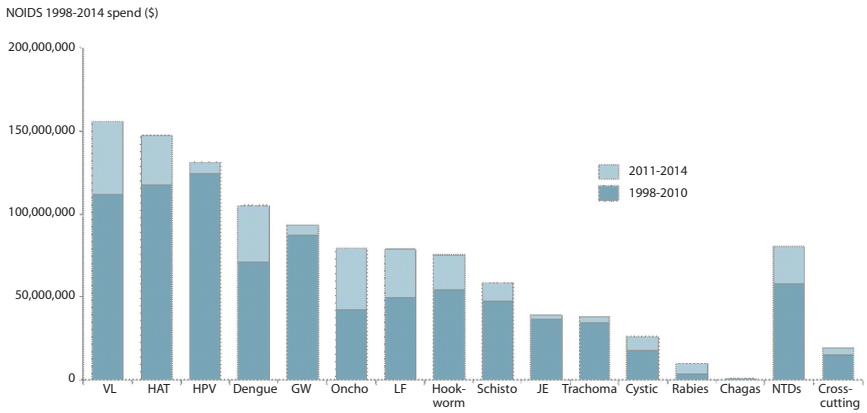

FIGURE A10-1 BMGF NOIDs investment by disease through 2010 with payments through 2014.
SOURCE: BMGF grants database.

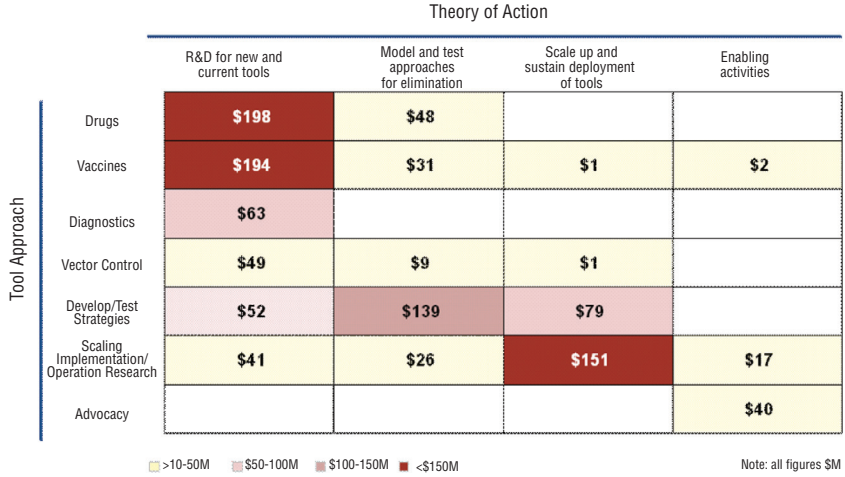

FIGURE A10-2 BMGF NOIDs commitments by tool and strategic approach through 2010.
SOURCE: BMGF grant database.

Bill & Melinda Gates Strategy Process

Grant investments from the foundation are guided through a process that has evolved and been refined over the first 10 years of the foundation's history. Strategies are in a constant state of development and refinement going through three distinct stages. First, is the primary Strategy Development, which is basically creating a de novo strategy. This happens only once in a disease area and is the result of a period of learning, consultation, and exploration that can range from months to years. The second stage is annual and is referred to as the Strategy Review. This is a yearly update for foundation leadership, which critically evaluates the progress against a strategy and may result in minor course corrections in response to shifts in knowledge and external factors. The third stage is known as the Strategy Refresh, which is a fundamental reexamination of a strategy with the expectation and openness to significant changes in strategic direction in light of developments in the environment either as progress, learning, or setbacks. This process happens every three to five years and is associated with an extensive evaluation process to guide the new strategic choices.

Currently, in 2011, we are conducting a Strategy Refresh for the NOIDs. During the Strategy Refresh, there is a multistep process taken on by a responsible cross-foundation team. The process is designed to question assumptions and bring in new evidence to refine our approach and define both priorities as well as potential areas of deemphasis. By the end of the process, each strategy redefines goals and how progress against reaching those global health goals will

be measured. Our attribution to achieving these goals can be indirect, as most programs and initiatives in which we are engaged are implemented through a number of grant and strategic partnerships where accountability and credit are shared. Critical steps to the refresh include the following:

- A historical "look back" to see what has been learned and what has changed;
- Scope of the problem and potential solutions, and examination of public health goals;
- Defining the theory of change (what the world needs to do to reach those goals);
- Developing a Theory of Action (strategic choices for foundation action);
- Estimating resource requirements;
- Creating an execution plan to implement the strategy; and
- Creating a monitoring, learning, and evaluation (MLE) plan to ensure that the right information is collected to evaluate progress and guide future choices.

This process and the questions we ask ourselves are further described in Table A10-1.

State of the Field

The epidemiology and pathology of the neglected diseases varies widely. Pathogens include viruses, bacteria, protozoa, and worms. Transmission is human-to-human for some diseases and via vectors or environmental contamination for others. In the cases of vectored transmission, vectors include multiple species of mosquitoes, flies, and snails. Some diseases are 100 percent fatal (e.g., untreated HAT, rabies); others are chronic, nonfatal conditions (e.g., soil-transmitted helminths). Some diseases have widespread prevalence (LF infects up to 120 million people globally); others are more geographically limited. (HAT, for example, only occurs in sub-Saharan Africa in a zone of 36 countries known as the tsetse-fly belt.) In addition, disease foci may be confined to only certain areas within countries (for instance, soil-transmitted helminth infections in Mozambique—though very high in the southern half of the country—are rare around the northern border with Malawi).

Clarity on agreed-upon public health goals for each disease has been extensively worked out by the relevant communities for some (onchocerciasis in the Americas, for example) but is still evolving for others (STHs). One key step in this process has been the assessment by the International Task Force on Disease Eradication of the biologic plausibility and feasibility of eradication versus control for a host of infectious diseases. For some diseases, the existence of animal reservoirs makes elimination or eradication biologically infeasible. For other

TABLE A10-1 Summary of the Bill & Melinda Gates Foundation Strategy Refresh Process

Area	Description	Strategic Questions
Look back	Review prior strategy: progress, challenges, lessons, implications; embracing mistakes	What are the lessons from the prior strategy and implications for our future work? How has the landscape changed and how would this modify our approach?
Scoping	Opportunity mapping: analysis of the problem and identifying potential areas of opportunity for change and progress	How can the problem be characterized? How can the problem be approached? Define alternative ways of addressing the problem? Which are most promising? Which are critical to success? What is not being done, and where are the gaps?
Theory of change	What needs to change to solve the problem?	How do we think change will happen? Has this changed?
Strategy choices	What needs to be done to solve the problem: theory of action, including solution leverage and partner leverage	What will we do and not do? Why? What are the tradeoffs? How are we maximizing solution leverage (i.e., getting the most out of an intervention or approach)? What is the role of our partners and how can we support this? What aligns with our strategic advantage in this space? What can we hope to achieve with this plan and over what period of time?
Resources	Resource requirements, risks	What are the resource requirements, financial and human, internal and external? What are the risks?
Execution plan	Timing, sequencing, and decision road maps	What is the timing and sequencing of initiatives? How will we measure our results?
	Monitoring, learning, and evaluation plan	What decision points lie ahead and how do they change future investments?

diseases, the goal of elimination or eradication has nearly been achieved (e.g., the remarkable progress on Guinea worm, and progressive elimination of onchocerciasis in the Americas). A critical evaluation of the investment case that evaluates the basis for the public health goals, looking at feasibility, careful assessment of technical tools, and resources, can be a powerful planning and advocacy tool and help achieve program impact.

Partner Landscape

Industry plays a uniquely critical role in the partner landscape for neglected diseases. Many pharmaceutical and biotechnology companies donate philanthropically to low-income countries, especially in times of emergency. In the neglected disease sphere, however, such firms also make long-term direct, or

"single-drug," donations. These occur in partnership with the specific disease community, have a targeted goal and a defined strategy, and have allocated volumes of drugs associated with them as well as at least a plan for obtaining additional program support.

The largest and oldest of the programs, the Mectizan donation program, was established by Merck in 1987 to treat onchocerciasis with ivermectin. In 1998, it was expanded in partnership with GlaxoSmithKline (GSK) to treat LF as well, using a combination of ivermectin and albendazole. Merck has pledged an unlimited supply of Mectizan for LF and onchocerciasis, and GSK an unlimited supply of albendazole for LF. GSK has even constructed a plant in Nashik, India, built specifically to produce albendazole for donation. At this point, more than 70 million treatments are approved for onchocerciasis in Africa and Latin America and 80 million for LF in Africa and Yemen each year, and more than 2 billion treatments have been dispensed. Each donation program has its own specifications and processes, but all are impressive commitments. Pfizer pledged its donation of azithromycin sufficient to reach elimination of blindness due to trachoma by 2020. Others, which historically were more limited in scope, such as Johnson & Johnson's donation of mebendazole, have recently expanded fourfold to 200 million tablets annually for the treatment of STHs. This was matched by an expansion of the GSK albendazole donation to cover STH needs in Africa, increasing its total donation to 1 billion tablets. One, praziquantel for schistosomiasis, still presents a particularly important gap between current programs and global need. An important but limited donation is available through Merck KGaA (German Merck), but the quantity does not meet the need, especially in light of the expanding programs. As summary is provided in Figure A10-3.

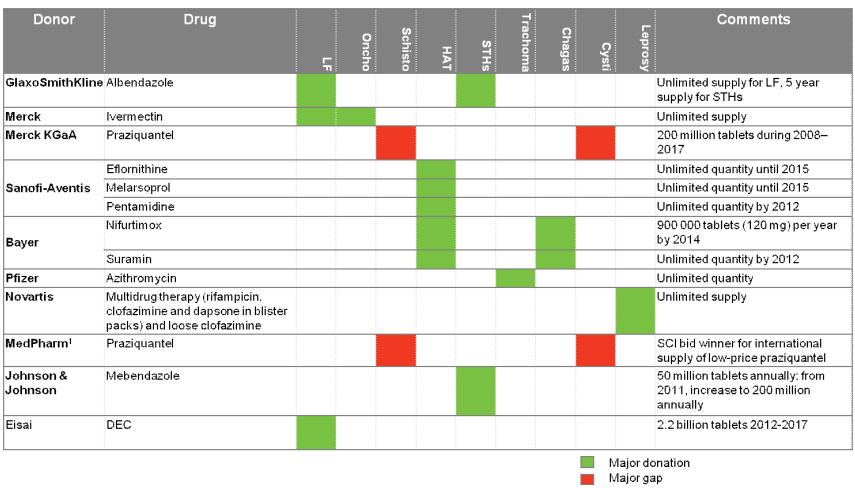

FIGURE A10-3 Overview of drug donation for the NTDs.

Rapid changes in the pharmaceutical industry have aided the growth of these donation programs. Companies' growing focus on improving their public perception, expanding their presence in emerging markets, and attracting and retaining talent are all fueling their interest in donation programs. There are also new opportunities for greater engagement of industry on R&D priorities. Recent examples include the GSK announcement committing intellectual property to a neglected diseases patent pool; the Novartis Vaccine Institute for Global Health creating affordable vaccine for neglected diseases; and the MDS Wellcome Trust Hilleman Laboratories in India, which are dedicated to vaccines for developing countries.

The key challenge for neglected diseases remains to ensure that they receive sufficient attention despite competing priorities. Endemic-country governments, nongovernmental organization (NGOs) under the global framework of the WHO, create a rich framework of key stakeholders in the delivery space (WHO, 2010). The past decade has witnessed a significant shift in the relationship between funding groups and the public health arms of endemic countries. The latter, rather than being viewed as beneficiaries, have become empowered delivery partners. Training and direction of government health workers, along with the development of investment cases meant to engender increased attention to neglected diseases, have become key priorities of funding groups. Civil society, including NGOs, has played and continues to play an essential role in support of countries both technically and programmatically according to their need.

In the R&D sector, product development partnerships (PDPs) have come to play a major role in the creation of new tools. The PDP model has been applied to address many NTD product needs through the Institute for OneWorld Health, the Drugs for Neglected Disease Initiative, the Program for Appropriate Technology in Health (PATH), the Foundation for Innovative New Diagnostics, the Sabin Vaccine Institute, and the International Vaccine Institute (IVI)/Pediatric Dengue Vaccine Initiative. For the diseases the foundation has prioritized, progress in R&D depends on national research funders, PDPs, and public/philanthropic funding, particularly because of the potential large-volume but limited-profit commercial market, particularly because donations are a keystone of the community-distributed mass drug administration (MDA) platform. Notable exceptions include dengue, HPV, and rabies, which have significant middle- or high-income markets, as well as products with agricultural or veterinary applications. Nevertheless, most neglected diseases represent an orphan market. As such, these partnerships working in NTDs are heavily reliant on philanthropic funding. Many donors have a long history of investment in this space and remain committed, playing an active role as seen in Figure A10-4. In this work done by G-FINDER for 2009, BMGF represents the second largest contribution to R&D in this space after the National Institutes of Health (NIH).

Emerging manufacturers are also playing an important role as partners to R&D efforts. These companies have shown they can deliver particularly low-cost

GLOBAL INVESTMENT FOR NOIDs R&D			
Rank	**Funder**	**Total funding ($M)**	**% total**
1	US National Institutes of Health (NIH)[3]	$101.9	30%
2	Bill & Melinda Gates Foundation	$66.4	19%
3	Aggregate Pharmaceutical and Biotechnology Company Respondents	$52.0	15%
4	The Wellcome Trust	$17.6	5%
5	European Commission: Research Directorate-General	$11.6	3%
6	US Department of Defense (DOD) including DOD Defense Advanced Research Projects Agency (DARPA)	$10.1	3%
7	Medecins Sans Frontieres (MSF) *[DNDi PDP]*	$7.8	2%
8	Brazilian Ministry of Health, Department of Science and Technology	$7.3	2%
9	UK Medical Research Council (MRC)	$6.6	2%
10	Institut Pasteur	$6.2	2%

Data from GFinder repot 2009. report does not include HPV, Rabies, JE, Echino., Guinea worm. FBT, Yaws. Combined, funding from the government of India (including the Indian Central Council for Research in Ayurveda and Siddha (CCRAS), Council of Medical Research (ICMR), Council of Scientific and Industrial Research (CSIR), Department of Biotechnology, Ministry of Science and Technology (DBT), and Department of Science & Technology) accounts for $11.4M, making it the 9th largest funder.

FIGURE A10-4 Research and development investments for NOIDs globally, 2009.

global health goods and solid global access commitments. One example is JE vaccine and the Chengdu Institute of Biological Products (CDIBP). The JE SA-14-14-2 live attenuated vaccine was wholly researched and developed in China but had the potential for broad use in Asia to address the uncontrolled outbreaks of JE plaguing endemic countries. In partnership with PATH, CDIBP engaged in, expanded, and improved GMP manufacturing with a commitment to low-cost access for public-sector use. The vaccine has now been internationally licensed and is the first new vaccine introduced and supported by the Indian government. Well over 100 million doses have been exported and the vaccine is now in use in India, Nepal, South Korea, North Korea, Cambodia, and Sri Lanka and the file for future WHO prequalification will soon be submitted to allow procurement by the United Nations Children's Fund. This type of success demonstrates the role that emerging manufacturers can play in solving these public health problems by committing their resources and know-how.

BMGF Investments Through 2010

In the late 1990s, the concept of the NTDs as a single field did not exist. There was a set of individual diseases that affected the most impoverished, with disease champions trying to push forward control efforts on behalf of affected communities. Even where drug donation programs existed, progress was limited because of limited delivery momentum and political will to implement. The

initial BMGF investments focused on the empowerment of the groups, often driven by civil society, to scale up and roll out these programs and test whether public health goals could be accomplished. One key strategy that evolved out of necessity was the need for integration of the MDA platform. The confluence of overlapping epidemiology of diseases controlled by once- or twice-a-year community administration of donated drugs, and the need for efficiencies to extend access, resulted in a delivery platform that has successfully reached high-risk communities with a coherent, evaluated set of drugs and interventions. This approach has also strengthened country programs.

Integration sounds simple and logical but is actually quite a challenge in the field. With results from BMGF projects exploring integration, the first investment through the U.S. Agency for International Development (USAID) was made into the rollout of the integrated NTD package addressing seven of the most common NTDs including onchocerciasis, LF, schistosomiasis, the three most common STHs (*Trichuris*, *Ascaris*, and hookworm), and trachoma. USAID applied the integrated MDA platform, expanding the scale significantly and increasing the lessons learned. The USAID program exceeded all of its targets in the first few years of the program. This impressed Congress and resulted, even with a change in administration, in a significant increase in U.S. government investment as well as an investment from the United Kingdom through its Department for International Development (DFID).

In addition to the integration platform, this initial progress and the challenges faced by the programs in scaleup informed the second phase of our investments. The next phase of investment for the MDA NTDs had two aspects: first, the sustainability of the programs and scale up to meet the need of endemic populations; and second, how to overcome the operational barriers in the specific disease areas that were discovered as the programs moved from smaller-scale programs, expanding and moving into new epidemiological settings. At the time, there was an ongoing debate about these vertical projects because they were reaching people at the end of the line and giving them one intervention when they and their communities were actually most frequently polyparasitized. This presented a huge missed opportunity and inefficiency within the parallel vertical programs. We participated in this global debate, and the next series of grants worked on integrating the approaches and aligning programs to work out the issues from each of the different disease perspectives to create a single platform addressing all of these diseases at the same time in endemic villages with the unifying platform of MDA.

Another learning from our investment was the need to identify and overcome disease-specific program barriers to achieve impact. In the initial rollout stage, each of the programs had identified weaknesses in its strategy and key gaps of knowledge that were holding back the program from reaching its full potential. Operational research projects were launched that went beyond the MDA platform

to include vector control and environmental issues and addressed disease-specific challenges. These investments started with LF as a priority to help the program attempt to reach its elimination goal in 2020. This was followed by similar grants that were made for trachoma and schistosomiasis.

Another group of diseases in the BMGF strategy are VL (Kala-Azar) and HAT (or sleeping sickness). Both of these diseases were plagued with poor tools both for treatment and diagnosis that have hindered the success of programs. Our approach to these 100 percent fatal diseases has been focused on improving the tools with significant investments in new tool development (drugs, diagnostics, and vector control) and understanding the drivers of transmission, including vectors, to be able to eliminate the disease.

The NOIDs have both benefited from and been a target of many of our vector control investments. Grants in this space cover a broad range of approaches, including very innovative and high-risk investments such as genetically modified mosquitoes through to evaluating very basic approaches with existing tools to create a home free of mosquitoes. In addition to tools that directly target the vector, we also have several investments looking at vectors for xenomonitoring disease transmission for dengue, HAT, and VL. New creative approaches to attack the vectors through their animal blood meal are also being evaluated for VL to decrease transmission and improve the chances of elimination of anthroponotic disease. These approaches have the chance to significantly affect the NTDs and increase the success of control and elimination of the vector-borne NTDs.

Our final area of investment in the NOIDs strategy focused on vaccines. JE, dengue, HPV, rabies, and hookworm all have had investments in either vaccine development or introduction and use. JE is the most advanced, with a low-cost vaccine now available, which has been introduced in several settings. HPV has two new successful vaccines (created without foundation investment), and our focus has been on evaluating and developing tools for appropriate diagnosis and treatment to support introduction of vaccine and elimination of cervical cancer. Our investment in rabies came after a significant time of looking at the options of what would generate impact. Our single investment evaluates a strategic approach for canid-transmitted rabies focusing on appropriate approaches to immunizing domestic dogs in low-resource settings. The most upstream investments are exploring the possibilities of a human hookworm vaccine and an animal leishmaniasis vaccine. Both diseases are immunologically challenging and are adding significant data to understanding the disease as well as potentially developing a vaccine.

The NTDs have been a significant investment for BMGF, which has resulted in significant progress in the field as a whole as well as significant health benefits for the world's most impoverished. Table A10-2 summarizes the disease areas and elements of our assessment of key areas of progress and challenges in the neglected diseases that have been part of our investment in the NTDs.

TABLE A10-2 Summary of Bill & Melinda Gates Foundation Investments in NOIDs Through 2010

Disease	Approach	Total Grant Commitment Through 2010 (US$)	Highlights	Future Considerations in the Field
Dengue	**Control of dengue through prevention** Development of a dengue vaccine. Early detection for implementation of new effective vector control.	145.1M	Vaccine candidates in clinical trials, including three into Phase I. Increased understanding of virus; more than 110 publications. Many vector approaches under development.	Dengue is an emerging infection, does this change priority? Middle-income market for prevention resulting in increased industry involvement.
Japanese encephalitis	**Prevention through vaccine development and adoption** Develop affordable effective safe vaccine for use in endemic countries. Enable sustained introduction.	39.0M	20-year commitment of supply of affordable (~25 cents), single-dose vaccine for public-sector use. More than 100 million doses given in Sri Lanka, India, Nepal, and Cambodia.	Still not prequalified and country introduction support still requested, though licensed.
Human papillomavirus (HPV)	**Prevention of mortality from cervical cancer** Support delivery of HPV vaccine. R&D on HPV screening tests.	131.1M	80 countries have now implemented pilots or HPV screening programs. China to screen 100 million women. Donated vaccine introduced in more than 10 developing countries. GAVI to issue call for early-adopting countries at end of 2011. HPV DNA test receives EMEA approval and CE Mark.	GAVI with insufficient funds to support significant uptake.

TABLE A10-2 Continued

Disease	Approach	Total Grant Commitment Through 2010 (US$)	Highlights	Future Considerations in the Field
Human African trypanosomiasis (HAT)	**Support programmatic control** New tool development (drugs, vector control, diagnostics). Understanding epidemiology/ burden.	147.5M	Current programmatic efforts are effective and cases are down under 10,000 for the first time in 50 years. Learned that right partners, right capability are necessary for tool development.	Current strategy may be too expensive to maintain as disease rates decrease.
Visceral leishmaniasis (VL)	**Supporting control efforts** Enhance delivery of existing tools. New tool development (vaccine, drugs, vector control, diagnostics).	156.0M	Paromomycin registration and adoption after early challenges. WHO treatment guidelines issued, and there is plan for country adoption. Improved diagnostic in head-to-head testing with industry partners. No vaccine has shown proof of concept. Proof of concept for cattle treatment to kill sand flies.	Is elimination of parasite possible? What is the role of asymptomatics in sustained transmission?
NTDs	**Integrate programs** Programmatic strategy to increase uptake and simplify messaging and increase funding.	80.6M	Integration has expanded access to treatment for NTDs. Funding base for programs has greatly expanded. However, "integration" interpreted and applied differently.	Should other interventions be included in the community outreach for MDA?

continued

TABLE A10-2 Continued

Disease	Approach	Total Grant Commitment Through 2010 (US$)	Highlights	Future Considerations in the Field
Cysticercosis	**Test feasibility of elimination/ eradication** Treatment of humans. Vaccination of pigs. Quality control of pork.	26.1M	Successful proof of concept of elimination in Peru at district level. Feasibility of sustainability and of implementation in other areas under question. Opportunity for treatment in MDA.	Emerging disease in Africa. What is MDA in Africa and Asia doing to taeniasis and cysticercosis? What if elimination is not sustained in Peru?
Lymphatic filariasis	**Supporting community goal of elimination** MDA in integrated programs. Operational research to overcome programmatic barriers, evaluate role of vector control, and ensure elimination.	79.3M	Believed to be the biggest public health program scale-up in history. 2020 goal very ambitious, not possible unless address *Loa loa.* Flexible operational research funds needed. Need for clear articulation and evaluation of eradication investment case.	How will we overcome *Loa loa*? Are we doing enough to reach 2020 and what are indicators?
Onchocerciasis	**Elimination in Americas, test feasibility in Africa** MDA twice annually with ivermectin in Americas for elimination. Evaluate feasibility of elimination in Africa.	79.8M	Steady progress in the Americas. Proof of concept of elimination in Africa successfully now changing the agenda and goals. Vector control essentially ignored.	Elimination in Africa may be feasible? What does this mean for program needs and resources requirements?

TABLE A10-2 Continued

Disease	Approach	Total Grant Commitment Through 2010 (US$)	Highlights	Future Considerations in the Field
Schistosomiasis	**Control and reducing burden** MDA to prevent morbidity and decrease transmission. Help address programmatic barriers with operational research.	58.7M	SCI helped kick-start programs on a national scale. Integration greatly helped programs expand and increase awareness. Drug cost still a barrier to expansion. New understanding of disease as being chronic.	New discussion on genital schistosomiasis as a risk factor for HIV; how does this change the program? Is it possible to eliminate?
Trachoma	**Reduce burden through prevention, treatment of blindness** Supporting SAFE strategy: MDA, surgery, and behavior change. Address barriers to program through operational research.	38.0M	Integrated MDA helping program expansion. Dynamic tension with drug and other program elements. Surgery required to prevent blindness. Elimination certification still undefined. Reorganized ITI making progress.	How do non-drug program components avoid neglect?
Hookworm and other STHs	**Reduce morbidity and mortality** Deworming treatment through MDA with anthelminthics. Preventative hookworm vaccine in development for long term.	75.4M	No real disease target set. Questions of resistance and effectiveness of single-dose platform need to be addressed. Need to look at how new products would be adopted and who would pay. Overlaps with water and sanitation, and nutrition.	New drug donations announced; how does this change the field? How do we better synergize with other programs (development and education)? Will revised DALYs change activities?

continued

TABLE A10-2 Continued

Disease	Approach	Total Grant Commitment Through 2010 (US$)	Highlights	Future Considerations in the Field
Rabies	**Demonstrate success of canine vaccination programs in Africa and Asia in preventing human rabies deaths** Demonstration projects to build evidence of feasibility and cost-effectiveness of this strategy.	10.0M	Grant just completed second year. Projects are able to achieve adequate coverage of dogs (70%). In countries without a dog rabies control program, very hard to start. Identifying how to reach dogs. Finding necessary resources.	Will not be applicable everywhere. Who would be strategic partner to carry this forward if it works?
Guinea worm (GW)	**Eradication by 2012** Quality, active surveillance. Isolation of cases and treatment of water sources to block transmission.	93.5M	99.7% decrease in disease. Niger/Nigeria declared GW free in 2010. Transition from active to passive surveillance is highly risky. Hard to maintain priority of eradication near the end and setbacks occur.	New cases in Chad question surveillance in some settings. Funding needs have increased with Chad and security issues in South Sudan.

Reflections and Learning from NOIDs

Much has been learned looking back over our 10+ years investing in NOIDs. The foundation approach has transitioned through the decade to be more proactive and evidence-based. We now better appreciate the need to clearly articulate goals and be increasingly realistic about how to achieve them as the backbone to our broader strategy. It is clear that more time, resources (both financial and human), and greater flexibility are required to achieve NTD goals than originally anticipated, particularly in the case of elimination and eradication programs. Each program needs to build an evidence base through operational research and a funding base through advocacy. Delivery partners need to be identified early. Success must be defined to ensure investments are focused and to create transparency that can allow us to better work with and within a multipartner landscape. Ultimately, we need to clearly communicate our strategy and priorities to the

field, to stakeholders, and to partners to help other donors plan their funding and to enable clear handoff points for sustainability and impact.

A multipronged investment approach is required to successfully carry through investments to impact. A key learning from the past decade is that the creation of transformative tools is necessary, but not sufficient. Within R&D, the foundation has learned the risks of basing success on the results of a single, large bet. Adequately resourcing fewer priority areas will allow us to take a portfolio approach to R&D investments and, therefore, increase our probability of success. Support for disease champions must be combined with robust target-product profiles and corroborated by stakeholder engagement, particularly the end user. Programs should be challenged and critiqued, even as they are supported. Although focusing on program priorities is critical, maintaining flexibility and having a broader perspective in case there are changes in each field is critical.

Our NOIDs strategy analysis has pointed to the potential for a foundation's involvement in research and development to be transformative. Even relatively small amounts of money can serve to attract others to the field and leverage, often sizable, investments by others. For example, our investments in integrated MDA were an entryway for investments from USAID and DFID, as well as significant investments from private-sector donors. Using challenge grants for Guinea worm doubled the size of BMGF contributions to these eradication efforts and increased awareness of their impressive progress for many additional donors that were engaged. In addition, the foundation leveraged areas where the original work was funded through other donors such as the NIH in a drug for trypanosomiasis, by the WHO Tropical Disease Research program, which we leveraged to develop a VL drug, and investments by the Chinese government in the SA 14-14-2 JE vaccine to successfully get a safe, efficacious, and affordable vaccine for the region.

At the time of the IOM meeting, the foundation NOIDS team is undergoing its Strategy Refresh. The aim is to provide clarity to our internal priority areas for additional investment, and equal clarity as to where the foundation will not engage. The strategy would ultimately define for each disease the areas for foundation action and leverage, including a detailed plan for MLE to define how success will be measured, and what data are required to answer those questions. The final goal, of course, is impact: the eradication of Guinea worm, and the progressive impact on individual diseases to decrease the suffering and disability caused. We are confident that the great progress that has marked the past decade will continue into the future in a richer and more complex landscape that can transform the neglected diseases to diseases of the past.

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A11

PROGRESS IN CONTROL AND ELIMINATION OF HUMAN AFRICAN TRYPANOSOMIASIS, 2010[16]

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Background

Although quinine had been used by the French in Senegal since 1822 and given in 1844 to railroad workers in the United States as a prophylaxis, its prophylactic use was demonstrated by Baikie in 1854 in his *Narrative of an Exploring Voyage up the Rivers Kwora and Binue*. This evidence established that steamships could be taken up the Niger and Benue rivers and was instrumental in opening the interior to foreign commerce: missionary stations were established, and more than 250 miles of previously unexplored river (Binue) were explored and charted. No lives were lost to malaria as a result of pioneering prophylactic use of quinine. Baikie's stay on the river proved that Europeans from temperate zones could penetrate the interior and survive there. Thanks to this evidence, the Berlin treaty signed in 1885 allowed colonial countries to rush inside central Africa. A few years later, they had to face a new killer: human African trypanosomiasis (HAT), also known as sleeping sickness. The disease existed before the arrival of Europeans, but penetrating the continent and breaking into the environment were responsible for its dissemination.

One century ago, HAT was felt to curb the development of colonial territories. As soon as the cause of the disease was clearly identified at the beginning of the 20th century—and fearing an unpopulated continent and a shortage of human labour to exploit natural resources—colonial authorities decided to establish extensive control operations, with high levels of political commitment and strong involvement from eminent scientists such as Pasteur, Ehrlich, and Koch. Needed funds were allocated.

Large and intensive campaigns of systematic screening, treatment, and patient follow-up were established in West and Central Africa for the *gambiense* form of the disease, whereas animal reservoir and vector control was mainly implemented in east and south Africa for the *rhodesiense* form.

By the 1960s, transmission was practically interrupted in all endemic areas, providing evidence that the elimination of the disease was feasible and could be

[16] This contribution is adapted from an article by the same authors to be published in *PLoS* (human African trypanosomiasis control and surveillance programme of the World Health Organization, 2000–2009: the way forward [Simarro, P. P., A. Diarra, J. A. Ruiz Postigo, J. R. Franco, and J. Jannin]).

achieved with basic tools and strong committment. "It has become commonplace to say that trypanosomiasis is almost eradicated in Africa. . . . Although foci are relatively rare, they are nonetheless irritating" (Labusquière, 1965).

Thereafter, the rarity of cases led to a loss of interest for a sustained surveillance, and the risk of reemergence of the disease was overlooked. Thus, in the 1980s the disease reemerged. By the 1990s, flare-ups were observed throughout the past endemic areas, leading to a worrisome increase in the number of reported cases. Bilateral cooperation continued to support National Sleeping Sickness Control Programmes (NSSCPs) in some historically linked countries, but many areas or countries remained without any support or control activities. At this time, nongovernmental organizations (NGOs) played a crucial role in the control of HAT. However, their interventions were mainly focused on remote and insecure areas. As emergency operators, their policy understandably excluded the support to NSSCPs, which resulted in (1) the establishment of substitute HAT control systems, (2) the maintenance of a large part of the population at risk out of the umbrella of NGOs' projects, and (3) the difficulty for national programmes to sustain control achievements after NGOs' withdrawal.

The card agglutination trypanosomiasis test (CATT) for serological screening of HAT *gambiense* populations at risk was developed during the 1970s (Magnus et al., 1978), but its large-scale production encountered many problems that hindered its availability (Smith et al., 1998). Use of CATT was not widespread because NSSCPs could not afford to buy it. In addition, the production of anti-trypanosomal drugs was seriously threatened because of the lower economical return for manufacturers.

Research for new diagnostic tools and drugs was scarce (Stich et al., 2003). Only eflornithine, initially developed for cancer treatment, was finally registered for the treatment of the *gambiense* form of the disease, and only in 1990, without guarantee of being produced (Sjoerdsma and Schechter, 1999). Its cost, complex distribution, and administration made it inappropriate for the under-equipped peripheral health services in remote rural areas where HAT was prevalent. Only some well-funded NGOs were able to afford the cost of eflornithine treatment.

During the 1990s, security constraints due to civil wars and social upheavals complicated HAT control by preventing access to a large number of HAT-endemic areas, leading to difficulties in reaching a large number of affected populations and consequently to a considerable lack of epidemiological information. The World Health Organization (WHO) Expert Committee on HAT control and surveillance held in 1995, considering the huge uncertainties between the reported cases and the factual field situation, estimated that the true number of cases was at least 10 times more than reported. Thus, from the 30,000 cases reported annually, it was estimated that some 300,000 infected individuals remained ignored in the field (WHO, 1998).

In 1997, the 50th World Health Assembly expressed its concerns about the major recrudescence of cases by adopting a resolution to raise awareness and

national and international interest (WHO, 1997). Subsequently, WHO enhanced its coordinating role and promoted networking with partners, developing a strong advocacy and awareness campaign. In 1999, a WHO treatment monitoring and drug resistance network was established with the collaboration of the Médecins sans Frontières (MSF) access campaign for essential drugs.

As a result, the private sector recognized its responsibility, which led Aventis Pharma to grant a substantial support to WHO in 2001 for the control and surveillance of HAT. This support included HAT drug donations and financial contributions, which allowed WHO to strengthen its support to disease-endemic countries (DECs). The establishment of this private–public collaboration marked the beginning of a new era in HAT control by expanding capacities for WHO control strategies.In 2002, Bayer Health Care began donating the last drug (suramin) to WHO.

The importance of the various components of the epidemiology of trypanosomiasis, (human, animal, vector control, agricultural activity, livestock production, etc.) and their impact on the development of rural Africa led WHO in 1995 to promote—together with the Food and Agriculture Organization (FAO), the International Atomic Energy Agency (IAEA) and the African Union Interafrican Bureau for Animal Resources (AU-IBAR)—an intersectoral initiative that, in 1997, ultimately became the Programme Against African Trypanosomiasis (PAAT).[17]

In parallel, during the African Union Summit in Lomé in 2000, the African heads of state and government established the Pan African Tsetse and Trypanosomiasis Eradication Campaign (PATTEC)[18] with the objective of rendering Africa a tsetse- and trypanosomiasis-free continent.

Current Situation

Between 2000 and 2009, out of 36 countries listed as endemic, 24 received the exclusive support of WHO either to assess the epidemiological status of HAT or to establish control and surveillance activities: Benin, Burkina Faso, Cameroon, Chad, Côte d'Ivoire, Gabon, Ghana, Guinea, Guinea Bissau, Kenya, Liberia, Malawi, Mali, Mozambique, Nigeria, Rwanda, Senegal, Sierra Leone, Swaziland, Togo, Uganda, United Republic of Tanzania, Zambia, and Zimbabwe; 6 received support from WHO as well as NGOs or through bilateral cooperation: Angola, Central African Republic (CAR), Congo, Democratic Republic of the Congo (DRC), Equatorial Guinea, and Sudan; and finally 6 countries, Botswana, Burundi, Ethiopia, Gambia, Namibia, and Niger, are listed as endemic but have not reported any cases in the past 20 years and have not yet received any support.

The 30 aforementioned countries received WHO support in the form of

[17] See http://www.fao.org/ag/againfo/programmes/en/paat/disease.html.

[18] See http://www.africa-union.org/Structure_of_the_Commission/depPattec.htm.

- *Technical assistance.* It is provided either by WHO staff or by WHO temporary advisers.
- *Access to diagnosis.* This support includes the equipment, reagents, logistics, and funds to allow the national teams to reach HAT transmission areas to perform active case-finding surveys and set up passive surveillance. Since 2007, WHO has provided, free of charge, more than 35 percent of the CATTs used by national programmes.
- *Training.* As part of capacity building, training was targeted at two technical levels: (1) training on site, hands on (410 technical staff from 23 disease-endemic countries were trained) and (2) participation in the International Course on African Trypanosomoses implemented in collaboration with the Association against Trypanosomiasis in Africa (105 programme managers or scientists from 22 countries have participated in either one of the five courses).
- *Access to treatment.* This covers the provision of drugs as well as a patient's accessibility. During the past decade, WHO has covered the need of DECs by distributing, in collaboration with MSF-Logistics, 594,200 vials of melarsoprol, 576,375 vials of pentamidine, 477,542 vials of eflornithine, and 13,597 vials of suramin.

One main objective of WHO in the "access to treatment" initiative, supported by a new agreement between WHO and sanofi-aventis, was to reduce the use of the arsenic derivative melarsoprol for the treatment of second-stage *gambiense* cases by making eflornithine—actually the sole alternative to melarsoprol—accessible. Indeed, during the period 2003–2006, despite the availability of eflornithine and the toxicity of melarsoprol, it remained widely used, and 88 percent of the second-stage *gambiense* cases were treated with this drug (Figure A11-1). Only well-funded NGOs could afford the costly and complex use of eflornithine as first-line treatment, while NSSCPs used eflornithine exclusively to treat melarsoprol relapses. This was demonstrated during the period 2003–2006 by an eflornithine distribution ratio of 9 to 1 for NGOs versus NSSCPs (Figure A11-2).

In 2006, a number of DECs requested the support of WHO to train their staff on the use of eflornithine and requested the provision of the necessary equipment to switch gradually from melarsoprol to eflornithine as a first-line treatment. Subsequently, a training of trainers was organized in southern Sudan, and a kit containing the drugs as well as all the materials needed to administer two full eflornithine treatments was designed by WHO and distributed with the collaboration of MSF-Logistics (WHO, 2009a). The kit for two eflornithine treatments weighed 40 kg at a cost of US$1,420. This particular effort in terms of logistics and funding allowed DECs to regularly decrease their use of melarsoprol for the treatment of second-stage *gambiense* cases. Consequently, in 2009 a 57 percent reduction in the use of melarsoprol was recorded (from 88 to 38 percent)

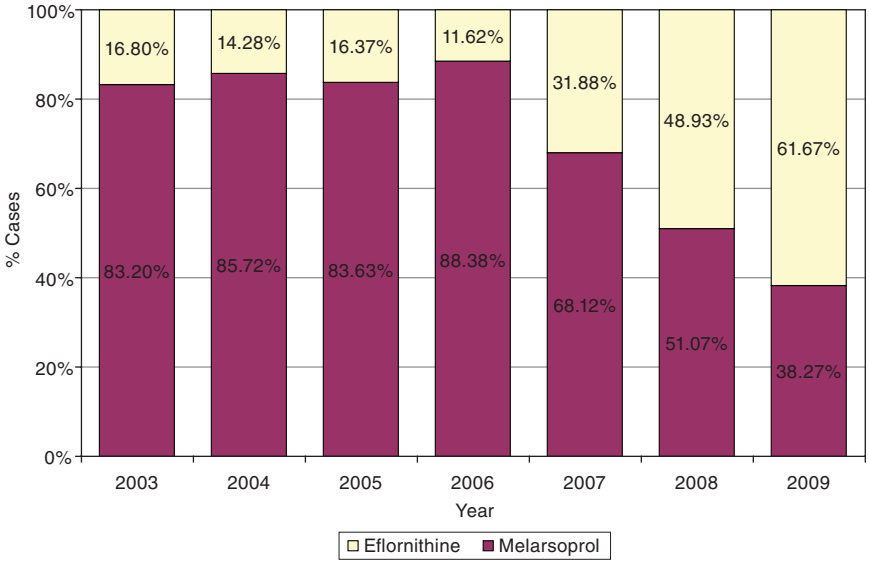

FIGURE A11-1 Drug rate use for the treatment of second-stage *T.b. gambiense*: eflornithine versus melarsoprol (2003–2009).

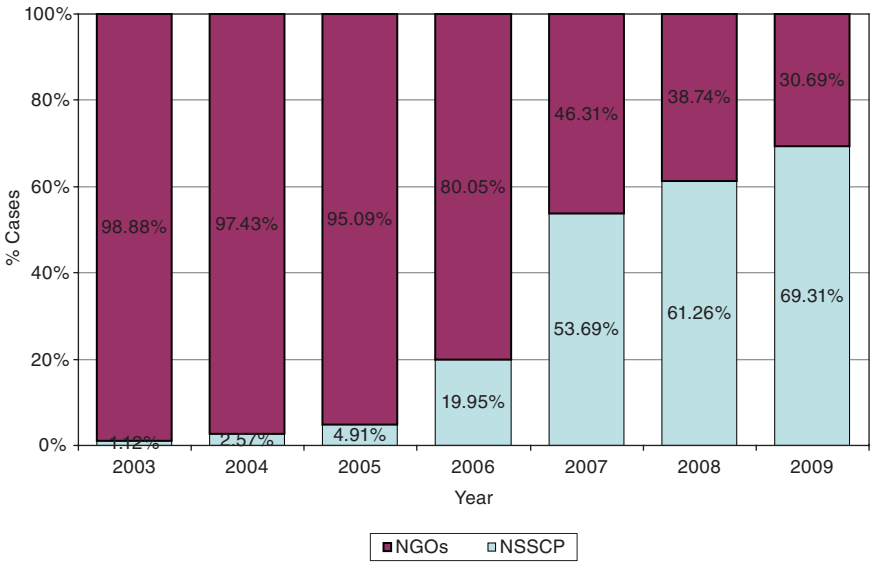

FIGURE A11-2 Institutional rate use of eflornithine: National Sleeping Sickness Control Programmes versus non-governmental organizations (2003–2009).

(Figure A11-1), and the use of eflornithine by NSSCPs increased by 250 percent (from 20 to 70 percent) (Figure A11-2).

Nifurtimox, registered for Chagas disease, showed efficacy during compassionate use in melarsoprol refractory cases (Pepin et al., 1989; Van Nieuwenhove and Declerq, 1981). To simplify the eflornithine schedule, attempts were made to demonstrate that a therapy combining nifurtimox and eflornithine could contribute to a simpler administration of the drugs; some trials took place in DRC during the late 1990s (Bisser et al., 2007) and in Uganda during the early 2000s (Checchi et al., 2007; Priotto et al., 2006).

In 2003, an extensive nifurtimox/eflornithine combination treatment (NECT) clinical trial started in Congo and later in DRC involving MSF, Epicentre, the Special Programme for Research and Training in Tropical Diseases, and Drugs for Neglected Diseases Initiative (DNDi). The trial ended in 2008. Results indicated that NECT presented no inferior efficacy and safety compared to the eflornithine monotherapy (Priotto et al., 2009).

Following the inclusion of the NECT on the WHO Essential Medicines List in May 2009 (WHO, 2009b), NSSCPs requested WHO to train their staff to incorporate this new combination in their national policy. A training for trainers was organized in Kinshasa in November 2009 for French-speaking countries and another for English-speaking countries in Uganda in February 2010 (WHO, 2010a).

Thereafter, a new kit for NECT treatment was designed to continue to facilitate access to the best possible treatment. Thanks to the reduction of drug quantity and materials, using the same packaging form as for the eflornithine monotherapy treatment kits, a new kit for four full NECT treatments weighted 36 kg at a cost of US$1,440 was produced. This kit has already been distributed to nine countries (reporting together 96 percent of all *T.b. gambiense* cases in 2009): Cameroon, CAR, Chad, Côte d'Ivoire, DRC, Equatorial Guinea, Gabon, Sudan, and Uganda.

However, NECT does not change the paradigm of HAT treatment because it remains logistically complicated to implement. Nevertheless, it is anticipated that NECT will contribute to sustain the already observed decreasing trend of melarsoprol use for the treatment of second-stage *T.b. gambiense* infections (WHO, 2009c).

During the period 2006–2009, WHO promoted research for a better knowledge of HAT epidemiology and for the development of new tools. With that objective in mind, 23 agreements for "performance of work" were concluded with institutions of 11 countries (Belgium, Burkina Faso, DRC, France, Germany, Italy, Kenya, Malawi, Tanzania, Uganda, and the United Kingdom). In 2006, WHO and the Foundation for Innovative New Diagnostics[19] signed a five-year Memorandum of Understanding to promote the development of simple and more sensitive and specific diagnostic tests. WHO took the responsibility to set up a specimen bank to facilitate the evaluation of relevant new diagnostic tools and to

[19] See http://www.finddiagnostics.org/.

reduce the need for field trials. Currently, samples from 1,700 people including patients, seropositive suspects, and controls have been collected from 14 sites in Chad, DRC, Guinea, Malawi, Uganda, and the United Republic of Tanzania. More than 20,000 samples (including serum, plasma, white blood cells, urine, saliva, and cerebrospinal fluid) are stored in the central repository bank at the Institut Pasteur in Paris.

Strong collaboration has been established with groups working on the development of new drugs, mainly the Consortium for Parasitic Drug Development (CPDD)[20] and DNDi[21]. In addition, the Division of Parasitic Diseases of the National Centre for Infectious Diseases, Centers for Disease Control and Prevention in Atlanta, Georgia; the Parasite Diagnostics Unit from the Institute of Tropical Medicine in Antwerp, Belgium; and the Research Unit of the Institut de Recherche pour le Développement based in the International Centre for Research and Development in Livestock in subhumid areas in Bobo-Diulaso, Burkina Faso, have been nominated as WHO Collaborating Centres.

In February 2008, WHO launched the initiative of the Atlas of HAT to map all reported cases for the period 2000–2009 at the village level. This initiative is jointly implemented with FAO in the framework of the PAAT. Presently, mapping includes 23 out of the 25 countries having reported at least one case in the last 10 years. In the two remaining countries, namely Angola and DRC, data processing is ongoing. The Atlas database also includes epidemiological information that can be used by NSSCPs, NGOs, and research institutions to monitor and evaluate the impact of control activities, to assess epidemiological trends, and to plan control or research activities (Simarro et al., 2010) (Figure A11-3).

As a consequence of these activities, the number of new cases reported to WHO in 2009 dropped below 10,000 for the first time in 50 years (WHO, 2010b). This represents a decrease of 63 percent since 2000 (Figure A11-4). In 2009, only two countries reported more than 1,000 new cases, namely CAR and DRC, representing 11 and 73 percent, repsectively, of the total cases reported. One country, Chad, reported more than 500 but fewer than 1,000 new cases; 3 countries reported more than 100 but fewer than 500 new cases: Angola, Sudan, and Uganda; 11 countries reported fewer than 100 cases: Cameroon, Congo, Côte d'Ivoire, Equatorial Guinea, Gabon, Guinea, Kenya, Malawi, United Republic of Tanzania, Zambia, and Zimbabwe.

Finally, 19 countries listed as being HAT endemic reported no cases in 2009. Seven performed regular surveillance: Benin, Burkina Faso, Ghana, Mali, Nigeria, Sierra Leone, and Togo. Nine have no regular surveillance activities but reported no cases in decades, namely Burundi, Ethiopia, Gambia, Guinea Bissau, Liberia, Mozambique, Niger, Rwanda, and Senegal; however, these latter countries deserve an assessment to clarify their epidemiological situation. Two

[20] See http://www.unc.edu/~jonessk/.
[21] See http//www.dndi.org/.

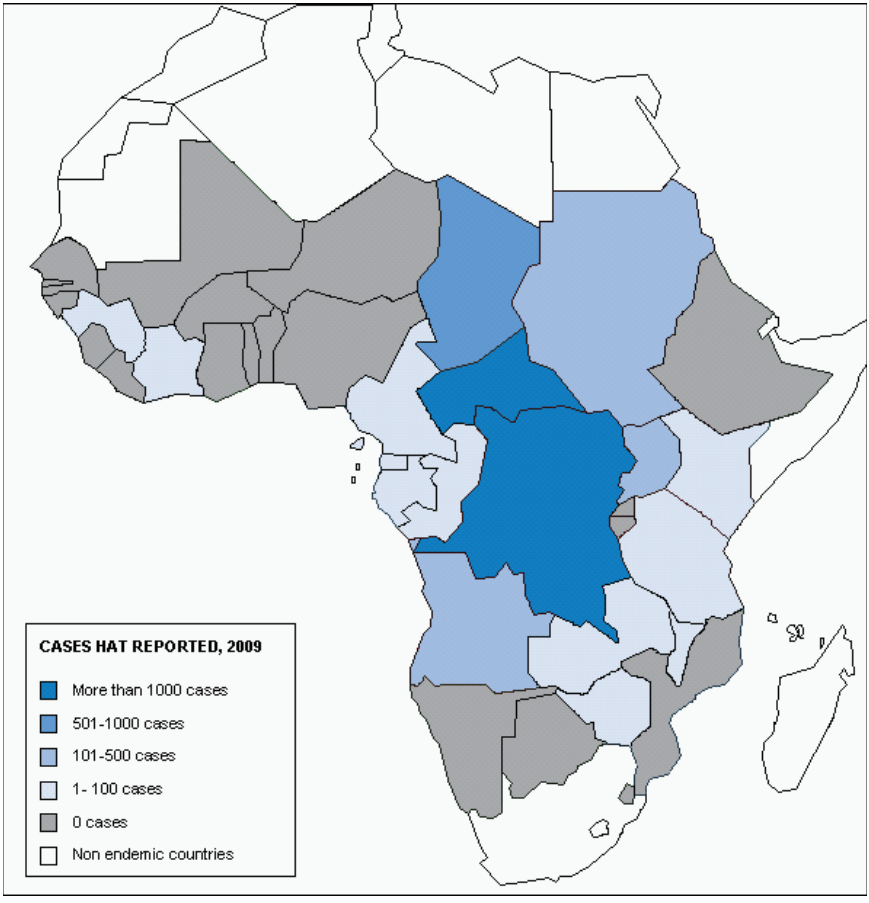

FIGURE A11-3 Classification of human African trypanosomiasis-endemic countries according to cases reported in 2009.

countries, namely Botswana and Namibia, are considered disease transmission free because of the recently implemented, successful tsetse elimination campaigns (Kgori and Modo, 2009; Kgori et al., 2006). Finally, Swaziland has been shown through an extensive tsetse survey to be free of HAT vectors (Saini and Simarro, 2008) (Figure A11-5).

Discussion

During the past decade, the WHO public–private partnership (PPP) established in 2001 with Aventis Pharma and renewed in 2006 by sanofi-aventis made it possible to carry out extensive HAT control activities and to strengthen the

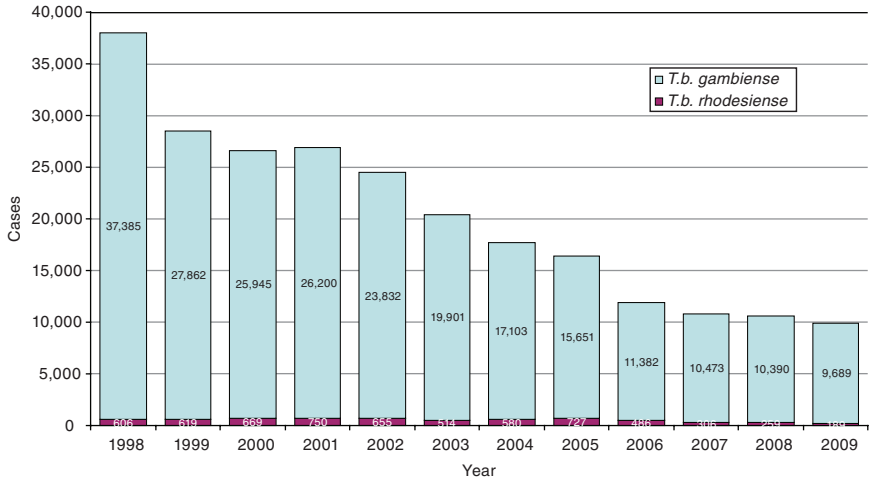

FIGURE A11-4 Evolution of reported cases of both forms of human African trypanosomiasis (1998–2009).

capacities of NSSCPs. The PPP has been complemented by bilateral cooperation, by NGOs, and by support from Bayer AG. Furthermore, the interruption of civil wars and social upheavals has also substantially facilitated access to HAT-endemic areas.

In 2009, the number of new cases of HAT reported to WHO has dropped below the symbolic number of 10,000, while in the period 2000–2009 the number of people screened increased because of the greater number of health care facilities involved in passive screening and through the improvement of the performance of active case-finding surveys. Owing to the improved knowledge of HAT distribution, WHO estimated in 2006 the factor gap between cases reported and cases infected to be three (WHO, 2006) instead of 10 as it was thought to be in 1995 (WHO, 1998).

Considering the next steps to be implemented, it is important to note that the disease situation is not homogeneous throughout the continent.

In several foci, the *gambiense* form of the disease has already reached a prevalence threshold compatible with the concept "eliminated as a public health problem." To consolidate such a result and ensure sustainability, an adapted control and surveillance approach will have to be implemented within the national health system. Whereas, in other foci, HAT remains a public health issue mostly because of accessibility problems or security constraints (François Chappuis et al., 2010), and therefore reinforced control measures must be maintained using the classical vertical approaches with the participation of existing health care structures.

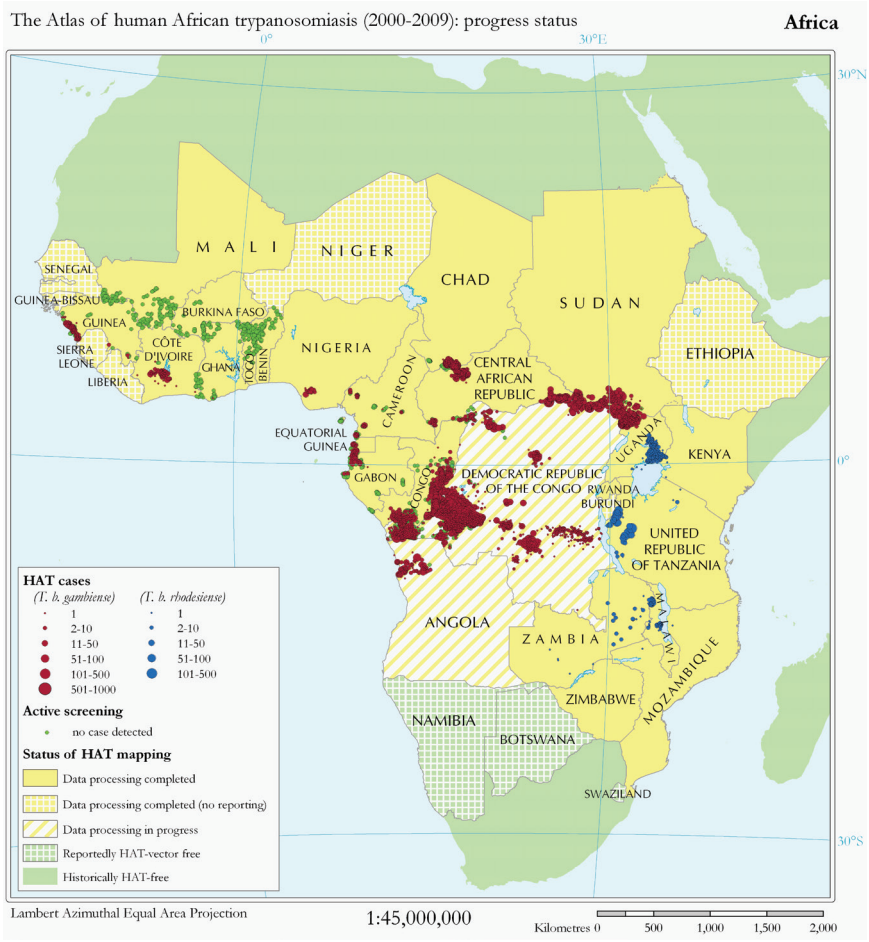

FIGURE A11-5 Atlas of human African trypanosomiasis.

The *rhodesiense* form is a zoonotic disease involving cattle and game in the transmission cycle. Cattle movement is a continuous threat of disease transmission and spread and subsequently a source of outbreaks (Fèvre et al., 2001). Furthermore, wildlife in protected areas are niches for contamination; there is a continuous risk for park rangers, surrounding population, and visitors to become infected. Controlling this form of the disease requires a multisectoral approach. Therefore, it is crucial to reinforce local health care capacities for diagnosis and disease management as well as to establish effective coordination with veterinary and natural resources management services in charge of domestic, wild animals, and vector control.

Despite the encouraging results and exciting perspectives, the process remains fragile. At this stage, some obstacles are anticipated in the course of future control activities, and a few issues should be carefully considered:

- The decline of contribution by NGOs and bilateral cooperation toward HAT control. During the period 2000–2009 there were 9 bilateral and 38 NGO HAT projects, while in 2010 there remained only 1 bilateral (DRC) and 5 NGO projects (CAR, DRC, Sudan, and Uganda). The positive aspect of this situation is the decrease of HAT-related emergencies and the substantial improvement of country self-managed HAT control activities.
- The "tyranny of DALYS (Disability Adjusted Life Years)" expresses the lack of interest of donors when the burden of the disease is decreasing. Then supporting institutions withdraw not only from HAT control but also from HAT research. With the reduced amount of funds available for control, it seems obvious that the responsibility to give "the last strike to the dying beast" will exclusively rely on the overloaded and weak health services. Also, the loss of support for research will definitely eliminate any hope to get the needed, long-awaited new tools not only to accelerate the current control process but also to boost the involvement of health services in surveillance and control of HAT to sustain the achieved results. Such a situation will likely open the door for reemergence of the disease.
- While the control of cattle as a HAT reservoir appears to be a reachable objective that would in turn allow the control of *T.b. rhodesiense* infections in affected areas (Kabasa, 2007), the control of the disease in wildlife and of the vector in protected areas and game reserves looks more complicated because of conservationist, ecological, and environmental considerations.
- Because many patients remain to be treated, and they deserve to be treated using safe drugs, new safe and easy-to-administer drugs need to be developed also to facilitate control, to decrease the cost of distribution, to remove the risk of drug resistance, and to help ensure decentralized surveillance.

Furthermore, close monitoring is needed to assess the impact of climate changes and demographic evolution (Cecchi et al., 2009; Courtin et al., 2008) in HAT transmission.

Conclusion

By the end of last century, WHO and its partners developed a strong and successful advocacy program to secure access to diagnosis and treatment, ensuring the availability of funds and drugs to support DECs. As a result, during the first decade of the current century, great advances have been made in HAT control.

In 2007 a WHO informal consultation of the heads of NSSCPs held in Geneva reached the conclusion that "elimination of the disease as a public health problem" was possible (WHO, 2007). This conclusion was based on the achievements obtained, on the current understanding of the epidemiology of the disease, and on the willingness of African heads of states and government to eradicate tsetse and trypanosomiasis as stated when PATTEC was established in 2000.

The time has now come to sensitize stakeholders to the pertinence and ethical duty to embark on an "elimination process of HAT as a public health problem" despite difficulties, obstacles, and threats that are expected in this process. Without such a hammering approach, there is a risk of stagnation of control and surveillance as occurred in the late 1960s and led ultimately to the return of the disease.

Today WHO and partners are committed to reinforce and coordinate actions toward a sustainable elimination process (WHO, 2010c). Although there are still technical aspects to be solved, the "elimination of HAT as a public health problem" will require social peace, institutional support, and adequate funding for its implementation. These last conditions are not exclusive to the control, elimination, and sustained surveillance of HAT but also for the overall development of DECs, which would also contribute to the control of HAT.

When targeting the "elimination of HAT as a public health" problem, the goal should be recognized as a major achievement but must never be considered an endpoint. Without appropriate discrimination, the use of the word "elimination" may lead to risky conclusions. The disease believed to "no longer exist" will reach oblivion, placing in the background the required pressing efforts for a sustained and effective surveillance. It must be kept in mind that "elimination" is not synonymous with "eradication." Elimination is only a point in time in the control process of the disease, at which stage the classical vertical control intervention approaches are no longer cost-effective. Thus, the national health system must take the ownership of sustaining elimination by integrating HAT surveillance in its services while keeping the capacity to react rapidly according to the analytical results of the surveillance outcome.

Elimination should be considered the beginning of a new process involving new actors. Therefore, elimination of HAT as a "public health problem" will require continuous efforts and innovative approaches. There is no doubt that new tools would facilitate the elimination process and the sustainability of results; thus, funding efforts for HAT control and research must continue based on a public health objective and no longer on the burden of the disease.

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A12

SCHISTOSOMIASIS: CHALLENGES AND OPPORTUNITIES

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Schistosomiasis Consortium for Operational Research and Evaluation

Background: The Parasite and Its Context

For more than 440 million people around the world, schistosomiasis (also known as bilharziasis) is a chronic disease caused by past or present infection with parasitic blood flukes of any of five *Schistosoma* species: *S. mansoni*, *S. japonicum*, *S. mekongi*, *S. intercalatum*, or *S. haematobium* (Sturrock, 2001). In their mature stages, adult *Schistosoma* parasites are 1- to 3-cm-long multicellular worms that reside in the venous circulation of their human hosts. Male/female

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worm pairs create disease by releasing highly immunoreactive eggs into tissues of the digestive or urinary tracts (King, 2001). About 50 percent of the eggs laid by female worms leave the body by ulcerating through the wall of the bowel into the stool (*S. mansoni*, *S. japonicum*, *S. mekongi*, and *S. intercalatum*) or through the bladder mucosa to reach the urine (*S. haematobium*). The remaining 50 percent of eggs remain trapped in host tissues and are destroyed by acute and chronic inflammation, which, in turn, results in local damage, scarring, and organ dysfunction (Ouma et al., 2001; Ross et al., 2002; Smith and Christie, 1986). The process of chronic inflammation also leads to systemic effects on patient metabolism that seriously impair growth, nutrition, and cognitive development (Coutinho et al., 2006a, 2006b; Ezeamama et al., 2005; Friedman et al., 2005a). When viable eggs reach freshwater, they hatch into free-swimming miracidia that infect the schistosome's necessary intermediate hosts (i.e., snails of local *Biomphalaria*, *Bulinus*, or *Oncomelania* species that are permissive for schistosomal development) (Sturrock, 2001). This phase of snail infection, in turn, amplifies parasite numbers via asexual division. The transmission cycle (Figure A12-1) is completed four to six weeks later, when infectious larvae (cercariae) are released by infected snails. Human infection occurs when cercariae penetrate through the skin of people who enter freshwater sites that contain these infectious schistosome larvae.

Although this transmission cycle appears highly complex, it is also highly

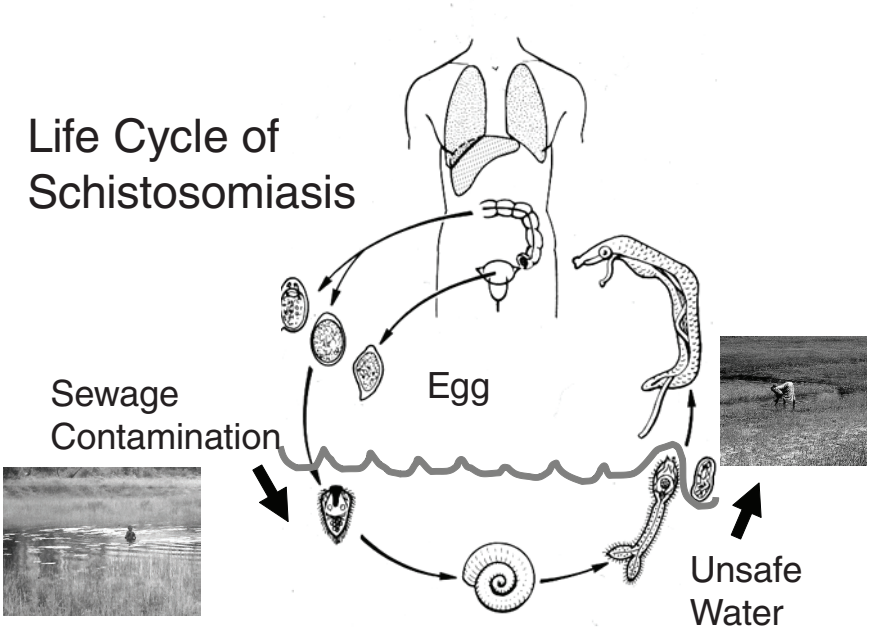

FIGURE A12-1 Life cycle of *Schistosoma* spp. parasites.

efficient when local conditions are favorable (Satayathum et al., 2006; Sturrock, 2001). The involvement of two different animal hosts for this long-lived parasitic trematode affords two effective ecological refuges if the process of transmission happens to be interrupted by protracted dry spells.

Schistosoma parasites are found in Africa, the Middle East, Asia, South America, the Philippines, and the Caribbean basin. If left untreated, a schistosomal worm will persist an average of two to five years (Anderson and May, 1991). People at risk will experience multiple waves of infection (during childhood and into young adulthood) wherever transmission occurs. The dynamics of infection and reinfection mean that people at risk will experience active *Schistosoma* infection for an average of 15 or more years.

A key feature of *Schistosoma* transmission (that often remains hidden in policy discussions) is its association with poverty and underdevelopment. Perpetuation of the *Schistosoma* life cycle requires water contamination by human sewage (lack of adequate sanitation), while exposure to infection results from a lack of safe, alternative water sources for agricultural, domestic, and recreational activities (Bruun and Aagaard-Hansen, 2008; el Kholy et al., 1989; Jordan, 1985; King, 2010). The world's rural-to-urban demographic transition is no panacea for schistosomiasis. In many unplanned developments in urban South America and Africa, very significant *Schistosoma* transmission continues within "city limits" (Barbosa et al., 2010; Ugbomoiko et al., 2010).

Current Challenges and Opportunities

Challenges

There are a number of significant challenges to formulating an effective 21st-century policy for schistosomiasis control. First, many health policy makers misunderstand what schistosomiasis really *is,* and they also misunderstand what schistosomiasis *does* to the average person (King and Dangerfield-Cha, 2008; King et al., 2005). Because of this confusion, there is a misperception of what antiparasitic treatments can and cannot accomplish for public health (King, 2010). This results in a corresponding lack of clarity about who needs to be treated. Finally, the very narrow scope of 20th-century assessments of *Schistosoma* infection–related disease (Mott, 2004; Warren, 1982) led to a serious underestimation of the potential benefits of transmission interruption in programs for schistosomiasis control (Jordan, 1985; King et al., 2006; Singer and Ryff, 2007; Wang et al., 2009).

Opportunities

Over the past decade, new opportunities for much broader schistosomiasis control have emerged (Fenwick, 2006). National efforts have delivered the anti-

schistosomal drug praziquantel to school-age children across Uganda, Tanzania, Zambia, Burkina Faso, Mali, and Niger in collaboration with the Schistosomiasis Control Initiative of Imperial College, London (Garba et al., 2009). Following on the heels of this program's success, broader deworming initiatives are now being implemented to combine schistosomiasis treatment with ongoing regional or national programs for the control of onchocerciasis, lymphatic filariasis, and/or the soil-transmitted helminths (STHs), hookworm, *Ascaris*, and *Trichuris*. Expansion of such programs is being actively supported by governmental programs from donor nations (e.g., the U.S. Agency for International Development, and the Department for International Development in the United Kingdom) and by many nongovernmental development organizations that are joining forces to develop national-level "deworming" projects in other sub-Saharan African countries. With a refocus on the lifetime impact of *Schistosoma* infection on childhood growth and and on later adult productivity, parasite control programs are beginning to consider the role of schistosomiasis *prevention* in the overall assessment of poverty reduction efforts. With the aim of attaining the United Nations' Millennium Development Goals, deworming (including schistosomiasis control) is coming to be seen as an essential part of the childhood and maternal health agenda.

Past Views of Schistosomiasis: 1970–1995

By definition, schistosomiasis is the *disease* caused by human infection with parasitic flukes of one of the five *Schistosoma* species that infect humans: *S. mansoni*, found in Africa and South America; *S. haematobium*, found in Africa and the Middle East; *S. intercalatum*, found in Central and West Africa; *S. japonicum*, found in China, Southeast Asia, and the Philippines; and *S. mekongi*, found in parts of Southeast Asia (Sturrock, 2001). The pathologic disease caused by schistosome infection was first described in the 19th century, and patient cases were first detected in the early 20th century in Egypt and the Caribbean.

Since the 1960s, extensive animal model studies have provided in-depth knowledge of the pathology associated with immune reaction to *Schistosoma* eggs deposited into host tissues. Despite this in-depth knowledge of *Schistosoma* infection–related pathology, it somehow became received wisdom among health policy circles that the majority of human patients with schistosomiasis were "minimally symptomatic" and that schistosomiasis was not much of a public health problem (Gryseels, 1989; Mott, 2004; Warren, 1982). Given what was known about *Schistosoma* infection in the medical and basic science literature, how could this have come about? In retrospect, the high cost of treating or preventing schistosomiasis in the 1960s to 1990s (Jordan, 1985; King and Mahmoud, 1989) influenced policy thinking solely toward finding ways to minimize the level of intervention, while still preventing "morbidity." In this context, however, morbidity was defined only in terms of the severest forms of *Schistosoma*-associated pathology (Warren, 1982; Warren and Mahmoud, 1976; WHO, 1993). As detailed below, a limited interpretation of the available research data led to the conclu-

sion that "most *Schistosoma* infections cause minimal or no disease" and could therefore be left untreated if health resources were inadequate.

Systematic Errors in Describing Schistosomiasis Disease Burden

In revisiting the health economics and policy literature of the 1960s and 1970s, one notes that a number of poorly substantiated claims were made in that era about the impact of schistosomiasis on endemic populations. Depending on the commentator's point of view, schistosomiasis was either the most significant health problem in any *Schistosoma*-affected area (Farooq, 1964) or only a minimal problem for local populations, who adapted quite well to their infection status (Walker et al., 1970). Epidemiologists of the period rightly took up the challenge of defining *Schistosoma* infection–associated disease on a population basis. Parallel community surveys were undertaken in Africa, the Caribbean, and Asia to identify symptoms and signs that could be specifically attributed to *Schistosoma* infection by any of the three major parasite species, *S. mansoni*, *S. haematobium*, and *S. japonicum*. The summary conclusion, based on a lack of significant statistical association between individual symptoms and egg-positive status (on parasitological examination) among the residents of endemic locations, was the following:

> [Although] . . . it is frequently claimed that chronic schistosome infections are associated with weakness and inability to work or attend school. Such symptoms have not been observed, regardless of the intensity of infection, in controlled studies in villages in St. Lucia, Kenya or the Philippines. Recent physiologic studies done in the Sudan with use of bicycle ergometry have shown significant impairment only in those with the heaviest levels of infection. (Warren, 1982)

What was wrong with this approach, and what was wrong with these conclusions? Research has since shown that nearly all residents of *Schistosoma*-endemic locations develop infection at some time during their lives (Shane et al., 2009). Standard egg detection assays based on stool or urine examination routinely miss up to 20 to 30 percent of active infections (Carabin et al., 2005; de Vlas et al., 1997; Savioli et al., 1990). Unless specimen testing is performed on multiple consecutive days, local "egg-negative" comparison groups are, in fact, 40 to 60 percent infected, and those who are not actively infected are likely to carry the morbid effects of prior infection. It was not surprising that those misclassified as "uninfected" (based on a negative egg test) were not significantly different from those passing eggs on the day that the symptom surveys were performed. Field studies of the era sometimes acknowledged the likelihood of misclassification. However, based on a loose correlation between egg counts and risk for certain pathognomonic findings caused by *Schistosoma* infection, it was often claimed that this was not an issue because only persons with easily detectable, heavy egg outputs were at risk for "disease" (Warren et al., 1979).

Many of these small studies were underpowered to distinguish the effects of

present or past *Schistosoma* infection on health conditions having more complex etiology, such as anemia, decreased fitness, and impaired childhood development (King et al., 2005). In the absence of a truly accurate diagnostic for active *Schistosoma* infection, only persons known to be excreting eggs were considered to "have" schistosomiasis. Often, only the late, *Schistosoma*-specific complications of infection were taken as the defining manifestations of the disease. Although it was known that complications of infection could persist into adulthood after infection ended, the prevalence of such problems was low (< 1 percent). In assessing the population impact of infection, the policy makers' conflation of egg-positive status with schistosomiasis led to the claim that the average person with schistosomiasis had minimal or no disease.

This theory may have held plausibility because, at the time, organ-specific disease was the focus of study (Smith and Christie, 1986), and "disease formation" was interpreted as the process of anti-egg granulomatous response within the tissues where adult schistosomes reside (the portal circulation for *S. mansoni* and *S. japonicum*, and the urinary venous plexus for *S. haematobium*). Both animal models and clinical research studies had shown that local anti-egg inflammation is down-modulated during the course of chronic infection (King, 2001). In many different endemic settings, adult humans had lower-intensity infections, suggesting that there was some sort of adaptation or reduction in *Schistosoma*-associated disease risk over time. Nevertheless, the bulk of clinical evidence used in these policy formulations was cross-sectional, and the inclusion of studies was selective, with interpretation of data apparently skewed by this prevailing theory of minimal disease risk from human infection.

Unacknowledged *Schistosoma*-Associated Disease

The World Health Organization (WHO) and World Bank's 1996 report, *The Global Burden of Disease* (Murray and Lopez, 1996), reflected the prevailing view that schistosomiasis had only minimal impact on the daily performance of the average patient infected with *Schistosoma* parasites. The disability weight assigned to schistosomiasis was 0.005, or one-half of 1 percent reduction in normal health. The effect of this decision resulted in disability-adjusted life-year (DALY) scores for schistosomiasis that seemed unrealistically low to many epidemiologists and to researchers familiar with schistosomiasis.

It was evident that "experts" on the disease were not used to considering a life path analysis of patients with schistosomiasis, nor could they provide accurate conditional probabilities of disease progression for children or adults living with infection in endemic areas (Kirigia, 1997). The essential quantitative data needed for accurate DALY calculations were lacking and, although disease burden estimates were felt to be too low, a more formalized evidence structure (beyond expert opinion) was needed to construct better DALY estimates.

Several limitations in the available data became apparent:

1. Because schistosomiasis is mostly found in locations with limited governmental and health resources, vital statistics (populations at risk, cause of death data) are disproportionately lacking for this disease.
2. Many descriptions of schistosomiasis morbidity were based on case series, and population-level risks were not reported.
3. There was a paucity of longitudinal studies to inform estimates of the incidence of individual complications of ongoing *Schistosoma* infection. Such estimates had had to be inferred from cross-sectional age-prevalence studies, with inherent limitations due to competing causes of morbidity and mortality (van der Werf et al., 2003).
4. Although several randomized placebo controlled trials of schistosomiasis treatment had been performed, and these could provide floor estimates of the impact of antischistosomal deworming, such trials were complicated by problems of rapid re-infection, which blunted the apparent effects of treatment. Analysis of treatment impact often avoided the issue of lifetime accrual of parasite-mediated disease, focusing only on short-term (1- to 12-month) effects of a single treatment on the disease course of study subjects.

At the same time, researchers studying the impact of STHs on population health also noted the same sort of limitations in the DALY assessments of the effects of intestinal worms on human health. Their reviews stressed that, in addition to the *contemporaneous* morbidity of active worm infection, there is a long-term (perhaps lifetime) impact of living with worms during childhood (Bundy et al., 2004; Chan, 1997; Guyatt, 2000). At the same time, in schistosomiasis research, newer studies began to examine the reversible and irreversible impact of *Schistosoma* infection on childhood nutrition and cognitive function. These studies posed the questions about the lifetime burden of schistosomiasis and its true impact among "average" populations living in endemic areas.

It was apparent that a new, evidence-based assessment of disease burden was necessary to regauge the impact of schistosomiasis on global health. A two-pronged approach was taken—first, long-term longitudinal studies were needed to follow the impact of repeated preventive treatments for *Schistosoma* infection; second, meanwhile, a formalized quantitative review (meta-analysis) of the available data on morbidity-related outcomes of schistosomiasis was needed to inform more realistic disability estimates.

Our meta-analysis, begun in 2002 and published in 2005 (King et al., 2005), reviewed the world's literature on schistosomiasis back to 1921 to identify population-based studies of the link between *Schistosoma* infection and disability. Rather than focus on immune responses, hepatosplenomegaly, or imaging outcomes, which were of uncertain significance to patient performance status, we focused on nine defined symptoms and nine objective laboratory measures that were linked to disability in other disease states (see Figure A12-2).

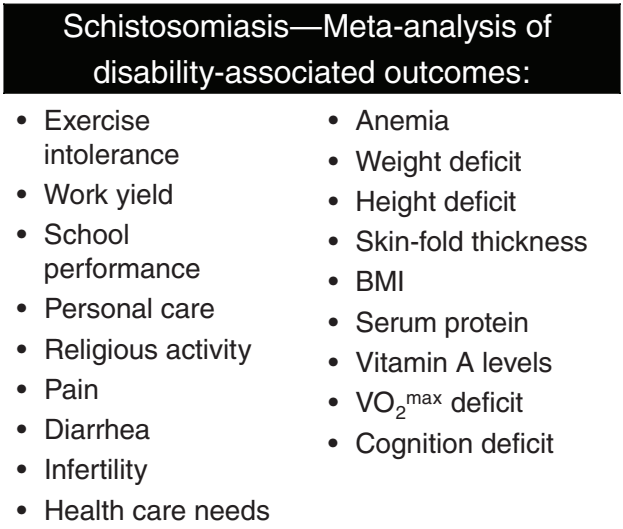

FIGURE A12-2 Disability-related health outcomes included in meta-analysis of schistosomiasis-related health impact.

An important revelation of this formalized analysis was the paucity of population-based studies of childhood or adult function in the presence of chronic schistosomiasis, despite its wide prevalence around the world. Of 482 published and unpublished reports screened for inclusion, 135 provided primary data on morbidity-related outcomes. Based on data integrated from multiple reports, schistosomiasis was significantly linked to anemia, chronic pain, diarrhea, exercise intolerance, and undernutrition (growth stunting) (King et al., 2005). Formal meta-analysis was not possible for some performance outcomes because of the low number of studies or because of differences in the measures used to assess them. Of nine studies reporting fieldwork output, six indicated infection-associated deficit in performance, and of four assessing cognitive ability of schoolchildren, three indicated infection-associated deficit in the cognitive skills tested. One detailed case-control study showed a significant deficit in personal care and in religious activity associated with heavy *S. mansoni* infection, and one survey study suggested an association between schistosomiasis and increased use of health care services (King et al., 2005).

Morbidities Now Linked to Schistosomiasis

In 2008, we revisited the available schistosomiasis literature on disability-related outcomes (King and Dangerfield-Cha, 2008). Many newer studies focused on the role of *Schistosoma*-related chronic inflammation on developmental health

outcomes, as well as more in-depth studies of the underlying mechanisms for such deficits. Expanded data were available on advanced disease occurring during the later phases of schistosomiasis (i.e., in adulthood). These include late pulmonary and neurological complications of schistosomiasis, and, of special note, the effects of *S. haematobium* on male and female reproductive health, including the association between urogenital schistosomiasis and primary and secondary infertility (King and Dangerfield-Cha, 2008).

Newer studies also included greater information on the longitudinal outcomes of treatment. Of note, even "light" levels of infection (Wamachi et al., 2004) or re-infection after successful cure (Koukounari et al., 2006; Leenstra et al., 2006) were associated with significant risk of disease in endemic settings. Inflammatory cytokine markers such as IL-6, C-reactive protein, and TNF-α were linked to anemia and to nutritional deficits among children with schistosomiasis, and the predominant form of anemia linked to *S. japonicum* infection was found to be anemia of chronic inflammation, caused by iron sequestration linked to hepatic production of hepcidin (Friedman et al., 2005b; Leenstra et al., 2006).

Serosurveys of early childhood exposure to infection indicated that children actually acquire infection and begin to experience schistosomiasis at a median age of 3.5 to 4.5 years (Shane et al., 2009; Stothard and Gabrielli, 2007), provoking new questions about the optimal timing of drug-based treatment interventions. Also for the first time, community studies reported on the very long-term (10- to 20-year) impact of childhood antischistosomal treatments in terms of later adult health benefits (Kjetland et al., 2008; Ouma et al., 2005).

Finally, the interaction of schistosomiasis with other infectious diseases became better defined. Links were established between schistosomiasis and the severity of hepatitis C virus inflammation in Egyptian patients (El-Awady et al., 2006; Kamal et al., 2006) and between genital schistosomiasis and HIV infection among Zimbabwean women (Kjetland et al., 2006). Large-scale studies were begun to define the interaction of polyparasitism (STH and other helminth and protozoan infections) in the causation of developmental disease in children. Of special interest were data indicating that maternal helminth infections (schistosomiasis or filariasis) can affect infant responses to vaccination during the first year of life. The results suggested that vaccine responses to the antituberculosis vaccine, BCG (Malhotra et al., 1999), and to *Haemophilus influenza* b vaccine (Figure A12-3) were significantly reduced among children of mothers carrying these parasites.

The overarching message of our review was that chronic helminthiasis (such as schistosomiasis) is qualitatively and quantitatively different from infectious diseases experienced in high-income countries of the developed world. Unlike the acute bacterial and viral infections familiar to most policy makers, chronic schistosomiasis affects personal performance for a lifetime. Given the nearly universal exposure to infection in endemic areas, and the lifelong consequences

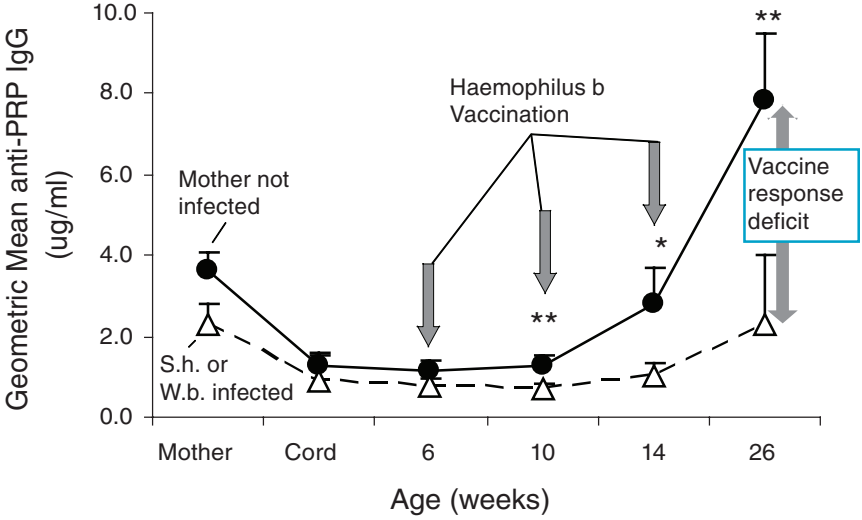

FIGURE A12-3 Reduced protective antibody response to anti-*Haemophilus influenza* b vaccination among children of mothers with schistosomiasis and/or filariasis during pregnancy.

of infection, it was not surprising that early patient surveys found no difference between egg-positive and egg-negative residents of the same area.

Although acute onset of the symptoms of schistosomiasis would normally trigger a visit to a health care facility, people living with schistosomiasis often did not seek medical care. This is not to suggest that affected individuals have successfully "adapted" to their condition (which implies that they do not experience significant DALY disability) (Murray and Lopez, 1996). Rather these individuals have no experience of a full health state and so have no comparison by which to evaluate their health condition (Kirigia, 1998). They have limited knowledge of the cause of their illness (Ukwandu and Nmorsi, 2004) and have had, so far, only limited access to effective treatment for their *Schistosoma* infections (de Vlas et al., 2004) that could reverse the disease burden of their schistosomiasis. Where worm infections were a way of life, they became mistaken for "normal" health. Taken together, these gaps tended to make schistosomiasis invisible in global health policy assessments.

Revisiting the Case Definition for Schistosomiasis

Most policy makers will agree that "*Schistosoma* infection is not the same thing as the disease schistosomiasis." In older control policy discussions, the

interpretation of this statement was that a person could have infection, but with little or no disease (Mott, 2004; Warren, 1982). By contrast, in recent analyses, it is evident that all individuals with chronic *Schistosoma* infection develop some form of disease, but the impact of infection can persist even after infection is lost. So, from a 21st-century perspective, "infection ≠ disease" because the *disease* we call schistosomiasis persists even after the worms are gone (Giboda and Bergquist, 1999).

Our *operational definition* is that schistosomiasis is a preventable, chronic inflammatory condition caused by present or previous infection with metazoan parasitic blood flukes of the *Schistosoma* species. The *disease case definition* for the new Burden of Disease 2005 program (Murray et al., 2007), which will be reevaluating and updating the DALY estimates for all diseases, should therefore be "a person who has, or has previously had, infection with *Schistosoma* spp. parasites."

Case Numbers

In light of this broadened case definition, the global estimates of schistosomiasis case numbers are substantially revised upward (Figure A12-4). Seroprevalence studies indicate that more than 90 percent of persons residing in high-risk transmission zones will acquire *Schistosoma* infection at some point in their lives, usually in the first decade of life (Shane et al., 2009; Stothard and Gabrielli, 2007). In areas of lower transmission risk (i.e., egg-positivity rates less than 5 percent), from 25 up to 40 percent of individuals experience schistosomiasis by the age of 35 (Alarcon de Noya et al., 2007). WHO reports nation-level statistics estimating the number of active (egg-positive) cases of *Schistosoma* infection in all countries (WHO, 2009). Starting with these data, linked with nomograms predictive of high- and low-prevalence subpopulations within each endemic area (van der Werf et al., 2003), we can estimate the number of persons per country who have, or who have previously had, *Schistosoma* infection, meeting the case definition of schistosomiasis. Figure A12-4 shows the regional distribution of schistosomiasis across the world, as estimated by this approach.

Revisiting Disability Weights for Schistosomiasis

Different Weights for Different Levels of Disease

Different manifestations have different levels of effects on patient health and performance. Schistosomiasis can be *mild*, with a small impact on performance; *intermediate*, with irreversible effects that moderately impair quality of life; or *advanced*, with significant chronic disabling impact. The risk for more advanced forms reflects the frequency of parasite exposure and the relative intensity and duration of infection. Thus, age distribution and area of residence help to predict

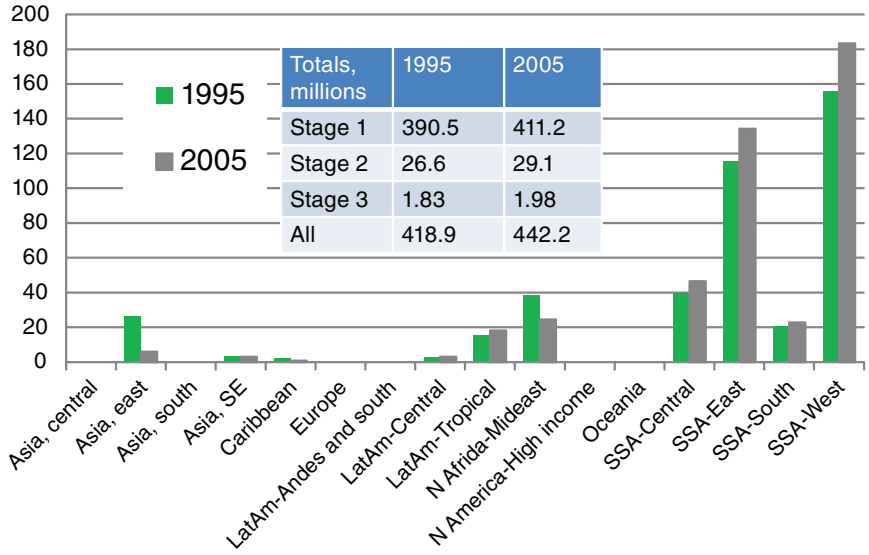

FIGURE A12-4 New estimates of schistosomiasis cases in 1995 and in 2005 according to the Global Burden of Disease Program's world regions. Significant interval declines are noted in Asia, the Caribbean, and in North Africa and the Middle East. Significant increases are noted in sub-Saharan Africa, where the vast majority of cases continue to occur.

the numbers of persons estimated to be in each of the intermediate and advanced groups for each country.

As mentioned earlier, in 1996 the Global Burden of Disease (GBD) Program's only disability weight for schistosomiasis was 0.005, implying a very minimal level of disability for "average" schistosomiasis (i.e., a disease impact that is on a par with that from mild goiter or facial vitiligo). In view of the restructured definition of schistosomiasis above, and in better appreciation of the subclinical but functionally important conditions associated with past or present *Schistosoma* infection, it was appropriate to refine schistosomiasis disability weights according to level of disease, using the following definitions for mild, intermediate, and advanced schistosomiasis. Our intent was to avoid either under- or overestimating the impact of schistosomiasis on affected individuals. Current disability weights are working estimates based on disability weights assigned to like conditions in the GBD 1996 program (Finkelstein et al., 2008; Murray and Lopez, 1996). For the Burden of Disease 2005 project (Murray et al., 2007), the draft definition of the schistosomiasis disease states is as follows:

Mild schistosomiasis (2 to 4 percent disability, onset with first infection) includes any of the following symptoms or manifestations: colonic polyposis, bladder polyposis, pain, fatigue, anemia, diarrhea or dysuria, bloody stool or cystitis and ureteritis, reduced work capacity, and reduced job/school performance.

Intermediate schistosomiasis (10 to 20 percent disability, onset about age 12 years) includes any of the following more severe or permanent manifestations: severe malnutrition (body mass index < 3rd percentile), severe anemia (< 9 g hemoglobin/dL), growth stunting, impaired cognitive development, glomerulonephritis, seizure disorder, dyspareunia, infertility, secondary infection (urinary tract infection, sexually transmitted disease, HIV), vaccine failure, massive splenic enlargement, and hypersplenism.

Advanced schistosomiasis (45 percent disability, onset about age 25 years) includes any of the following advanced complications of *Schistosoma* infection: renal failure, bladder cancer, low birth weight, fetal loss, advanced liver fibrosis, portal hypertension, variceal bleeding, ascites, advanced malnutrition, depression, divorce, social stigma, motor dysfunction/paraparesis, pulmonary inflammation, and hypertension.

In each case, the duration of the untreated disease state is for the remaining lifespan of the affected individual.

Implications for Treatment Strategies

As we revise our view of schistosomiasis based on the significant lifetime impact of infection on health status, the focus of treatment shifts from the current "morbidity control" strategies (focused on limiting advanced complications of schistosomiasis) (WHO, 1993), toward truly preventive strategies aimed at limiting the developmental pathologies that affect children who reside in endemic areas (WHO, 2006). We know from randomized, placebo-controlled trials that antischistosomal therapy can reverse deficits in fitness, caloric reserves, cognition scores, and hemoglobin levels and can reduce pain symptoms associated with *Schistosoma* infection. What has not been well studied is the ability of repeated treatment to prevent disease formation. For this purpose, new programs sponsored by the Schistosomiasis Consortium for Operational Research and Evaluation, and by the Danish Bilharzia Laboratory/University of Oslo/University of KwaZulu-Natal consortium, will prospectively examine the long-term benefits of two to four praziquantel treatments during childhood or adolescence in prevention of specific mild and intermediate forms of schistosomiasis. Validation of the Preventive Chemotherapy "regular deworming" approach through school-age years (WHO, 2006) will provide greater impetus to continue this effort in all affected areas.

Net Benefits of Long-Term Control

A better appreciation of the timing and kinetics of disease formation combined with a better knowledge of the true prevalence of *Schistosoma* infection in endemic areas allows us to reconsider recommendations for timing and frequency of drug-based interventions for disease control. Current schistosomiasis treatment guidelines (WHO, 1993) are focused on morbidity control by reversal of the more obvious organ-specific complications of *Schistosoma* infection such as hepatosplenomegaly, hepatic fibrosis, portal hypertension, and colonic polyposis (for the intestinal forms of schistosomiasis caused by *S. mansoni*, *S. japonicum*, *S. intercalatum*, and *S. mekongi*) and bladder thickening, ulceration, and polyposis, along with hydronephrosis and renal dysfunction (for urinary schistosomiasis caused by *S. haematobium*). For this purpose, it was suggested that a single treatment in midadolescence might be sufficient alone to "control" schistosomiasis-associated morbidity (Gryseels, 1989).

However, our new knowledge of the developmental impacts of chronic schistosomiasis through childhood and early adolescence, and evidence that early *Schistosoma* re-infection results in the recurrence of anemia and other inflammation-related morbidities (Koukounari et al., 2006; Leenstra et al., 2006), now favors a schedule of regular deworming that will minimize the impact of repeated infection (Singer and Ryff, 2007). Antischistosomal treatments can be integrated with drug delivery by other antiparasite campaigns and can be focused on local conditions, as appropriate, through school- or community-based delivery programs for combined control of multiple parasites (Mohammed et al., 2008).

Following the initial years of implementation of antischistosomal drug treatment, various options become available for improving the efficiency of drug delivery. Figure A12-5 indicates the differences in personal lifetime *Schistosoma* burden (egg-years) that would be expected when following different strategies for screening and treating infection in a high-risk, high-endemicity area where *Schistosoma* transmission still persists after the program is implemented. In such settings, community-wide treatment is more effective in suppressing overall lifetime experience with *Schistosoma* infection. Undoubtedly, there will be trade-offs in terms of costs and efficiency of control. However, if such high-risk areas can be easily identified, continued community-wide treatment may offer both economies of scale and increased efficiencies that will make this the most attractive option until other interventions can be implemented to significantly reduce transmission (Garba et al., 2009).

Recommendations for National and Regional Control

A very important question remaining to be resolved is whether broad-based community treatment will substantially reduce transmission in most affected areas. Early recommendations for school-based treatment of schistosomiasis assumed that, because children have the highest prevalence and the highest intensity

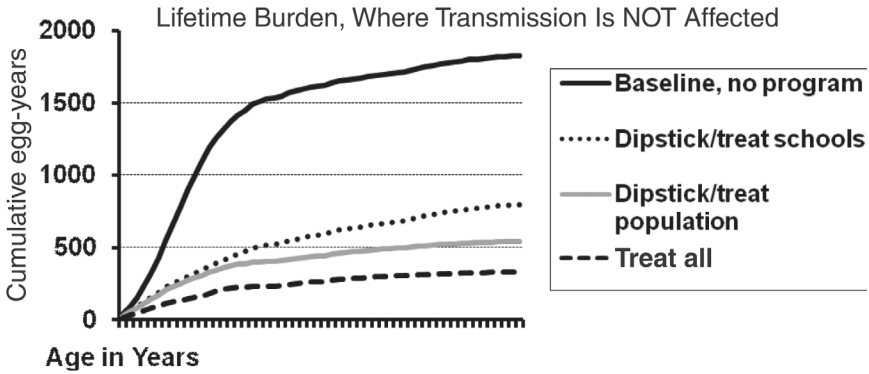

FIGURE A12-5 Projected impact of different antischistosomal treatment strategies for *S. haematobium*, in which dipstick screening for hematuria may be used (as a proxy) to detect active infection. The Markov model incorporates age-specific risk of infection and re-infection, data on the sensitivity and specificity of screening tests, as well as population data on typical adherence with screening and treatment campaigns.

of *Schistosoma* infection, treatment-related reductions in their egg output would naturally reduce local transmission (Warren et al., 1989).

This proved not to be the case in both medium- and high-endemicity areas (Garba et al., 2009; Satayathum et al., 2006). In considering the process of *Schistosoma* transmission in greater detail, it is evident that the process of transmission is highly patchy, highly leveraged, and, in fact, much more efficient than predicted by early models of transmission. In most treatment programs, nonadherence to treatment does not occur at random. Children not at school tend to go missing from the program on most treatment visits. These out-of-school, untreated children are also more likely to be active in contaminating transmission sites during the day (Bruun and Aagaard-Hansen, 2008; Hussein et al., 1996). Such are the very practical limitations of drug-based treatment programs in high-risk areas.

Experience in China with aggressive treatment campaigns indicates that under drug pressure local prevalence of *Schistosoma* infection will be reset to lower levels. However (as modeled in Figure A12-6), once intensive treatment is suspended, the ongoing processes of local transmission will always restore human infection levels to pretreatment values over time (Liang et al., 2006).

In this situation, it is evident that additional efforts are needed to completely minimize *Schistosoma* infection in the local population. Additional efforts at snail control and habitat modification (and, for the zoonosis *S. japonicum*, treatment, vaccination, or elimination of local animal reservoirs) may be needed (Garba et al., 2009; King et al., 2006; Liang et al., 2006; Wang et al., 2009).

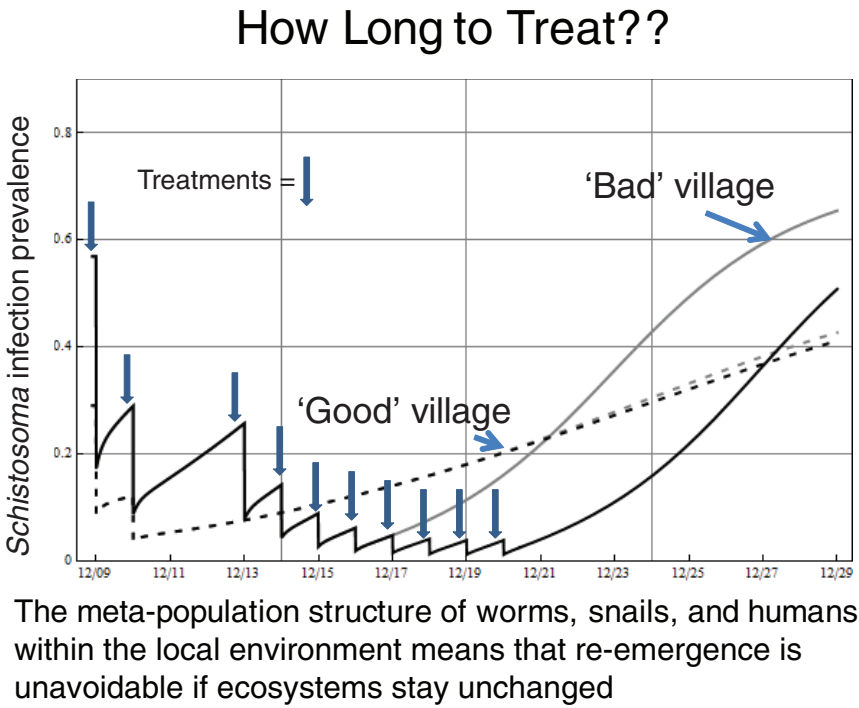

FIGURE A12-6 How long to treat: Without some modification of the local ecological factors that favor *Schistosoma* transmission (sewage contamination, snail habitat, and local surface water use) there is a tendency for local levels of schistosomiasis to recur within 10 to 15 years of stopping a drug treatment campaign.

Ultimately, control of the world's burden of schistosomiasis will require a comprehensive strategy to limit, and then interrupt, transmission in all at-risk areas. Reductions in schistosomiasis-related chronic morbidities will undoubtedly aid the process of development, and, in turn, development will help to provide resources to break the vicious cycle of parasite transmission. Opportunities for integrated multiparasite control are emerging, and schistosomiasis control can clearly be a part of such comprehensive strategies (Molyneux et al., 2005). Our new appreciation of the lifetime impact of schistosomiasis, with a renewed focus on disease *prevention* rather than just "control," will garner the greatest benefits for susceptible populations.

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A13

NEGLECTED ZOONOTIC DISEASES

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Animals and people often live close together throughout the developing world. People are especially dependent on livestock and poultry for food, clothing, fertilizer, draught power, and an important degree of financial security. At the same time, these animals and their products create disease risks for the populations who most depend on them.

A zoonosis is an infectious disease that can be transmitted from an animal to humans. The transmission may be direct such as with rabies or indirect through either vectors such as ticks and mosquitoes (trypanosomiasis) or through food, water, or soil (helminths). A neglected zoonotic disease (NZD) is a zoonosis that is commonly associated with poverty and impacts the lives and livelihoods of millions of poor livestock keepers or those living in periurban slums primarily in

developing countries. Some NZDs are part of existing lists of neglected tropical diseases (NTDs) or comprise their own list but all share similar characteristics and attributes.

A key characteristic of NZDs is that they are closely associated with poverty and they disproportionately affect neglected populations. Poor people are more at risk of contracting many zoonoses. For example, anthrax, bovine tuberculosis, and brucellosis are primarily occupational diseases, and small livestock producers worldwide are at risk and more frequently acquire these infections from their animals. The Food and Agriculture Organization estimates that, globally, there are between 500 million and 900 million food-insecure livestock keepers, and livestock contributes to the livelihoods of 70 percent of the world's rural poor (WHO et al., 2006). The poor are also more vulnerable to diseases associated with consumption of livestock products and are at risk for zoonotic diseases such as cysticercosis and other parasitic and food-borne illnesses. In addition, vectors, water, and the environment can also be sources of NZDs. Once infected, it is the poor that are least likely to get proper medical care. The impact of NZDs is also worse in poor households where a dual burden is borne because both people and their animals are involved. Thus, NZDs not only make members of families ill, but also at the same time, limit the productivity of their livestock and poultry and, thus, take away the funds that would be used for emergencies, their family's well-being, and funds used to cope with these illnesses.

As our world grows progressively interdependent and the populations of people, domestic animals, wildlife, and animal products also increase and expand globally, we can expect more interactions among these groups and certainly the era of emerging and reemerging zoonoses will also expand and grow proportionately (Tomley and Shirley, 2009). As the human–animal interfaces intensify and accelerate, there is a growing concern with the emergence and reemergence of more zoonoses and animal-associated diseases, including leptospirosis, leishmaniasis, Q fever, toxoplasmosis, anaplasmosis, food-borne trematodes, ehrlichia, bartonella, Chagas disease, and toxocariasis. Although most of these diseases can be considered in the category of neglected diseases and are increasingly associated with slums and periurban locations, some of these diseases are also found in developed countries because of the relocation of human populations, global travel, and the movement of food and animal products as part of the rapidly expanding global food system.

Of the 27 infectious diseases tracked by disability-adjusted life-years by the World Health Organization (WHO), 20 are classified as zoonotic and 7 others show that animal transmission cycles are important considerations (WHO et al., 2006). Thus, understanding these diseases by viewing them through the lens of animal health and veterinary medicine not only gives us a different perspective but also reveals new potential intervention strategies to reduce the significant burden of this group of diseases.

With the exception of zoonotic trypanosomiasis, which is restricted to parts

of Africa, the rest of these zoonoses are found worldwide. The significance of neglected zoonoses is expanding, and their health and socioeconomic impacts are increasingly being experienced by many countries, particularly in the developing world. The prevention and control of this group of diseases has proven especially difficult ,and they continue to further burden public health systems as well as to undermine efforts to improve and expand livestock production and exports (WHO, 2010).

The morbidity and mortality of NZDs are difficult to assess. Many of the NZDs may be difficult to diagnose, may be found in poor communities lacking surveillance or adequate medical or veterinary care, and are both under-reported and underappreciated. Yet we do know that toxocara infections may produce asthma in addition to visceral and ocular migrans; Chagas disease can result in severe heart disease, especially in Hispanics; cystocercosis, the pork tapeworm, is now considered the leading cause of epilepsy among Hispanics; ascariasis is a helminth that is a leading cause of impaired child development; and strongyloides also leads to developmental impairment, especially in immune-compromised patients. Rabies is responsible for an estimated 50,000 to 60,000 deaths each year, and children are disproportionally impacted. The cost of rabies is substantial considering that approximately 10 million people received postexposure prophylaxis annually (CDC, 2009). Finally, like other NTDs, many of the NZDs impact personal health and productivity over an entire lifetime and result in chronic disease conditions. In some rural locations, they may significantly reduce the labor pool of agricultural workers in the very communities where their work is most critical.

There is a compelling case to address NZDs worldwide based on moral consideration, human rights, economic impact, global health, and the reduction of pain and suffering in both human and animal populations. NZDs have a dual burden because they can be devastating to both public health and animal health and the most vulnerable people are the millions of poor livestock keepers found globally.

With the expansion of occurrences and increased socioeconomic and health impacts of NZDs, a new paradigm to address this group of diseases must emerge. We can no longer view these diseases as individual crises in agriculture that are disconnected from public health authorities and programs. Rather, there is now a need to design and implement integrated responses for these diseases that cross species lines and health communities. This makes medical and epidemiological sense because many of these diseases are concentrated in remote rural areas or in urban slums, and interventions can be focused accordingly. Those afflicted with NZDs commonly have co-infections as well, so the treatment of multiple diseases in individuals may represent only a marginal cost increase and, thus, very favorable cost-benefit considerations.

The principal concern with NZDs is that these diseases have divided constituencies and authorities. There is a critical gap between public health needs and veterinary responsibilities. Government authorities are often slow to respond and

may be perceived to be in competition for limited funds. For NZDs, the risk of human health is understood; yet the most effective control route is usually via the infected animals (WHO Department of Food Safety, Zoonoses, and Foodborne Diseases, 2009). Thus, investments in animal health and veterinary infrastructure can have a dual benefit for improving both human and animal health. We now recognize that most emerging and reemerging pathogens are zoonotic and that these microbes readily move across a continuum between species, seeking new niches for survival. In today's complex and interconnected world, the microbes will continue to have unprecedented opportunities to readily move across species, find new niches and hosts, and remain as significant threats to our health and economic well-being as they have for centuries past. It is time to shift our attention "upstream" and focus our prevention and interventions at the origins of these diseases. Certainly, there is new hope, and progress in attacking NTDs that needs to include the NZDs.

NZDs lack critical research and policy support, and as governments and nongovernmental organizations take on greater roles in global health, they lag behind. Eric Fèvre stated, "While malaria is undoubtedly a very serious health issue, its over-diagnosis hides other problems. To compound this, people in marginalized communities can easily fall off the policy radar—many may be born, live and die without official record being made of them and, as such, they have a weak, or nonexistent, political voice. Thus, while these diseases are grouped as 'neglected zoonotic diseases,' it would be equally correct to identify them as 'diseases of neglected populations' (Doble and Fèvre, 2010). Unfortunately, the severity of health and socioeconomic impacts of NZDs remain unclear. Surveillance, diagnostics, interventions, training, program delivery, and integrated health planning still continue to be done separately with regard to public and animal health. Yet an integrated "One Health" focus and strategy would result in more diseases being prevented and/or treated in more cost-effective methods, and not only would lives be improved and saved for both animals and people, but we would also create a new opportunity to help alleviate poverty and achieve the key Millennium Development Goals of eradicating poverty and hunger, reducing child mortality, and combating diseases.

One Health is defined as the collaborative effort of multiple disciplines—working locally, nationally, and globally—to attain optimal health for people, animals, and our environment (AVMA One Health Task Force, 2009). As the lives of billions of animals, people, and products converge globally in an unprecedented biological mixing bowl that is embedded in rapidly changing ecosystems, the world of zoonoses is getting more attention. One Health teams and strategies must be created and implemented as integrated strategies to prevent and reduce disease, especially those focusing on the millions of impoverished people who depend on livestock and poultry for their livelihoods. The wonderful progress to reduce and eliminate NTDs such as river blindess, lymphatic filariasis, trachoma, and Guinea worm demonstrate that NTDs can be successfully addressed. How-

ever, it is time to implement new frameworks to address NZDs and their global burdens, with a special emphasis on integrative and collaborative programs and with the same focus, energy, political will, and resources used to reduce these other NTDs. If not, the 21st century will continue to exclude those in need and their animal populations that also need care, support, and attention to improve their health. Improving animal health is now an important strategy for improving human health, and reducing the burdens of NZDs and other zoonoses is key to helping to helping to alleviate poverty.

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A14

DIAGNOSTIC NEEDS FOR NTD PROGRAMS

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Overview and Background on NTDs

Neglected tropical diseases (NTDs) are bacterial and parasitic infections that disproportionately affect poor and marginalized populations around the world (WHO, 2010a). As discussed elsewhere in this volume, there is no consensus on the number of diseases that should be considered NTDS; nonetheless, NTDs can be operationally classified into two large groups based on the public health strategies used to address them. Some NTDs, including leishmaniasis, African

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trypanosomiasis, Chagas disease, and Buruli ulcer, require clinical interventions at the level of the individual patient; for these diseases, case-finding and extensive patient follow-up with an emphasis on individual-level management are required. The second group of NTDs, including lymphatic filariasis, onchocerciasis, schistosomiasis, trachoma, and intestinal helminth infections, can be targeted effectively through mass drug administration (MDA). These NTDs are not considered to cause appreciable mortality; however, they are associated with high levels of morbidity because of the chronic nature of the infections or their sequelae. Blindness and disabling physical deformities due to these NTDs increase in prevalence with age, reducing the productivity of adults. Intestinal helminths, among the commonest of infections, have profound effects on the growth and cognitive development of children. These infections may also increase susceptibility to other diseases, exacerbate the pathology of co-infections, or decrease vaccine efficacy. The strategy to use MDA to control NTDs in this group is called preventive chemotherapy because early treatment of infections can reduce development of morbidity.

Once ignored by policy makers and donors, effective advocacy has directed greater levels of attention to these diseases of the bottom billion (Hotez et al., 2009; Molyneux, 2010; Molyneux et al., 2005); in addition, World Health Assembly resolutions calling for control or elimination of NTDs have galvanized political support (Box A14-1). The past five years have seen significant increases in the number of countries implementing NTD programs and in the number of persons being treated; according to World Health Organization (WHO) statistics, nearly 670 million persons were treated for one or more NTDs in 2008 (WHO, 2010a). These increases are the direct result of generous donations of drugs from pharmaceutical manufacturers and new funding support from the U.S. Agency for International Development and the U.K. Department for International Development, among others.

BOX A14-1
World Health Assembly Resolutions Targeting NTDs

- WHO Resolution 50.29 (1997) calls for global elimination of lymphatic filariasis as a public health problem. Target date 2020.
- WHA Resolution 51.11 (1998) calls for the elimination of blinding trachoma by 2020.
- WHA Resolution 54.19 (2001) calls for scaling up treatment programs for schistosomiasis and intestinal helminths to reach 75 percent of children at risk of these infections.
- Resolutions CD35.R14 (1991) calls for elimination of onchocerciasis in the Americas as a public health problem, and CD48.R12 calls for interruption of transmission by 2012.

Tools Are Needed Across the Spectrum of NTDs

For all NTDs, the need for improved diagnostics represents a consistent theme, although the specific diagnostic tool needed is a function not only of the disease in question, but also of the nature of the program. NTDs that require approaches based on individual case management present particular challenges from the diagnostic perspective because the effectiveness of the clinical management is based on the ability to diagnose and treat individual patients. Poor-quality diagnostics may delay or prevent appropriate treatment, resulting in unnecessary treatment with therapies that may be poorly tolerated, or both. Because NTDs are typically found in settings with fragile health care systems with weak laboratory infrastructure, sensitive and specific point-of-care diagnostic tests are needed; however, the absence of a profitable market has discouraged commercial firms from investing in development of tests for NTDs.

For diseases targeted by MDA, tests are needed to provide data to guide programmatic decisions on the transition from MDA to targeted treatment and finally to verify elimination of transmission. These tools will be the principal focus of this paper. Tool needs for the group of MDA NTDs—currently lymphatic filariasis, onchocerciasis, schistosomiasis, trachoma, ascariasis, trichuriasis, and hookworm infection (although this list may be extended in different epidemiologic settings to include other NTDs)—change over the life cycle of the programs (Figure A14-1). During initial phases of the program, information on the distribution of NTD infections is required in order to guide public health decisions about MDA. Treatment decisions are based on WHO-defined thresholds for population disease or infection prevalence; consequently, diagnostic methods for individual patients need not be quantitative. In addition, with the exception of trachoma, for which rigorous sampling protocols have been developed, testing of at-risk populations can employ convenience sampling to reduce costs. Despite the molecular revolution in biology, little of the new-found knowledge of parasite genes and gene products has been translated into tools that can be used in the field to guide program decisions. Available tools for mapping and monitoring program impact are still, with few exceptions (e.g., the immunochromatographic card test [ICT] rapid antigen detection test for lymphatic filariasis), conventional parasitologic methods based on microscopy (Table A14-1). These techniques, though simple and low cost, are relatively labor intensive. In addition, traditional parasitologic methods lack sensitivity as the prevalence of infection decreases, and they are not adequate for programs focused on reaching elimination endpoints. More sensitive diagnostic tools such as antigen detection or polymerase chain reaction (PCR) assays for parasite DNA are needed as markers of infection or transmission in low-prevalence settings. When transmission has been interrupted, serological methods to detect antibodies in children can serve as markers of exposure to infection in the postelimination surveillance phase. As discussed in greater detail below, validated tools for surveillance are not available for any of the NTDs targeted for elimination through MDA.

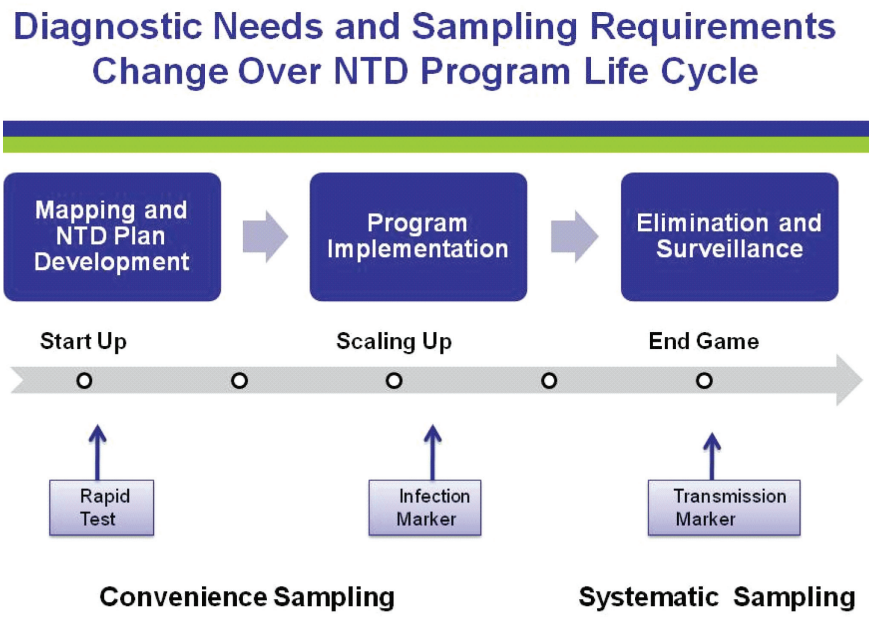

FIGURE A14-1 A generalized NTD program life cycle is presented schematically in this figure.

As programs move from initial phases toward elimination endpoints, infection prevalence declines, and tool needs and sampling considerations evolve from lesser to greater sensitivity and from less robust to more robust sampling, respectively.

TABLE A14-1 Tests Commonly Used by NTD Programs

Infection	Mapping	Monitoring Impact	Program Decisions	Surveillance
Lymphatic filariasis	Thick film (Mf) ICT	Thick film (Mf) ICT	Thick film (Mf) ICT, BRUGIArapid™	ICT? BRUGIArapid™?
Onchocerciasis	Skin snip (Mf) Nodules	Skin snip (Mf) Nodules	Skin snip (Mf) Nodules	Ov16?
Schistosomiasis	Kato Katz Hematuria	Kato Katz Hematuria	Kato Katz Hematuria	?
Intestinal helminths	Kato Katz	Kato Katz	Kato Katz	—
Trachoma	Eye exam	Eye exam	Eye exam	?

Surveillance

Two of the MDA NTDs, lymphatic filariasis and trachoma, have global elimination by 2020 as a target (Box A14-1). Onchocerciasis has a regional elimination goal in the Americas, but recent results offer some encouragement that elimination in Africa may be possible in some foci (Diawara et al., 2009). Elimination of schistosomiasis, although admittedly challenging, has been achieved in some settings (WHO, 2010c). All of these infections thus have the potential to present the global health community with the need to develop surveillance tools and strategies after MDA has ceased. Conceptual approaches to surveillance are similar across the MDA NTDs. If transmission has been interrupted, young children will have been protected from acquisition of infection and, therefore, represent a useful sentinel population to assess the impact of interventions on transmission. In this context, antigen tests are useful for documenting incident infections and, indeed, this approach is recommended for lymphatic filariasis (LF) because of the availability of sensitive and specific antigen tests (WHO, 2005). For helminth infections for which antigen tests are not yet available, it is possible that parasite-specific antibody responses may serve as a proxy for infection. Parasite-specific IgG4 responses are characteristic of many chronic helminth infections; titers decline following successful therapy of LF and strongyloidiasis (Loutfy et al., 2002; Page et al., 2006; Wamae et al., 1992). Additional work is needed to determine if IgG4-based serologic tests can be used to monitor infection levels at the population level. For other antibody isotypes, antibody responses may reflect exposure or cumulative exposure to infection and, thus, antibody assays may provide a more sensitive tool to monitor transmission patterns. For infections with long prepatent periods such as LF, antibody responses may be measurable from months to years before infection is detectable based on antigen or microfilaremia testing, providing a significant benefit for monitoring for recrudescent transmission (Figure A14-2). In trachoma-endemic communities, serum antichlamydial antibody profiles and their response to MDA are currently incompletely understood. The potential advantages of antibody-based tests for post-MDA surveillance argue that increased efforts also should be made to develop a standard platform for such tests, opening opportunities for integrated surveillance for NTDs.

Disease-Specific Diagnostic Tools

Lymphatic Filariasis

LF programs in a number of countries are now reaching the point at which MDA can be stopped (Bockarie and Molyneux, 2009; WHO, 2010c). WHO's Monitoring and Evaluation Working Group has recently reviewed and endorsed a new protocol for assessing transmission in order to facilitate decision making by countries regarding stopping MDA. This protocol is based on the use of lot qual-

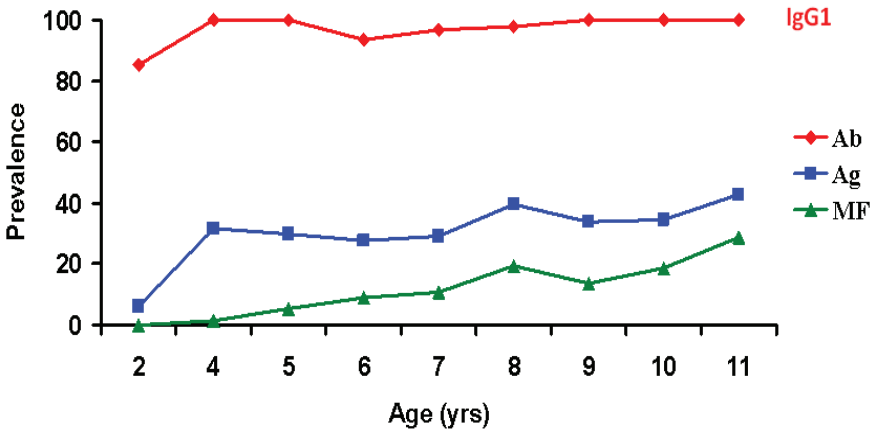

FIGURE A14-2 Age-specific prevalence of *Wuchereria bancrofti* microfilaremia, antigenemia, and antifilarial antibody reactivity. Children resided in LF-endemic communities in Leogane, Haiti. Microfilaremia was assessed by thick blood film (20 µl), antigenemia by Og4C3 ELISA, and antifilarial antibody was measured using extracts of filarial worms. Data are collated from published and unpublished studies (Beach et al., 1999; Lammie et al., 1998).

ity assurance or cluster sampling designs to test young children for antigenemia (*Wuchereria bancrofti*) or antifilarial IgG4 (*Brugia* spp.). As noted above, with effective MDA, transmission should be interrupted and few, if any, antigen- or antibody-positive children should be detected. Existing tests (the ICT, Og4C3-ELISA for *W. bancrofti*, and BRUGIArapid™ for *Brugia* spp.) are adequate for making programmatic decisions about stopping MDA (Weil and Ramzy, 2007); however, WHO's Strategic and Technical Advisory Group for NTDs recently highlighted the inadequacy of current tests in the setting of post-MDA surveillance (WHO, 2010b). Proposed survey designs are not adequately powered to detect increases in antigenemia. Antibody detection tests (using recombinant Bm14, BmR1, or WbSXP antigens in conjunction with the recently developed survey methodology) could provide evidence for transmission interruption, but these assays are expensive, and cross reactivity with antibodies to *Loa loa*, *Onchocerca volvulus*, and *Mansonella* spp. limits their utility in Africa where co-infections are common (Lammie et al., 2004). New, more specific assays are a clear priority. In addition, laboratory capacity in LF-endemic countries will have to be expanded to support testing of specimens at program scale unless suitable rapid diagnostic tests can be developed. Xenomonitoring (using, for example,

PCR-based detection of parasite DNA in vector mosquitoes) is another potential option for assessing the presence or absence of ongoing transmission, but neither the testing nor the sampling methodologies have been standardized sufficiently to recommend their use in the programmatic context (Farid et al., 2007).

Onchocerciasis

Programmatic decisions for the Onchocerciasis Program in the Americas also are based on testing of sentinel children as part of a regional initiative to eliminate onchocerciasis. The decision to stop MDA is based on the absence of antibodies directed against recombinant *O. volvulus* antigens in school-age children, along with low levels of *O. volvulus* infection in black fly vectors, as tested by PCR (Lindblade et al., 2007). These assays are currently carried out in a limited number of laboratories. In addition, elimination criteria based on the use of these tests have not been sufficiently validated for use in Africa (WHO, 2010b). In African countries where ivermectin is used to control onchocerciasis in hyper- and mesoendemic areas, new tests would also be useful for defining the geographic extent of hypoendemic areas as programs shift their objectives from control to elimination.

Schistosomiasis

Decision making for schistosomiasis control programs at present is based on collection of stool or urine samples to detect parasite eggs. As a practical consideration, these samples are often challenging to collect in the field. Conventional parasitologic diagnosis is labor intensive and the sensitivity of detecting infection is compromised by day-to-day fluctuations of egg excretion, making identification of low-worm-burden infections difficult. PCR tests for stool and urine show increased sensitivity compared to traditional parasitologic methods, but they are too expensive and complex for field application. Immunodiagnostic techniques have the advantages of much higher sensitivity. A rapid antigen test to detect genus-specific circulating cathodic antigen (CCA) in urine is currently being field tested (Stothard, 2009). Initial reports suggested excellent correlation between CCA concentration and number of eggs of *S. mansoni* per gram of feces in high-prevalence areas (Shane et al., 2011), but the test has less-than-optimal sensitivity for *S. haematobium* and there are few data on its performance in low-transmission-intensity areas (Stothard et al., 2006). Antibody-detection tests have been used successfully to document the presence (and absence) of transmission of schistosomiasis, but most tests are based on crude or partially purified parasite extracts, limiting the supply of antigen and hampering assay standardization. In addition, current antigens used for antibody testing are unable to distinguish active infection from past infections. Recent work with carbohydrate antigens sug-

gests that antibodies to these epitopes are lost following successful cure (Nyame et al., 2004). Progress in use of carbohydrates as targets has been enhanced by new methods to generate adequate quantities of these reagents. In settings where schistosomiasis elimination is potentially feasible, new serologic tests would be useful for defining foci of residual transmission and for documenting the absence of infection in children through active surveillance.

Intestinal Helminths

Traditional parasitologic techniques based on stool exams are likely to remain the cornerstone of intestinal helminth control programs. These programs do not have an elimination endpoint; nonetheless, programs do need to collect information periodically in order to make decisions about treatment frequency. Sensitive multiplex PCR tests that can detect hookworm, *Ascaris*, and *Strongyloides* infections in a single stool sample are useful for research studies or individual patient diagnosis, but they are not yet practical for control programs. There are presently no serological tests that can reliably determine the presence or absence of current infection with the soil-transmitted helminths. If such assays could be developed, then it is possible that they would find some value as a replacement for stool exams for making programmatic decisions about treatment frequency.

Trachoma

Trachoma control programs rely on the use of conjunctival examination for the clinical sign of "trachomatous inflammation–follicular" for starting and stopping programs. Following MDA, conjunctival inflammation may persist or recur in the absence of detectable bacteria, an important limitation of decision making based on clinical exams (Solomon et al., 2008). PCR-based assays for *Chlamydia* are available as the gold standard test, but they are technically complex and too expensive for routine program use (Solomon et al., 2004). A dipstick-based immunoassay based on detection of chlamydial lipopolysaccharide has recently been developed (Michel et al., 2006). This assay detects all *C. trachomatis* serovars in the American Type Culture Collection (Maryland). It performed well in initial field testing in northern Tanzania, demonstrating a sensitivity of 83.6 percent and specificity of 99.4 percent compared to PCR. Further trials in Senegal and The Gambia were less encouraging, as problems with false positivity were noted (Harding-Esch, 2010). In principle, antibody-based tests might be used to monitor exposure to trachoma in children following MDA as the basis of surveillance activities, but to date there has been little effort to develop and validate such tests.

Defining Product Profiles

As noted above, an overarching need for NTD programs based on preventive chemotherapy is the need for surveillance tools. At a recent WHO workshop of NTD experts (July 2010), the status of current tool development efforts was reviewed (Solomon et al., manuscript submitted). This workshop brought together individuals with a broad spectrum of intersecting disease- and discipline-specific interests to consider the issues surrounding integration of diagnostic systems and to enable the development of product profiles. In the surveillance phase, demands on test performance are high. High sensitivity is needed to detect rare events, and high specificity is needed to limit the number of false positives that could trigger a requirement for epidemiologic investigation and follow-up. As new tests are developed, it will be important to validate test performance in the field through rigorous multicenter testing in the field (Banoo et al., 2006).

Summary

LF, trachoma, schistosomiasis, onchocerciasis, intestinal helminths, and other NTDs are found in overlapping populations and are amenable to public health solutions based on MDA. Similarities in approach to program implementation provide a general framework for characterizing the diagnostic needs of the programs over their life cycles (Figure A14-1), from mapping to monitoring impact to documenting program endpoints. Although NTDs may differ with respect to their epidemiologic and population distributions, programmatic similarities lend themselves to integrated monitoring and evaluation strategies and diagnostic approaches. At all stages of program maturity, NTD control and elimination programs require diagnostic tools to guide decisions on the required intensity, frequency, and duration of interventions. Although not discussed here, diagnostic tools can and should also be employed to provide early warning of emerging drug resistance to antibiotics or antihelminthics.

Diagnostic needs change as disease control programs evolve from baseline mapping to impact monitoring to postelimination surveillance. Conventional clinical and parasitologic techniques for LF, trachoma, schistosomiasis, onchocerciasis, and intestinal helminth infections that are useful at early stages of program development are not adequate for later stages of the program, including guiding programs through specific decision points. It is clear from other public health initiatives that tools drive programs. This is especially true for other NTDs, which, in principle, could also be targeted by MDA (e.g., strongyloidiasis or food-borne trematode infections). Improved diagnostic tools can improve the quality of program data and this, in turn, could enhance the commitment of donors and policy makers to the control and elimination programs for these diseases by providing increased confidence that elimination goals are being met. It also is likely that significant savings in human and financial resources could be obtained by integration

of diagnostic tools and approaches for these diseases. At present, multiplex assays provide a robust alternative for laboratory-based antibody measurements and integrated surveillance. Perhaps rapid tests also could include antigens from multiple agents in one field-friendly platform. Downstream, the ideal system might be a portable modular diagnostics platform, capable of performing multiple assays for several infections of interest, on one or a small number of sample types. This platform should be sufficiently versatile to allow the simultaneous detection of antigen and antibody from a single biological sample. In the absence of a commercial market, investments in test development and validation will necessarily come from public sources. These efforts should be a clear priority.

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A15

NEGLECTED TROPICAL AND ZOONOTIC DISEASES AND THEIR IMPACT ON WOMEN'S AND CHILDREN'S HEALTH

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Introduction

For the global effort to address neglected tropical diseases (NTDs) to be effective, it is essential to examine how NTDs affect the world's most vulnerable populations. Throughout the world today, a billion people are suffering from NTDs because of the heavy toll of global poverty (Hotez, 2008). Within the "bottom billion" are two populations whose biological and social realities put them at greater risk for the negative impacts of NTDs and zoonotic diseases—women and children (Figure A15-1).

FIGURE A15-1 Young woman with infant daughter in Papau Province, Indonesia, seeks medical care.
SOURCE: Figure courtesy of Steven Stewart, CDC.

This chapter addresses neglected tropical and zoonotic diseases and their impact on women's and children's health. It considers NTDs overall, with a focus on the seven most common NTDs, which are considered "tool ready" or having an available method of prevention and control; these are the soil-transmitted

[25] The findings and conclusions in this publication are those of the author and do not necessarily represent the views of the Centers for Disease Control and Prevention.

helminths (STHs; hookworm, ascariasis, and trichuriasis), lymphatic filariasis, schistosomiasis, ochocerciais, and trachoma. The chapter begins by exploring some helpful constructs and models that provide the context for understanding neglected tropical and zoonotic diseases, referred to throughout as NTDs, in women and children. Next, specific ways that NTDs affect women's health and children's health are examined, followed by a discussion of NTD comorbidities and co-morbidities with other global infectious diseases of concern. The final section explores what is needed to effectively address NTDs in women and children.

Frameworks, Models, and Context

Millennium Development Goals

One of the most significant global collaborations of recent history is the effort surrounding the Millennium Development Goals (MDGs) (Figure A15-2). The MDGs are development goals for the year 2015 that were adopted by 189 United Nations (UN) Member States in 2000 (WHO, 2010). The MDGs, which were described by World Health Organization (WHO) director Margaret Chan as "the most ambitious attack on human misery in history" (Chan, 2010), are an essential reference point for examining NTDs in women and children.

The MDGs are broad and bold in scope, addressing poverty and inequality head on. They are important for understanding current global initiatives aimed at improving women's and children's health and well-being. MDGs 3–5 specifically address women's and children's well-being, including gender equality, child survival, and maternal health. MDGs 1 and 2 are about fundamental conditions that shape women's and children's health—poverty, malnutrition, and education. MDG 6 addresses the need to combat diseases that are a major source of global

FIGURE A15-2 The Eight Millennium Development Goals (MDGs).

mortality, as well as "other diseases," namely, neglected tropical and zoonotic diseases.

Although progress on the MDGs has been uneven (Bernstein and Hansen, 2006; UN, 2010a), the MDGs remain an indisputable international touchstone for progress, and as such offer a useful framework for reducing the burden of disease, including NTDs, in women and children.

Social Determinants of Health

As the MDGs were becoming a material force in international policy and planning, a new framework for viewing how social forces shape health was being developed and disseminated. The social determinants of health framework is rooted in decades-long discourse about achieving equity in health (Braveman, 2006; Whitehead, 1991). In the early 2000s, WHO convened a commission on the social determinants of health, which developed an analytic framework that enjoys widespread influence today (WHO, 2007). This framework lays out how fundamental social determinants of health (such as economic standing and governmental programs and policies) in turn influence intermediary determinants of health (such as access to health care) to shape individual health status, and how these forces interact in both directions to determine the health of populations. After extensive deliberation, the Commission released its findings in August 2008 in a report that recommends that global efforts to address social determinants and promote health equity do three things (WHO, 2008a):

- Improve daily living conditions;
- Tackle the inequitable distribution of power, money, and resources; and
- Measure and understand the problem and assess the results of action.

The social determinants of health is a crucial framework for NTDs, because infectious disease prevention and control in the 21st century cannot be effective if limited to traditional views of the causes of disease. It must involve socially focused as well as biologically focused solutions.

Microbial Threats to Health: The Convergence Model

Another valuable construct that implicitly utilizes the social determinants of health perspective is the convergence model, developed by the Forum on Microbial Threats (IOM, 2003) (Figure A15-3). The convergence model examines the human–microbe interface in the context of an array of factors: genetic and biological; physical and environmental; ecological; and social, political, and economic. Because the convergence model is based on an analysis of infectious disease prevention and control, it is especially useful for examining NTDs and neglected zoonotic diseases in women and children. Using the convergence

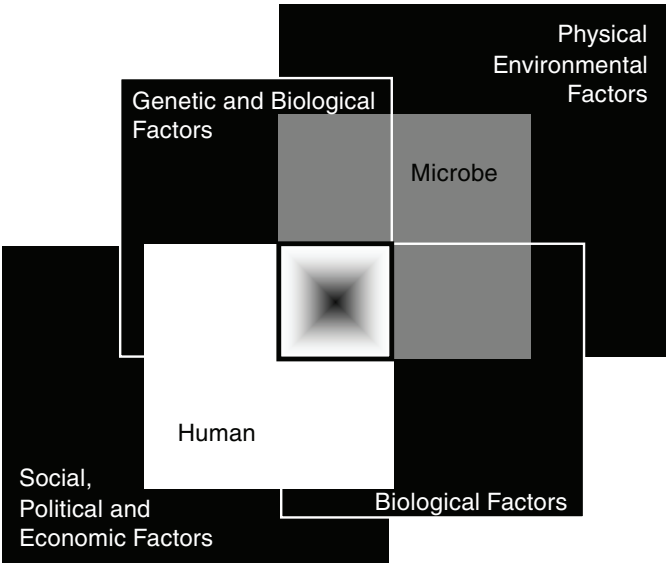

FIGURE A15-3 The convergence model.
SOURCE: IOM (2003).

model, quadrant by quadrant, we explore some of the specific and unique factors that shape the realities of NTDs in women and children.

Applying the Convergence Model to NTDs in Women and Children

NTDs and Women and Children: Genetic and Biological Factors

Genetic and biological factors are key to understanding the impact of NTDs in women and children. Women are vulnerable because of the reproductive functions of pregnancy and childbirth, which create a range of health risks for women. Maternal mortality—defined as the death of women during pregnancy, birth, or postpartum—remains a serious problem globally. More than half a million women die in pregnancy, birth, or postpartum each year, and 99 percent of these deaths are in developing countries (WHO, 2009, p. 40). A woman in Africa may face a lifetime risk of death in pregnancy of 1 in 31, whereas the risk for women in developed regions is 1 in 4,300 (WHO et al., 2010, p. 17). NTDs exacerbate maternal health problems by causing or contributing to a number of pregnancy-related conditions (Hotez, 2009).

Women are biologically vulnerable to sexually transmitted infections (STIs), in terms of both acquisition and health impact (WHO, 2009). Women are more likely than men to have asymptomatic infections that can result in delayed diagnosis and treatment (Faro, 2001; Schmid, 2001). Women have more severe

complications from STIs, including infertility, ectopic pregnancy, and increased risk of HIV (WHO, 2009). Women are vulnerable to sexual coercion and the infections that result from it (Beck-Sague et al., 2004).

Children are biologically vulnerable to infectious diseases and their impacts (Katz et al., 1998); they are exposed to microbial threats through play, work, and substandard living conditions. They are more vulnerable than adults to environmental exposures and developmental stresses, because their immune systems are not fully developed, and their developing bodies are biologically more susceptible to the effects of environmental assaults.

These vulnerabilities are central to understanding how NTDs affect women and children. For example, STHs contribute to anemia in pregnant women, jeopardizing the pregnancy and the woman's health overall. STHs in small children cause a range of health problems.

NTDs and Women and Children: Physical and Environmental Factors

Problems associated with physical and environmental factors are universal and not unique to women or children. Among such factors is the global trend toward urbanization. It is estimated that, by the year 2050, 69 percent of the world's population will live in cities (UN, 2010b). Unfortunately, the global trend toward urbanization is one that has developed hand in hand with urban poverty (Kjellstrom and Mercado, 2008). Today, 1 out of every 3 people living in a city anywhere in the world lives in a slum area (COHRE, 2008). For many women, movement to urban areas is forced by displacement from farmlands because of desertification, conflict, or widowhood. In both rural and urban areas, substandard housing, poor sanitation infrastructure, and crowding all contribute to the transmission of NTDs.

NTDs and Women and Children: Ecological Factors

Problems associated with ecological factors are also not unique to women and children, but the consequences differ. For example, women and children are 14 times more likely to die in a natural disaster than men; this is due in part to lack of self-protection skills like swimming and climbing trees (Brody et al., 2008, p. 6). In many areas of the world where NTDs are prevalent, there are limited sources of safe water for drinking, cooking, and bathing, leading to a wide range of water-related diseases and health concerns (IOM, 2009; Mara and Sleigh, 2010).

Water problems are women's problems. Women shoulder the largest burden of collecting water globally, accounting for 64 percent of water collection, as opposed to men, who perform 25 percent of water collection. Girls are engaged in 7 percent and boys 4 percent of water collection (WHO and UNICEF, 2008). The water collection task is extremely time-consuming and can expose the col-

lector to contaminated water, infectious disease vectors, and, in regions where conflict is rife, violence.

These ecological factors contribute to NTDs in women and children. For example, a woman collecting water or washing clothes can be exposed to schistosomiasis. A child without access to safe water for drinking and bathing can contract a wide range of water-borne diseases, including schistosomiasis (Bethony et al., 2004).

NTDs and Women and Children: Social, Political, and Economic Factors

The factors with the largest impact on women and children are the social, political, and economic. Some of the social, political, and economic factors relevant to NTDs in women are poverty, illiteracy, lack of education, lack of land ownership, lack of political power, and gender inequality (Conteh et al., 2010; Okwa, 2007; RDI, 2009). Children's poverty, lack of access to health care services, and conflict and war are also factors.

Women make up the vast majority of the world's poor, its illiterate, and its landless. Women make up the largest numbers of the world's poor living on less than $1 a day (ILO, 2009; UN, 2010c). Poverty and illiteracy go hand in hand for women. Literate persons are defined as those age 15 and older who can read and write. Approximately 64 percent of illiterate people in the world are women (UNESCO, 2008). Globally about three-fourths of a billion people are illiterate, which means nearly half a billion women are illiterate (UNESCO, 2008).

Globally, a very small proportion of women—5 percent—own land (Benschop, 2004; RDI, 2009). As for women's political power, it remains limited. Women's proportion of seats on representative bodies such as parliaments is less than 23 percent for most parts of the world—9.5 percent in Arab states (IPU, 2010).

NTD prevention must bear these harsh realities in mind—for if a woman has no economic resources, has not been educated, cannot read, and does not enjoy social or political influence, she will be struggling just to survive day to day to care for her family and will not be able to focus on NTDS as a problem, even if they are deteriorating her children's and her own health. NTD prevention and education efforts must be developed with an appreciation of these conditions.

Gender Inequality

The aforementioned realities are rooted in and exacerbated by gender inequality, which is pervasive globally and is manifested in many ways (ICRW, 2005b; WEF, 2005). Gender roles create burdens (such as water collection) and limit opportunities, promoting women's poverty. Gender inequality means that women-controlled infectious disease protection is limited or non-existent. Essentially, gender inequality inhibits infectious disease prevention in women

(Manderson et al., 2009). The poverty women face globally, and the limitations poverty places on women, creates conditions in which NTDs can flourish. NTDs in turn hurt women in ways that reinforce poverty, creating a cycle that must be broken.

Gender inequality supports a wide range of social policies and practices that limit women's and children's lives, opportunities, and development. These include violence against women, child marriage and child labor, and gender inequality–based practices (social practices that flow directly from systemic gender discrimination) (UNOHCHR, 2008).

Violence Against Women

A key social determinant that reinforces women's status is violence against women (DCAF, 2005). Globally, up to 6 out of 10 women experience physical and/or sexual violence in their lifetimes (UNIFEM, 2010). The prevalence of physical and/or sexual violence by a partner varies, from 15 percent in urban Japan to 71 percent in rural Ethiopia, with most areas being in the 30 to 60 percent range. Violence against women takes many forms and can include withholding, which includes aspects of food, shelter, money, etc., as well as sexual and physical assault, rape, and murder (UNIFEM, 2010). A woman who lives in fear of physical, mental, or sexual abuse faces serious challenges in taking care of her children and herself, in accessing health care, and in making life changes. Put another way, a woman facing violence is less likely to be concerned about NTDs than a woman who feels safe.

Child Marriage

Poverty plays a role in the prevalence of child marriage. In many countries—including India, Niger, and Uganda—more than half of girls are married before they turn 18. Some girls are as young as 7 or 8 years old. Once married, girls are pressured to bear children quickly, often before their bodies are ready to handle the stress of childbirth (ICRW, 2006a, 2006b, 2006c, 2006d, 2006e; Nour, 2009).

Gender Inequality–Based Practices

Gender inequality–based practices include but are not limited to so-called "honor" killings (Nasrulleh et al., 2009; UN General Assembly, 2002; UNOCHCR, 2008), dowry-related burnings (Nasrulleh and Muazzam, 2009; Peck et al., 2008; Sawhney, 1989), and female infanticide, defined as murder of a female infant through neglect, poison, or other maltreatment (Coale, 1991; Ferrell, 2002; Sahni et al., 2008; Sen, 1990; Srinivasan and Bedi, 2008; Sumner, 2009).These practices reinforce gender inequality and limit women's capacity to act as agents for infectious disease prevention, including the prevention of NTDs.

Children's Poverty and Child Labor

Of the 2.2 billion children in the world, 1.9 billion are living in developing countries. The number of children living in poverty is 1 billion, or every second child. Poverty plays in role in the prevalence of child marriage (UNICEF, 2005). Child poverty is rooted in limited educational opportunities and the push toward child labor. In many regions, children may be forced to work at very young ages. Globally, 7.3 percent of children ages 5–17 were engaged in hazardous work in the years 2004–2008; sub-Saharan Africa has highest incidence of child labor, where 1 in 4 children are involved (Diallo et al., 2010). Child labor exacerbates the problem of children's poverty and is detrimental to children's health; it limits children's ability to access education and thus reinforces poverty while exposing children to numerous health hazards.

Limited Health Care Services

Lack of adequate health care services has harsh consequences for women and children. Skilled care at childbirth is extremely limited in some regions, and evidence suggests that in Africa access to care in the antenatal, delivery, and postpartum period has declined in recent years (WHO, 2009). A paucity of adequate health care services in underdeveloped countries leaves many women without care for pregnancy and birth, and children without preventive services that are crucial for child survival. In terms of NTDs, this means lack of access to diagnostics, treatment, and follow-up, in addition to prevention.

Conflict, War, and Human Trafficking

Conflict and war uproot families, communities, and villages, creating large numbers of internally displaced persons in many countries, and creating waves of refugees, of which women and children are the vast majority. Conflict situations make control of infectious diseases extremely difficult, as prevention effects are thwarted by limitations on mobility and resources (Berrang-Ford et al., 2010; Beyrer et al., 2007).These conditions in turn create vulnerabilities for women and children being trafficked for sex and/or slave labor (Beyrer, 2004; Polaris Project, 2009; Willis and Levy, 2002).

What do these factors mean for the global burden of NTDs in women and children? These social determinants shape how NTDS impact women and children globally. They set up the many barriers that have led to these being widespread, devastating, and neglected diseases (Figure A15-4).

NTDs and Women's Health

NTDs affect hundreds of millions of women in a number of ways, constituting a substantial global burden on women's health and well-being. They affect ev-

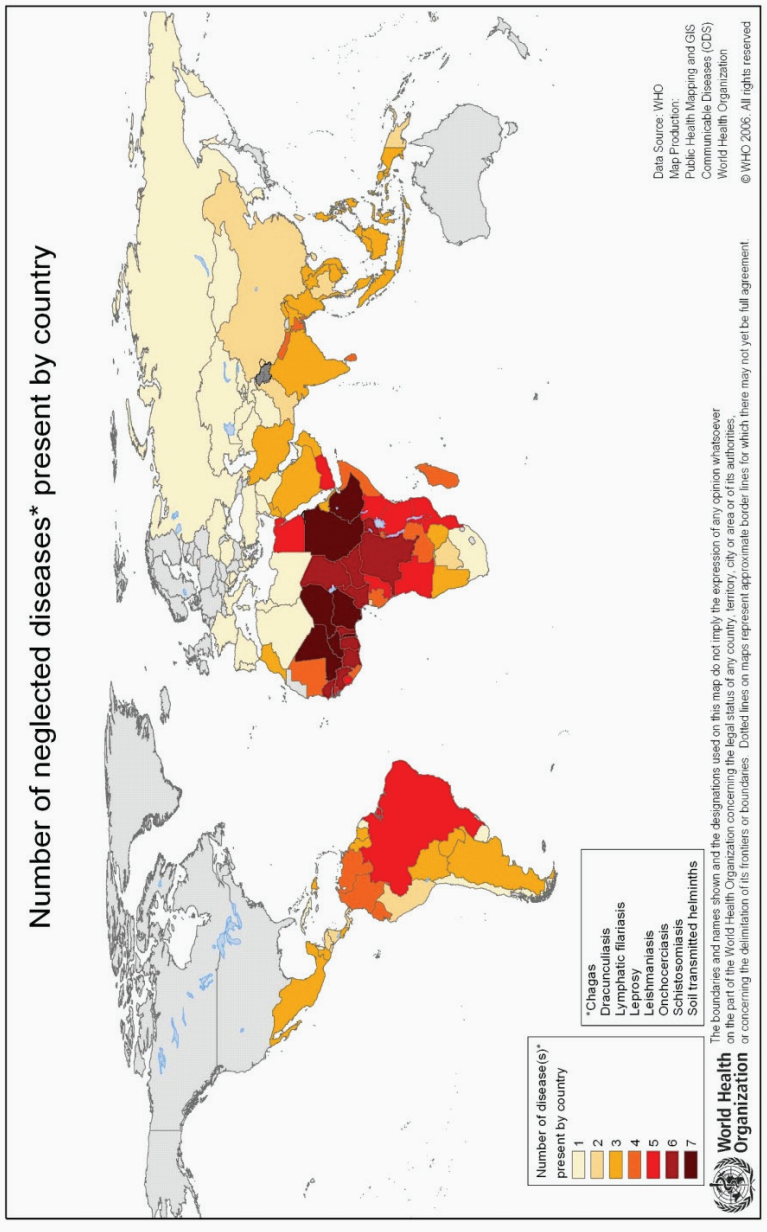

FIGURE A15-4 Global distribution of NTDs.
SOURCE: WHO (2006). *Number of neglected diseases present by country* [map]. Geneva: WHO. Map produced by Public Health Mapping and GIS, Communicable Diseases, WHO (2006). Reprinted with permission from the World Health Organization.

ery aspect of women's lives: physical, reproductive, sexual, emotional, social, and economic. NTDs affect women's health overall, leading to a range of problems from anemia to blindness and putting women at risk for acquiring other diseases. NTDs affect women's reproductive health, including fertility, pregnancy, labor and delivery, and neonatal health (Hotez, 2009). They affect women's sexual health, increasing the risk of some sexually transmitted infections and disrupting sexual functioning. They affect women's social health by promoting exclusion and stigma (WHO, 2010). And they affect women's economic health, by affecting women's ability to work.

Each of the NTDs is unique in terms of its natural history, its known effects on human health, and the current state of the science about how it can be prevented, diagnosed, and treated. Examining the toll of trachoma, lymphatic filariasis, and schistosomiasis on women's health underlines the urgency of addressing NTDs for women. Examining the impact of NTDs on reproductive health offers a sobering glimpse at the implications of these diseases for future generations.

Women, Trachoma, and Blindness

Trachoma is a bacterial infection caused by *Chlamydia trachomitis*, spread from person to person via hands and clothing and by flies that carry the bacterium. Some 84 million people are infected worldwide, and 1 million women are blinded by trachoma each year (Carter Center, 2009; WHO, 2009).

Women's gender-proscribed roles as caregivers are directly related to their increased risk of acquiring trachoma and becoming blinded by it. Trachoma disproportionately affects women because women get infected in the course of caring for infected children, who may be swarmed with flies that carry the disease (APPMG, 2008/2009; IOM, 2009) (Figure A15-5). Women are two to three times more likely than men to be permanently blinded by the disease, because women have greater exposure and less access to treatment and care (Carter Center, 2009; Hotez, 2008).

Blindness for women means more than not being able to see. It affects a woman's ability to earn a living and the chances of her becoming married, thus promoting poverty and decreasing opportunities for education. Blindness also affects a woman's ability to care for her children. The majority (57 percent) of the world's blind persons are women, a proportion that rises with age, as women develop cataracts but often are unable to get cataract surgery (WHO, 2009).

Women, Stigma, and Lymphatic Filariasis: "Can It Be That God Does Not Remember Me?"

Lymphatic filariasis (LF) is a vector-borne disease caused by the filarial parasite *Wucherria bacrofti*. LF can lead to lymphedema, a swelling of the legs and genitals. This can in turn lead to disfiguring and disabling elephantiasis, a chronic

FIGURE A15-5 Child swarmed with flies, which cause infection leading to trachoma. SOURCE: APPMG (2008/2009). In The Neglected Tropical Diseases: A challenge we could rise to—will we? 2008/2009 with permission from Alan Fenwick of the All-Party Group on Malaria and Neglected Tropical Diseases.

condition in which the infected person's leg grows to resemble an elephant's leg. The swollen leg can become infected with bacteria and ulcerated, requiring special care and causing decreased mobility.

LF causes extreme stigma for all affected by the disease (Wynd et al., 2007). For men, LF can lead to painful and stigmatizing enlargement of the scrotum known as hydrocele. For women, LF brings about a devastating cascade of consequences, including painful social stigma and isolation (Person et al., 2009). LF affects women's ability to support themselves, especially those engaged in agriculture, where physical demands are intense. Women who develop the disease when they are young may be kept from getting an education and are often unable to get married. Without established social networks, young women with LF may experience lifelong social disconnectedness (Person et al., 2007).

Women with LF suffer psychological distress, hopelessness, shunning, and discrimination (Okwa, 2007; Person, 2008). The despair brought on by the disease can challenge even those women with deeply held religious beliefs, as

reflected in the question posed by one woman with LF: "Can it be that God does not remember me?" (Person et al., 2008, p. 349).

Women and Schistosomiasis

Schistosomiasis is a waterborne parasitic infection caused by a flatworm; the three major species are *S. haematobium*, *S. mansoni*, and *S. japonicum*. The infection is contracted by contact with infested waters via bathing or swimming. More than 207 million people are infected with schistosomiasis, which causes a range of serious health problems (Figure A15-6). These include damage to the bladder, liver, and intestines, as well as hematuria and anemia. In addition, it can cause chronic abdominal pain, decreased tolerance for exercise, and reduced work capacity. Schistosomiasis can be effectively treated with the drug praziquantel (PZQ).

Historically, efforts to address schistosomiasis primarily acknowledged the severe manifestations of the disease such as hydronephrosis, which can lead to renal failure, or bladder cancer. In recent years the disabling chronic conditions of schistosomiasis have received greater attention and focus, and research has begun to examine wide-ranging knowledge gaps (Colley and Secor, 2007; King and Dangerfield-Cha, 2008). Part of this trend has been attention to urogenital schistosomiasis in women, or female genital schistosomiasis (FGS) (Friedman et al., 2007; Nour, 2010; Poggensee et al., 1999; Rollinson, 2009; Swai et al., 2006).

FIGURE A15-6 Women walking in river, South Asia.
SOURCE: CDC (Centers for Disease Control and Prevention) Public Health Image Library. http://phil.cdc.gov. Photo Credit: Stanley O. Foster, CDC/World Health Organization.

Female genital schistosomiasis Schistosomiasis takes an extremely heavy toll on women. An estimated 40 million women of childbearing age suffer from schistosomiasis (Friedman et al., 2007). Schistosomal lesions of the female genital tract have been found in the ovaries, fallopian tubes, uterus, cervix, vagina, and vulva. The lesions have been associated with infertility, retarded puberty, ectopic pregnancy, anemia, miscarriage, preterm delivery, carcinoma, and higher risk for sexually transmitted diseases (Poggensee et al., 1999). FGS is associated with dyspareunia and sexual dysfunction (King and Dangerfield-Cha, 2008). Ectopic pregnancy in women with schistosomiasis is more likely to be caused by fallopian lesions (Friedman et al., 2007; Laxman et al., 2008). A cross-sectional study in Zimbabwe found an association of FGS with infertility (Kjetland et al., 2010a). Damage to the cervix by schistosomal lesions may predispose infected woman to HPV infection and possible cervical cancer (Kjetland et al., 2010b; Petry at al., 2003).

FGS and HIV/AIDS Long-standing questions exist regarding the relationship of schistosomiasis infection in girls and women and acquisition of HIV (Colley and Secor, 2007; Poggensee et al., 1999). A cross-sectional study in Zimbabwe found a threefold risk of HIV infection in women with schistosomiasis (Kjetland et al., 2006). These data and observation of the spatial overlay of HIV and schistosomiasis endemicity have prompted some to suggest that schistosomiasis treatment is a viable strategy for HIV prevention (Hotez et al., 2009; Lillerud et al., 2010; Stoever et al., 2009).

In 2009, WHO hosted a meeting on schistosomiasis and HIV risk, or more specifically about "genital schistosomiasis" (which affects both men and women) (WHO, in preparation). Increased susceptibility to HIV infection in the schistosomiasis-infected woman is biologically plausible because of breaks in the epithelial barrier and/or to immune response. While exploring ways that HIV and schistosomiasis infection may interact and influence each other, the consultation noted that the relationship between FGS and HIV is complex.

Schistosomiasis and pregnancy Concern about HIV and schistosomiasis exists hand in hand with concern about schistosomiasis in pregnancy. The number of pregnant and lactating women worldwide with schistosomiasis is unknown; in Africa, 10 million women each year have schistosomiasis during pregnancy (Friedman et al., 2007). The direct effects of the disease on pregnancy include anemia, ectopic pregnancy, miscarriage, and preterm labor, in addition to difficulties in becoming pregnant (Ajana et al., 2006; Kjetland et al., 2010a).

Because of the potential dangers of schistosomiasis in pregnancy and because women with schistosomiasis may be infected with other diseases that can be effectively treated, the inclusion of pregnant women in mass drug administration (MDA) programs has been a challenge for public health. Preventive chemotherapy, the main intervention for control of STHs, LF, schistosomiaisis, and

onchocerciasis, is carried out through mass distribution of seven broad-spectrum anthelminthic medications: albendazole, diethylcarbamazine, ivermectin, levamisole, mebendazole, PZQ, and pyrantyl (WHO, 2010). The drugs' safety records for nonpregnant persons and limited side effects make their administration in a single oral dose possible without the need for individual diagnosis.

In 2002, WHO reviewed the evidence about use of PZQ in pregnancy and concluded that PZQ was safe for use in the second and third trimesters of pregnancy (WHO, 2002). Observing that women ages 18–45 living in schistosomiasis-endemic regions may spend as much as a quarter of their reproductive years pregnant and 60 percent of that time lactating; the exclusion of pregnant or lactating women from schistosomiasis MDA programs means that women go without treatment for a substantial portion of their lives (WHO, 2002, p. 11).

The WHO report also noted: "Pregnant and lactating women are as susceptible to end organ damage as anyone else. The fact that lesions may develop more rapidly than was previously thought means that delays in treatment of an infected woman until she is no longer pregnant or lactating are likely to result in major end organ morbidity" (WHO, 2002, p. 12).

Although there was no evidence of harm from PZQ when it was used during pregnancy, the lack of clinical population-based safety trials data and lack of Food and Drug Administration approval led to many countries refusing to treat adolescents and even some women of childbearing age who *might* be pregnant. The need for safety data was clear. The result was the development of two clinical trials for treatment of pregnant women with PZQ. The first one, in Kampala, investigated use of PZQ and/or albendazole for deworming in pregnancy; it showed no harm from PZQ but also no statistically significant benefit from treatment (Ndibazza et al., 2010). A second clinical trial is under way in the Philippines (Charles H. King, personal communication, October 17, 2010).

Reproductive Consequences of NTDs for Women

The challenges of schistosomiasis prevention and control for women underline the need for heightened attention to the numerous reproductive consequences of NTDs for women (Friedman and Acosta, 2008; Hotez, 2009). NTDs are known to contribute to maternal morbidity, to promote anemia in pregnancy, and to contribute to preterm labor, low birth weight, stillbirth, and neonatal death (Yatich et al., 2010a). NTDs can also have a negative impact on sexual health, leading to dispareunia and sexual dysfunction, and can result in infertility (King and Dangerfield-Cha, 2008).

NTDs and pregnancy Under the best of circumstances, pregnancy is a time of needed care and caution to ensure a healthy outcome; in areas where NTDs are endemic, such circumstances often do not exist. In pregnancy, a number of physiological changes take place, such as increase in blood volume, and changes

in the maternal gastrointestinal and cardiovascular systems as well as the immune system (Cono et al., 2006). Because of the physiological changes of pregnancy, pregnant women are particularly susceptible to a wide range of infections (Jamieson et al., 2008; Theiler et al., 2008) and may be especially susceptible to NTDs (Adegnika et al., 2007), although not all studies have confirmed this (Herter at al., 2007). Infections in pregnancy can cause severe complications and adverse outcomes, and physiologic changes of pregnancy can alter the effectiveness of medications (Cono et al., 2006; Rasmussen et al., 2007).

Among women globally, most pregnancies are unintended and unplanned; in sub-Saharan Africa, some 14 million unintended pregnancies occur each year (Hubacher et al., 2008). Few precise assessments of the number of pregnant women with NTDs exist. An estimate of the burden of hookworm infection in pregnant women in sub-Saharan Africa utilized population estimates of 148 million women of reproductive age (defined as ages 15–49) in 2005 in sub-Saharan countries where hookworm is endemic, further estimating that 37.7 million women of reproductive age are infected with hookworm. Using live birth data from sub-Saharan Africa, it was estimated that 25.9 million women were pregnant in 2005, of whom 6.9 million were infected with hookworm (Brooker et al., 2008, p. e291).

NTDs can have a number of negative effects on pregnancy, and many pregnant women are infected with more than one NTD (Belyhun et al., 2010; Nguyen et al., 2006). The negative reproductive consequences of NTDs include ectopic pregnancy, preterm labor and low birth weight, stillbirth, postpartum hemorrhage, and small size for gestational age (Yatich et al., 2010b; Zapardiel et al., 2010).

Anemia in pregnancy is a widespread problem in the developing world (WHO, 1994). Anemia is associated with risks to pregnancy and childbirth, increasing pregnant women's risk of dying in pregnancy and the likelihood of low birth weight (Brooker et al., 2008; Kavle et al., 2008). Increased risk of anemia in pregnancy has been noted in infection with STHs (Laroque et al., 2005) and schistosomiasis (Ajana et al., 2007). These realities have led to the recommendation of regular deworming for women of childbearing age and regular inclusion of pregnant women in MDA (Brooker et al., 2008; Casey et al., 2009; Phuc et al., 2009; WHO, 1994, 1998).

Mass drug administration and pregnancy challenges The most effective strategies for prevention and control of NTDs is MDA—which has particular challenges for pregnant and lactating women. Because globally most pregnancies are not planned, and many women have serial pregnancies, practices have developed that effectively exclude many women, pregnant or not, from treatment.

For example, STHs can be treated safely in pregnancy, but pregnant women may not always receive treatment (Hotez et al., 2007). As noted above, schistosomiasis treatment in pregnancy with PZQ was recommended by WHO in 2002, but lack of pregnancy safety trials has limited its use in pregnant women to date.

TABLE A15-1 MDA and Pregnancy

Disease	Treatment Drug	First Trimester	Second and Third Trimester	Lactating	Comments
STHs: Hookworm Ascariasis Trichuriasis	Benzimidazoles Albendazole	No	Yes	Yes	WHO, 1994[a]
Onchocerciasis	DEC Ivermectin	No No		Yes	
Lymphatic filariasis	DEC	No	No	No	Maintains disease reservoir
Trachoma	Zithromax	Yes	Yes	Yes	
Schistosomiasis	Praziquantel	No	Yes	Yes	WHO, 2002[b]

[a] WHO recommends MDA for treatment of hookworm in girls and women (WHO, 1994).
[b] WHO recommends use of PZQ in second and third trimesters and during lactation (WHO, 2002); lack of safety trials limit implementation.

LF cannot be treated in pregnant women, leaving pregnant women vulnerable to LF and a potential disease reservoir, which may pose a challenge to current plans for elimination. Treatment of onchocerciasis is contraindicated in pregnant women (Okwa, 2007).

Given the mixed use and safety of drugs for NTDs in pregnant and lactating women (Table A15-1), special attention needs to be given to devising strategies for the safe and consistent inclusion of pregnant and lactating women in MDA programs whenever and wherever possible. It is also necessary to develop accurate assessments of the effect that a lack of treatment of pregnant women can have on the control of NTDs overall, which may vary by disease and region.

NTDs and Children's Health

NTDs are a scourge on children's health globally, damaging children's health and development in a number of ways. They also take children's lives. NTDs are often considered diseases that make people sick but do not kill them. That is not the case with children, because NTDs contribute to global child mortality (Black et al., 2010; Global Network, 2010; WHO, 2008b).

Child Health Consequences of NTDs

For children who survive and live with NTDs, there are severe health consequences (Table A15-2). An infant born to an infected mother can be low birth weight, which can jeopardize the infant's chances of survival, or small for ges-

TABLE A15-2 Selected NTDs and Children's Health and Development

Neglected Disease	Anemia	Undernutrition	Stunting	Poor Learning	Cognitive Impairment	Blindness	Social Stigma	Decreased Vaccine Effectiveness	Mass Drug Treatment Available
Lymphatic filariasis				X			X		X
Onchocerciasis						X			X
Schistosomiasis	X	X	X	X	X			Suspected[a,b]	X
STH: Ascariasis	X	X	X	X	X			Suspected[a,b]	X
STH: Hookworm	X	X	X	X	X			Suspected[a,b]	X
STH: Tricariasis	X	X	X	X	X			Suspected[a,b]	X
Trachoma						X			X +SAFE[c]

[a] King and Dangerfield-Cha (2008).
[b] LaBeaud et al. (2009).
[c] IOM (2009).

tational age. NTDs cause anemia in children and promote malnutrition (WHO, 1994).

NTDs also make it harder for children to fight diseases, harming their immune response. There is some evidence that NTDs in early childhood may hamper the effectiveness of vaccinations (King and Dangerfield-Cha, 2008; LaBeaud et al., 2009). NTDs also may put children at greater risk of acquiring HIV through vertical transmission as well as childhood acquisition (Borkow et al., 2007; Gallagher et al., 2005; Secor, 2006). Evidence also suggests that NTDs may put children at heightened risk for malaria (Brooker et al., 2007; Hotez, 2008).

The STHs ascariasis, trichuriasis, and hookworm are the most common NTDs among children and are a major cause of child morbidity globally (Bethony et al., 2006). STHs are a widely recognized cause of anemia in children (Knopp et al., 2010). Hookworm causes malnutrition when the intensity of infection causes blood loss and iron deficiency anemia (Smith and Brooker, 2010). *Ascaris* worms can cause intestinal obstruction and gastrointestinal bleeding (Sangkhathat et al., 2003). *Trichuris* worms can cause colitis and dysentery.

Child Development and NTDs

Both STHs and schistosomiasis stunt children's physical growth and cognitive development, contributing to the toll NTDs take on physical growth and development for children globally. Children with NTDs are stunted in growth and are smaller in stature throughout childhood. Schistosomiasis can cause undernutrition, growth retardation, cognitive delays, and poor performance in school. NTDs contribute to the lifelong disabling effects of childhood diarrhea, which include growth deficits, impaired fitness, impaired cognitive function, impaired test performance, and delayed age starting school (Brooker, 2010; Guerrant et al., 2004).

NTDs are known to lead to cognitive impairment and poor school performance in children, damaging children's ability to learn and to remember (Brooker et al., 2004; Bundy and de Silva, 1998; Hotez et al., 2004). Some believe that a serious legacy of NTDs and other infectious diseases over generations is a reduced cognitive capacity in communities and geographical regions, and they believe NTDs play a role in reduced intelligence worldwide (Eppig et al., 2010).

NTDs also affect social and psychological development. A child who is infected with LF may develop hydrocele, which can be stigmatizing and isolating as well as physically uncomfortable. Poor school attendance and performance may also stigmatize children suffering from NTDs.

Although the toll of NTDs on children is devastating, there is good news for childhood NTD prevention and control (Table A15-2). Preventive chemotherapy—through school-based and community-level programs that administer MDA for

STHs, schistosomiasis, and onchocerciasis—has proven effective (Hotez et al., 2007; WHO, 2010). For trachoma, the SAFE strategy (surgery, antibiotic treatment, face washing, and environmental control) is effective in preventing and controlling the disease; antibiotics can be administered as part of MDA (IOM, 2009).

Co-morbidities and NTDs in Women and Children

To speak of co-infection and co-morbidity for NTDs in women and children is a little like inquiring about the blueness of the sky. Co-infection and co-morbidity are unfortunately the norm, not the exception, in the landscape of NTDs in women and children. Many women and children are infected with more than one NTD, or "polyparasitized." Co-infection with multiple NTDs is common in some regions of the world, and it is why the MDA strategy is a necessity (Clements et al., 2010; Molyneaux et al., 2005; Richards et al., 2006).

Co-infection of NTDs with other serious infectious diseases is also common. Malaria and STHs are a common co-infection; the interrelationship of the two infections is an important arena of research and prevention efforts (Brooker et al., 2007; Druilhe et al., 2005; Wiria et al., 2010). Co-infection with STHs and HIV is a complex infectious disease challenge (Assefa et al., 2009; Borkow et al., 2007; Fincham et al., 2003; Walson et al., 2010). How infection with STHs and malaria might affect mother-to-child transmission of HIV is yet another question for research and prevention (Gallagher et al., 2005).

Co-infection of schistosomiasis and HIV is a global concern, as the bidirectional disease effects appear to be distinct and require specific treatment and response (Secor, 2006). A growing body of evidence indicates schistosomiasis may accelerate HIV disease progression (Rollinson, 2009; Secor and Sundstrom, 2007). Indeed, this new knowledge may begin to influence strategies for global HIV prevention and control (Sawers and Stillwaggon, 2010). Research on the relationship of FGS and HIV acquisition has found that women with genital schistosomiasis lesions have a heightened risk of HIV infection (Kjetland et al., 2006). Young girls infected with schistosomiasis may develop genital lesions that damage the epithelial layer long before sexual debut, underlining the need for preventive treatment of schistosomiasis of girls in endemic areas (WHO, in preparation).

Addressing NTDs in Women and Children

It will take a great global effort to end NTDs—or at least to get to a point where they have gotten the attention they need and will no longer be deemed neglected (Hotez et al., 2007; Liese et al., 2010; Spiegel at al., 2010).

Addressing Women's Poverty

One of the essential steps in this direction is addressing women's poverty (Kristof and WuDunn, 2009; UN, 2010c). Steps in this direction must include the following:

- universal education for girls and women (ICRW, 2005a);
- economic development initiatives for women, such as microfinance, cooperatives, and training (Smith and Thurman, 2007);
- ban or reversal of policies based on gender inequality (UNOHCHR, 2008);
- enforcement of laws regarding violence against women; and
- promotion of women's leadership in science and health.

To address poverty and the challenges of NTDs in women and children, it is necessary to understand how health is transmitted across lifetimes and generations. The cycle of opportunity or obstacles, as Paula Braveman has called it, is real and inexorable (RWJF, 2008) (Figure A15-7). Adult health is shaped by the social and economic opportunities adults face, along with the living and working conditions experienced, which in turn shape family health and well-being. Family health and well-being shape childhood health, which forms the basis of health in the adult. The global cycle of poverty and substandard living conditions is what must be broken in order to address NTDs and make them neglected no more.

What Is Needed to Address NTDs in Women and Children?

The Forum on Microbial Threats will consider many strategies for effective prevention and control of NTDs. To ensure that these efforts meet the particular challenges of NTDs in women and children, a number of steps should be considered.

One step is to move from a global public health approach that focuses on mortality only to one that focuses on chronic and disabling diseases, directly addressing and acknowledging human suffering. In this regard, considering expanded development and use of indicators that measure the quality of life, such as quality-adjusted life-years (QALYs), may be appropriate (Dasbach and Teutsch, 2003).

NTD prevention efforts need to educate polyparasitized populations about risks for the diseases they face, to counter fatalist views, and to promote prevention. Development of NTD prevention innovations like the insecticide-treated bednets that have been such a boon for malaria prevention and control should be encouraged and supported.

It is essential that data be disaggregated by gender to improve identification of risk factors for women and girls; all too often work is based on estimates of

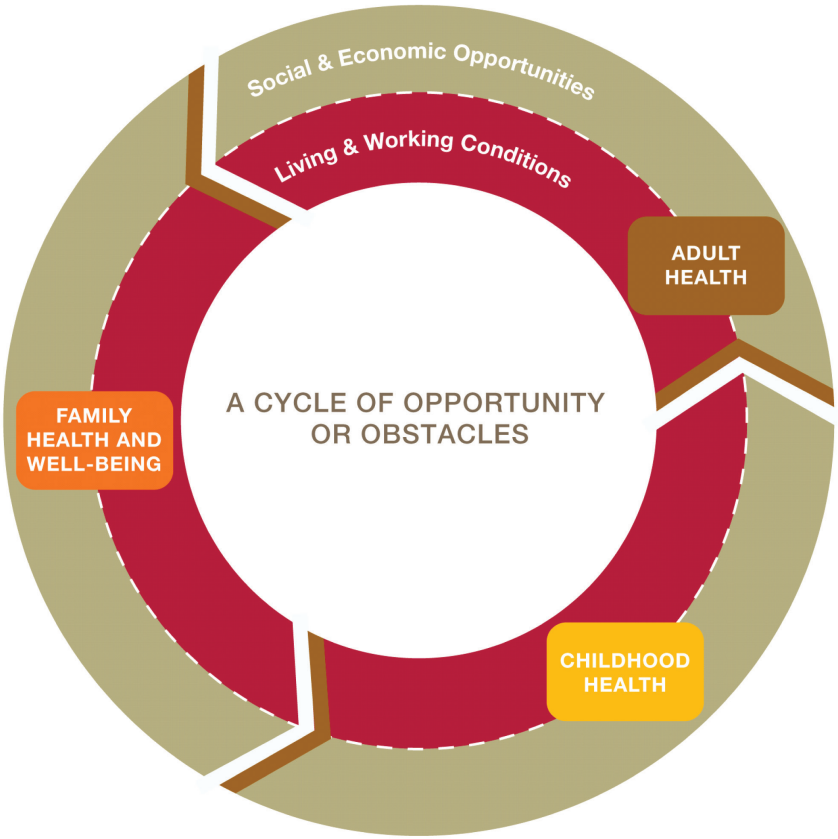

FIGURE A15-7 To address NTDs, the cycle of poverty must be broken.
SOURCE: RWJF (2008). Copyright 2008 Robert Wood Johnson Foundation/Overcoming Obstacles to Health.

disease burden. NTD surveillance efforts, research studies, and prevention programs should all collect data on gender (along with data on age and ethnicity) and develop gender-based analyses that can inform further research and practice.

The challenges that exist for MDA in pregnant women are many; they must be carefully considered and addressed. In order to do this, research on prevention of NTDs in pregnant women, as well as research on NTD prevention throughout women's life course, must be intensified. Similarly, research on the mechanisms through which NTDs impact children's health, and how these mechanisms can effectively be addressed, must be expanded.

FIGURE A15-8 Women are key to NTD prevention efforts.
SOURCE: CDC (Centers for Disease Control and Prevention) Public Health Image Library. http://phil.cdc.gov. Photo Credit: Chris Zahniser, CDC.

Enhance Women's Role in Fighting NTDs

In all efforts, enhancing women's role in fighting NTDs should be central. One way to do this is to implement the "women-centered" focus of the Global Health Initiative as a way that promotes skill-building and leadership in women. NTD training for a wide range of health care providers, including lay providers who work directly with women, should be developed (Figure A15-8). In higher education, new NTD fellowships and other training opportunities for women and men must be developed, both to meet new prevention demands and to address the attrition of skilled NTDs professionals globally.

Conclusion

The stakes for addressing NTDs in women and children are high. Ignoring NTDs or not addressing the specific ways they affect women and children is acquiescing to poverty, suffering, and despair. Preventing NTDs in women and children, on the other hand, will benefit everyone. It will help solve difficult global research and prevention questions, while improving the lives of families, communities, nations, and regions. An adage from the women's health arena is particularly relevant to the challenge of addressing NTDs in women and children:

> "Improve women's health, improve the world." (WHO, 2009, p. 89)

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A16

GLOBAL FUNDING OF NEW PRODUCTS FOR NEGLECTED TROPICAL DISEASES

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Policy Cures

New drugs, vaccines, and diagnostics are regularly developed for diseases that affect wealthy countries; however, they are never more needed than for so-called neglected tropical diseases (NTDs). These are infectious diseases such as dengue and helminth infections that collectively afflict hundreds of millions of poor patients in developing countries.

The cost and time to develop new pharmaceutical products is substantial. Taking the cost of failure into account (an important factor in this high-risk area), each new diagnostic is likely to have development costs in the range of US$2 million to US$10 million spread over a development time of 3–5 years (averaging US$0.5 million to US$0.75 million per diagnostic per year). Each new drug is likely to cost in the low hundreds of millions spread over 7–12 years (averaging

$15 million to $30 million per drug per year); however, we note that drug reformulations or new fixed-dose combinations of existing drugs can have particularly low risks and costs. And each vaccine can cost up to hundreds of millions invested over 12–15 years of development (averaging US$35 million to US$60 million per vaccine per year).[26]

However, the level of investment into research and development of new products for NTDs, as reported in the annual Global Funding of Innovation for Neglected Diseases (G-FINDER) surveys, shows that few NTD areas receive anywhere near the level of funding required; and that funding, when it is available, is rarely allocated in a manner likely to move products through the pipeline to patients.

Global Funding of Neglected and Tropical Diseases

The G-FINDER surveys report global funding for neglected disease research and development (R&D) on an annual basis. These show a marked disparity not only between funding for neglected diseases and diseases that affect the developed world, but also among the neglected diseases and, in particular, the NTDs.

The G-FINDER survey defines 31 diseases as neglected, ranging from diseases such as HIV/AIDS, tuberculosis (TB), and malaria through diarrheal diseases and bacterial pneumonia and meningitis, to the NTDs. The 15 NTDs for which G-FINDER reports research and development funding are the following:

- Kinetoplastids
  - Chagas' disease
  - Leishmaniasis
  - Sleeping sickness (human African trypanosomiasis)
- Dengue
- Helminth infections
  - Roundworm (ascariasis)
  - Hookworm (ancylostomiasis and necatoriasis)
  - Whipworm (trichuriasis)
  - Strongyloides
  - Elephantiasis (lymphatic filariasis)
  - River blindness (onchocerciasis)
  - Schistosomiasis
  - Tapeworm (cysticercosis/taeniasis)
- Leprosy
- Trachoma
- Buruli ulcer

[26] For example, discovery and development costs of a novel tuberculosis (TB) drug have been estimated at US$115 to US$240 million, including cost of failure, while vaccine development from research and discovery through to registration has been estimated at US$200 to US$500 million—also including cost of failure), with other estimates being even higher.

For each disease, the survey reports global R&D investment into drugs, vaccines, diagnostics, microbicides, or vector-control products, identifying the proportion of funding going to basic research; product discovery and preclinical development; clinical development; and the early product implementation phase (Phase IV trials). The survey collects data from more than 200 funders and recipients, including governments, multinational pharmaceutical firms, biotech companies, product development partnerships (PDPs) and public researchers and developers; and surveys 44 countries including most Organisation for Economic Co-operation and Development (OECD) countries as well as several low- and middle-income countries (India, Brazil, South Africa, Thailand, Ghana, and Colombia).

In 2008, these funders invested just under $3.1 billion ($3 billion in adjusted baseline dollars)[27] into R&D for new products for the 31 nominated neglected diseases (see Table A16-1). By comparison, the global spend on all pharmaceutical R&D is around $100 billion (European Commission, 2008).

Nearly three-quarters (72.8 percent) of this funding went to HIV/AIDS, TB, and malaria, diseases that are often prioritized in global health policies and frameworks such as the Millenium Development Goals and the Global Fund to Fight AIDS, Tuberculosis, and Malaria. Collectively, these three diseases received US$2.2 billion of the total global investment, including HIV/AIDS (US$1.2 billion, 39.4 percent), malaria (US$542 million, 18.3 percent), and TB (US$446 million, 15.1 percent).

By contrast, the 15 NTDs collectively received only 12 percent of global investment, or US$347 million dollars (see Table A16-2). No NTD area (including disease groups such as helminths or kinetoplastids) received more than a 5 percent share of global funding, while three diseases (leprosy, trachoma, and Buruli ulcer) received less than a 0.5 percent share.

Who Funds NTDs?

Investment into R&D for the NTDs relies on a handful of global funders, with 12 organizations accounting for 86 percent of global NTD funding (see Table A16-3) and two donors (the National Institutes of Health [NIH] and the Bill & Melinda Gates Foundation) accounting for nearly half (49 percent). Contributions by most NTD funders are below US$20 million per year and, in many cases, a few hundred thousand dollars or less (see Figure A16-1).

Two points need to be drawn from these global NTD funding patterns. The first is the heavy reliance on U.S. investors, both public and private, who provided one-third (33.5 percent) of all NTD R&D funding. The second is the role of innovative developing country (IDC) governments (Brazil and India) who collec-

[27] All G-FINDER funding figures are adjusted for inflation and reported in 2007 U.S. dollars, as this is the baseline year against which investment trends are tracked.

TABLE A16-1 Neglected Disease R&D Funding 2008

Disease	FY2007 (US$)	FY2008 (US$)[a]	FY2008 Nominal (US$)[b]	FY2007%	FY2008%	FY2007 Rank	FY2008 Rank
HIV/AIDS	1,083,018,193	1,164,882,551	1,215,841,708	42.3	39.4	1	1
Malaria	468,449,438	541,746,356	565,985,827	18.3	18.3	2	2
Tuberculosis	410,428,697	445,927,582	467,538,635	16.0	15.1	3	3
Kinetoplastids	125,122,839	139,207,962	145,676,517	4.9	4.7	4	4
Diarrhoeal diseases	113,889,118	132,198,981	138,159,527	4.4	4.5	5	5
Dengue	82,013,895	126,752,203	132,470,770	3.2	4.3	6	6
Bacterial pneumonia and meningitis	32,517,311	90,844,284	96,071,934	1.3	3.1	8	7
Helminth infections (Worms and Flukes)	51,591,838	66,837,827	69,518,274	2.0	2.3	7	8
Salmonella infections	9,117,212	39,486,243	41,079,293	0.4	1.3	9	9
Leprosy	5,619,475	9,769,250	10,073,184	0.2	0.3	10	10
Rheumatic fever	1,670,089	2,179,609	2,268,099	0.1	0.1	13	11
Trachoma	1,679,711	2,073,659	2,225,330	0.1	0.1	12	12
Buruli ulcer	2,412,950	1,954,465	2,140,303	0.1	0.1	11	13
Platform technologies	9,997,190	16,298,028	16,569,978	0.4	0.6		
Core funding of a multi-disease R&D organization	110,921,673	101,097,348	110,403,054	4.3	3.4		
Unspecified disease	51,619,120	74,707,997	78,179,894	2.0	2.5		
Grand Total	2,560,068,749	2,995,964,344	3,094,202,328	100.0	100.0		

NOTE: FY2007 figures only include typhoid and para-typhoid fever R&D investments. In FY2008, the scope of the survey was broadened to include other samonella infections, specifically non-typhoidal *Salmonella enterica* (NTS) and multiple salmonella infections.

[a] Figures are adjusted for inflation and reported in U.S. dollars.

[b] Figures are in current (2008) U.S. dollars.

TABLE A16-2 NTD R&D Funding 2008

Disease	FY2008 Amount (2007 US$)	Share of Global Funding 2008
Kinetoplastids	139,207,962	4.7%
Dengue	126,752,203	4.3%
Helminth infections (Worms and Flukes)	66,837,827	2.3%
Leprosy	9,769,250	0.3%
Trachoma	2,073,659	0.1%
Buruli ulcer	1,954,465	0.1%
Total NTD Funding	346,595,367	11.7%
Total R&D Funding	2,955,964,344	100.0%

tively provided nearly 10 percent of global NTD funding. This differs markedly from diseases such as HIV/AIDS, TB, and malaria, where IDC contributions are generally dwarfed by spending from Western governments and companies, and it appears to reflect both a general Western neglect of NTDs as well as the domestic importance of these diseases to some IDCs.

For all NTDs except dengue, new product development is predominantly or exclusively supported by "charitable" funding from public or philanthropic organizations, with little or no contribution from the pharmaceutical industry. This is the case for leprosy (100 percent, with just over half from IDC governments), kinetoplastid diseases (98 percent), trachoma (95 percent), helminths

TABLE A16-3 Top 12 Funders of R&D for NTDs, 2008

	Funder	FY 2008 (US$)	Share of Global Funding 2008
1	U.S. National Institutes of Health (NIH)	103,053,401	30.0%
2	Bill & Melinda Gates Foundation	66,395,102	19.0%
3	Aggregate Pharmaceutical and Biotechnology company respondents	52,038,941	15.0%
4	The Wellcome Trust	17,604,896	5.0%
5	U.S. Department of Defense (DOD)	11,576,763	3.0%
6	European Commission	10,140,230	3.0%
7	Brazilian Ministry of Health, Department of Science and Technology	7,806,694	2.0%
8	Médecins Sans Frontières (MSF)	7,275,268	2.0%
9	State of Sao Paulo Research Foundation (FAPESP)	6,589,595	2.0%
10	Institut Pasteur	6,194,538	2.0%
11	UK Medical Research Council (MRC)	5,168,186	1.0%
12	UK Department for International Development (DFID)	3,733,433	1.0%
Subtotal R&D Funding of Top 12 Funders		297,577,046	85.9%
Total NTD Funding		346,595,367	

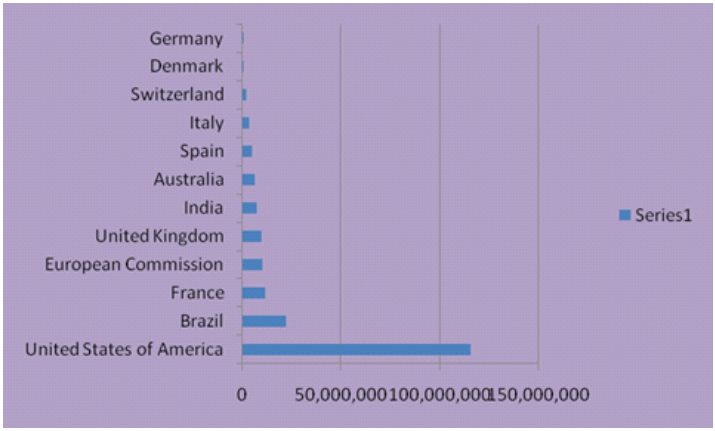


FIGURE A16-1 Top country funders of NTD R&D, 2008.

(92 percent), and Buruli ulcer (85 percent).[28] This funding pattern has significant implications for both the type of research being funded and the likelihood of new products being developed, as discussed below.

Funding Patterns Across NTDs

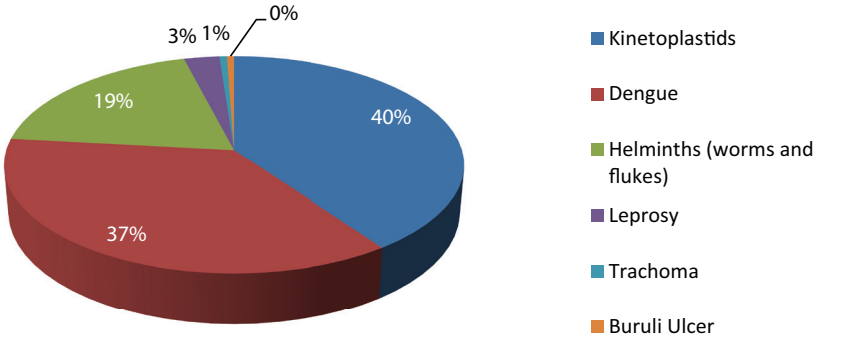
There is a marked discrepancy not only between funding for NTDs and other neglected diseases, but also of funding across NTDs (see Figure A16-2). The kinetoplastid diseases and dengue received more than three-quarters (77 percent) of all NTD funding in 2008, with R&D for leprosy, trachoma, and Buruli ulcer collectively receiving less than 5 percent of the already modest global NTD investment (see Figure A16-2).

There are also marked differences in funding patterns between diseases, including both their funding sources and how funding is allocated within each disease area.

Kinetoplastids

The kinetoplastids are the fourth highest funded neglected disease area globally after HIV/AIDS, TB, and malaria, with kinetoplastid investment in 2008 being around one-third (31 percent) of TB investment. Ninety percent of kinetoplastid R&D funding comes from 12 organizations, virtually all public and philanthropic funders; industry provides only 2 percent of global kinetoplastid

[28] We note that the relatively larger percentage industry investment in Buruli ulcer translates into a very modest dollar amount, because global funding for this disease is below US$2 million per year.



DISEASE	FY2008 (US$)
Kinetoplastids	139,207,962
Dengue	126,752,203
Helminths (worms and flukes)	66,837,827
Leprosy	9,769,250
Trachoma	2,073,659
Buruli Ulcer	1,954,465
Disease Total	346,595,367

FIGURE A16-2 Share of NTD funding by disease, 2008.

investment (see Figure A16-3). As with most other NTDs, NIH and the Gates Foundation are the mainstays of funding, providing more than half (56 percent) the 2008 global investment into kinetoplastid R&D (see Figure A16-3).

The high level of kinetoplastid funding relative to other NTDs reflects several factors, the most important being the presence of an active PDP in this area. The Drugs for Neglected Diseases initiative (DNDi) is a PDP developing new kinetoplastid drugs. These include drugs for human African trypanosomiasis (HAT) (fexinidazole in Phase I trials; nitromidazoles and oxaborole in preclinical development); for visceral leishmaniasis (sitamaquine and tafenoquine in clinical trials; new formulations of Amphotericin B in preclinical); and for Chagas disease (azoles and a pediatric formulation of benznidazole in clinical development) (DNDi, 2009). They also have a discovery portfolio across all three diseases. With an active advocacy arm, DNDi generated US$24.4 million for kinetoplastid drug development in 2009, including from many of the top 12 kinetoplastid funders

FUNDERS	FY2008 (US$)
U.S. National Institutes of Health (NIH)	48,561,566
Bill & Melinda Gates Foundation	28,973,211
The Wellcome Trust	12,360,489
Médecins Sans Frontières (MSF)	7,275,268
European Commission	4,628,687
U.S. Department of Defense (DOD) including DOD	4,059,615
Brazilian Ministry of Health, Department of Science and Technology	3,758,220
UK Department for International Development (DFID)	3,733,433
UK Medical Research Council (MRC)	3,464,747
Spanish Ministry of Foreign Affairs and Cooperation for Development (MAFC)	3,279,119
Institut Pasteur	2,932,088
Aggregate Pharmaceutical and Biotechnology Company Respondents	2,912,298
Subtotal Top 12 Funders for Kinetoplastids	125,938,739
Kinetoplastids Total Funding	139,207,962

FIGURE A16-3 Top 12 funders of kinetoplastid R&D, 2008.

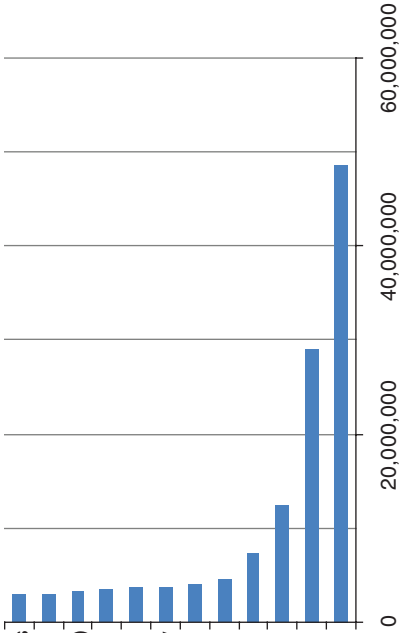


FIGURE A16-3 Continued

such as NIH, the Gates Foundation, Médecins Sans Frontières, the European Commission, the U.K. Department for International Development (DFID), and Spain.

Funding is spread unevenly across the kinetoplastid diseases, even though all three need investment into basic research, drugs, vaccines, and diagnostics, while Chagas disease and sleeping sickness also require funding of new vector-control products. Leishmaniasis receives 41 percent of global funding, sleeping sickness receives 25 percent, while Chagas' disease is particularly poorly served, receiving only 11 percent of overall kinetoplastid investment. (The remaining 23 percent is cross-disease research.)

A closer examination of how the US$139 million of kinetoplastid funding is invested shows it is unlikely to result in generation of several badly needed new products (see Figure A16-4). Around 45 percent (US$62.9 million) of total funding was directed to basic research, a further 38 percent (US$53.5 million) to drug development (of which nearly half went to DNDi), and 8 percent (US$11.5 million) to diagnostics. Ongoing investments into these product areas at these levels, if allocated to high-capacity groups, are sufficient to move product development forward even if not as quickly as desirable. However, vaccine development received only US$7.8 million (6 percent of annual kinetoplastid funding), and there was no reported funding of vector-control R&D in 2008. At the disease level, the picture was even grimmer, with Chagas disease having no realistic investment for drugs, vaccines, or diagnostics despite the wide therapeutic gaps it currently suffers from, and HAT vaccine research was almost nonexistent (only US$131,000 was invested in 2008).

It is important to note that these funding patterns do not reflect an evidence-based assessment of need; rather they are the cumulative effect of who provides the funding and who is available for product development. In the kinetoplastid field, nearly two-thirds of global funding comes from governments, who generally show a preference for basic research over high-cost and high-risk product development; there is only one vaccine in development[29]; and there are no companies or product development groups working to develop new control products. Only in the drug field are there both funders willing to invest and product development groups available to create new kinetoplastid products—explaining the predominance of drug R&D funding over that for other kinetoplastid products.

Dengue

Currently, dengue management relies on the control of transmission and on supportive therapy to minimize patient dehydration and shock from hemorrhagic fever. Investment is needed in a vaccine that covers all four dengue serotypes;

[29] The Infectious Disease Research Institute and GlaxoSmithKline Biologics is developing leish-111f + MPL-SE, which is in Phase I.

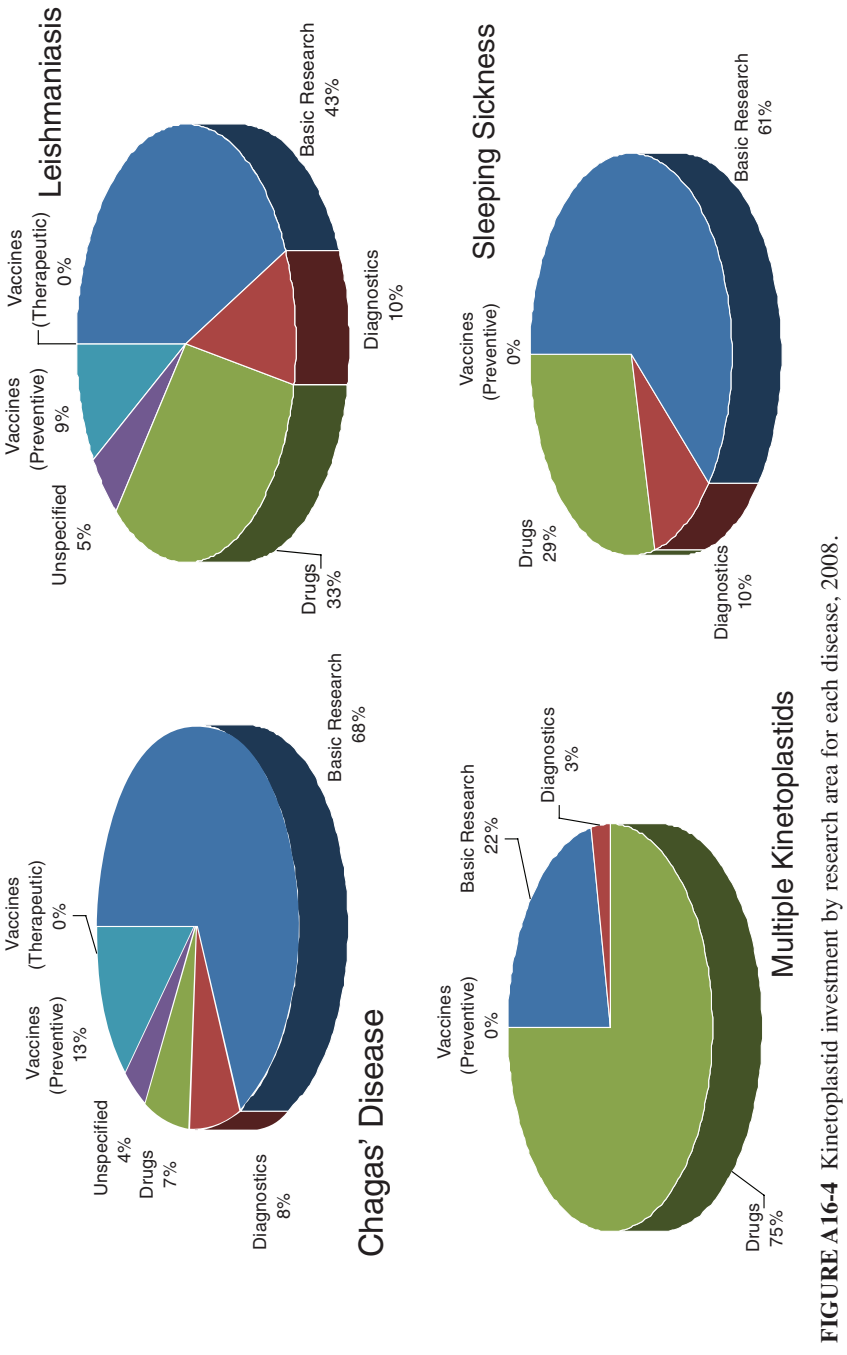


FIGURE A16-4 Kinetoplastid investment by research area for each disease, 2008.

diagnostics able to detect early stage disease, to differentiate between serotypes, and to distinguish dengue from other fevers (WHO, 2007)[30]; and antiviral drugs that are effective once infection has occurred.

In 2008, dengue was the second-best funded of the NTDs, receiving a little less than the kinetoplastids (US$126.8 million in 2008) and just over one-quarter of the funding invested in TB research each year. It has the distinction of being the only "commercial" NTD, with the pharmaceutical industry providing just over one-third (35 percent, US$43.8 million) of R&D funding. Dengue is more attractive to companies than other NTDs because its disease burden is concentrated in higher-income developing countries in Asia and Latin America, where governments can afford to purchase new tools and may wish to defray the high costs of treating dengue, particularly hemorrhagic dengue fever, which requires hospitalization and intensive care support.

If industry figures are excluded, it is apparent that dengue funding is otherwise highly concentrated, with NIH and the Gates Foundation providing well over half (57 percent) the remaining global funding (see Figure A16-5). The role of IDC funders seeking to address their local dengue burden is also notable—Brazil in particular, but also India, collectively providing 12 percent (US$15 million) of global dengue R&D funding. This means that, unlike all other NTDs, dengue product development does not rely chiefly on "charitable" funding but is rather driven by commercial industry interests and the needs of emerging IDC governments: together, these two sectors provided nearly half (46 percent) of the 2008 global investment into new dengue products.

Dengue funding patterns correlate moderately well with product needs, with nearly two-thirds (63 percent, US$80.9 million) of funding channeled into vaccine development, which is the most commercially viable area and also supported by a strong public health case (because supportive treatment for dengue is effective but only if instituted very early, which can be difficult in some developing world settings) (see Figure A16-6) There are currently at least two dengue vaccine candidates that have advanced to Phase II clinical trials, one that is in Phase I and four in preclinical stages. However, investment into dengue diagnostics (US$5.4 million) was modest, even taking into account their low development costs, while funding for development of drugs (US$7.6 million) and vector control products (US$2.0 million) was well below the level needed to create either of these.

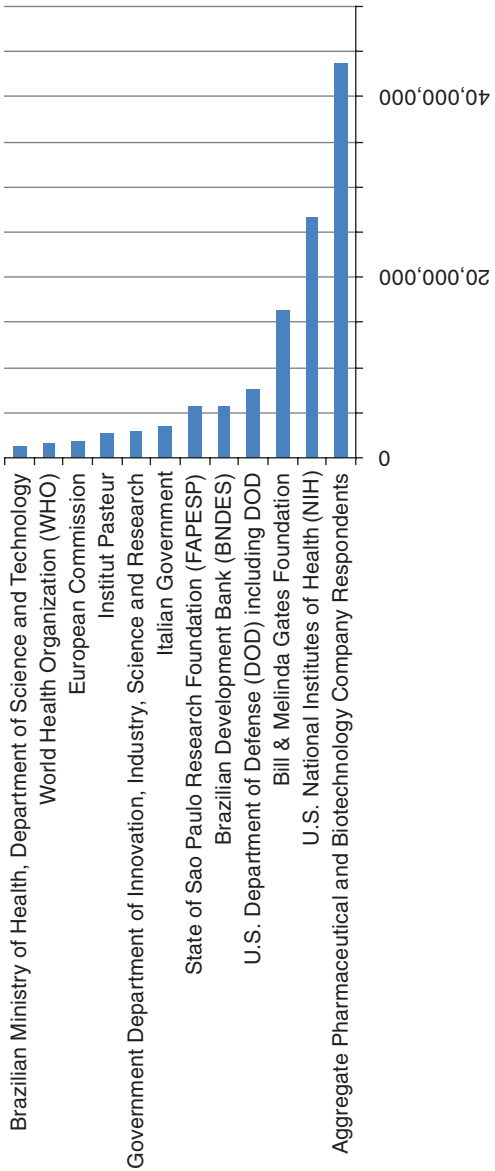
Helminths

The large family of helminth infections was significantly underfunded, with 2008 funding for all helminth R&D being US$66.8 million, around half the annual dengue investment and only 6 percent of the annual R&D investment for HIV/AIDS.

[30] Currently available diagnostic kits also need to be evaluated.

FUNDERS	FY2008 (US$)
Aggregate Pharmaceutical and Biotechnology Company Respondents	43,793,998
U.S. National Institutes of Health (NIH)	26,603,478
Bill & Melinda Gates Foundation	16,305,526
U.S. Department of Defense (DOD) including DOD	7,517,148
Brazilian Development Bank (BNDES)	5,780,347
State of Sao Paulo Research Foundation (FAPESP)	5,780,347
Italian Government	3,442,915
Australian Government Department of Innovation, Industry, Science and Research	2,866,725
Institut Pasteur	2,727,968
European Commission	1,748,863
World Health Organization (WHO)	1,723,507
Brazilian Ministry of Health, Department of Science and Technology	1,334,847
Subtotal Top 12 Funders	119,625,671
Dengue Total Funding	126,752,203

FIGURE A16-5 Top 12 funders of dengue R&D, 2008.



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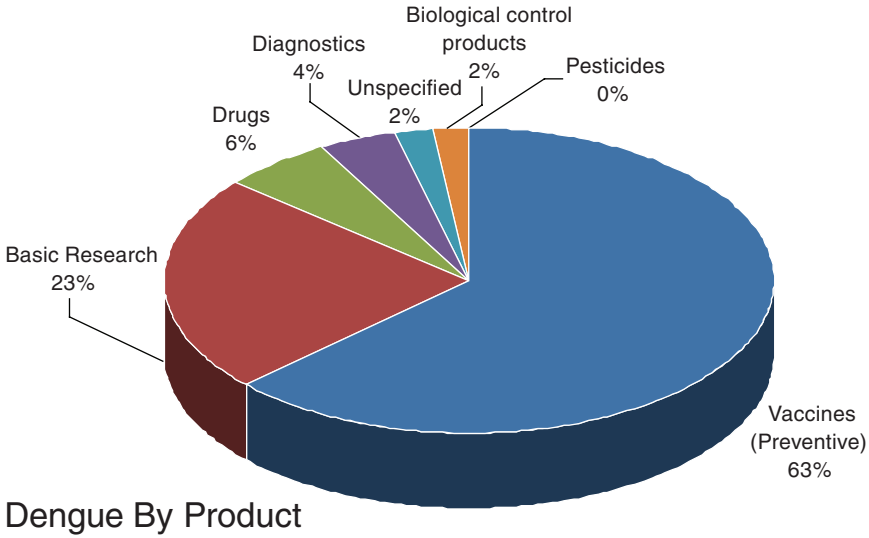


FIGURE A16-6 Dengue funding by product area, 2008.

As with other NTDs, helminth R&D was heavily reliant on a small handful of donors (when industry investment is excluded, 11 donors provided 86 percent of helminth R&D funding), in particular NIH and the Gates Foundation, who between them funded two-thirds (67 percent) of helminth research and product development (see Figure A16-7).

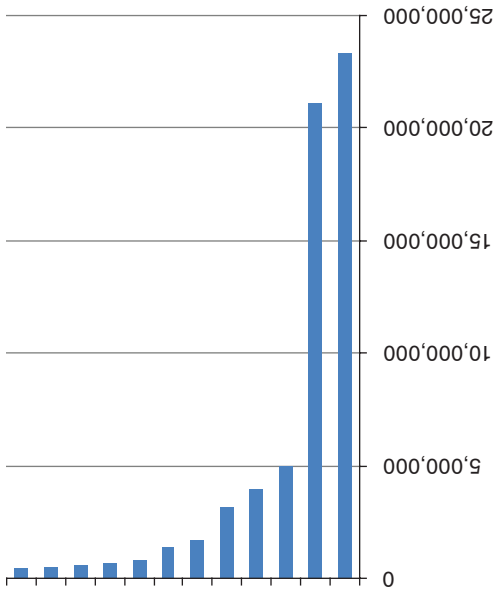
This R&D funding was distributed very unevenly across the helminth infections, even though all need basic research and new drugs; three diseases (schistosomiasis, onchocerciasis, and strongyloides) need new diagnostics; and four diseases (schistosomiasis, onchocerciasis, lymphatic filariasis [LF], and tapeworm) need new vector-control products. Vaccine development—by the far the most expensive R&D area with costs in the hundreds of millions—is also needed for schistosomiasis, onchocerciasis, strongyloides, and hookworm (see Figure A16-8).

Several points can be drawn from helminth funding patterns. The first is that funding is simply too low across the board to create new helminth products in a timeframe that could be considered reasonable. The maximum 2008 funding for drug development for any helminth disease was US$4.7 million (for LF) while maximum vaccine funding was US$7.2 million (for hookworm). For most other helminth products, funding was well below these levels; for example, hookworm drug development received only US$721,000 and onchocerciasis vaccine development just under US$11,000.

The second is that helminth funding has little or no correlation with product

FUNDERS	FY2008 (US$)
U.S. National Institutes of Health (NIH)	23,308,515
Bill & Melinda Gates Foundation	21,116,365
Aggregate Pharmaceutical and Biotechnology Company Respondents	4,950,621
The Wellcome Trust	3,959,257
European Commission: Research Directorate-General	3,137,023
Australian National Health and Medical Research Council (NHMRC)	1,666,179
UK Medical Research Council (MRC)	1,396,827
State of Sao Paulo Research Foundation	809,249
African Programme for Onchocerciasis Control (APOC)	674,374
Butantan Institute	558,767
Inserm-Institute of Infectious Diseases	524,659
Anonymous Donor	463,780
Subtotal Top 12 Funders	62,565,617
Helminths Total Funding	66,837,827

FIGURE A16-7 Top 12 funders of helminth R&D, 2008.



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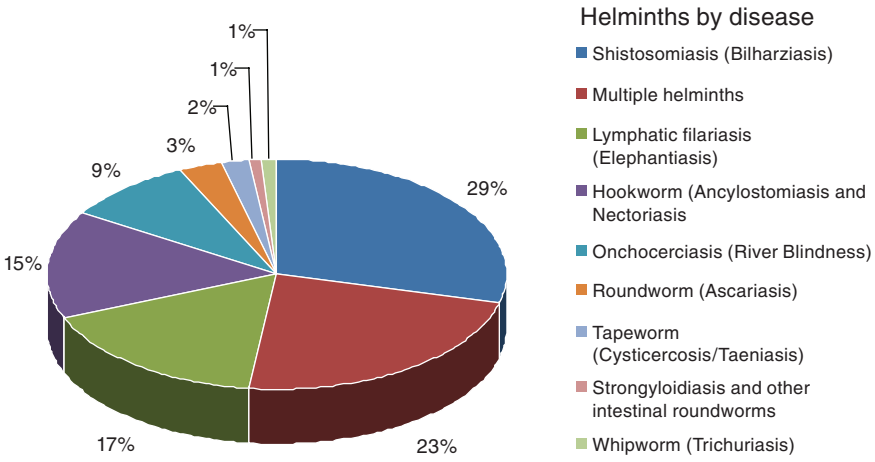


FIGURE A16-8 Helminth funding by product area, 2008.

need for each disease: for instance, both schistosomiasis and onchocerciasis need new products in all areas as well as basic research, yet schistosomiasis received 29 percent (US$19.7 million) of global helminth R&D funding while onchocerciasis received only 9 percent (US$5.9 million).

However, the most striking conclusion is that the vast majority of helminth funding is invested not in new product development but in basic research, ranging from 40 percent for elephantiasis to 60 percent for tapeworm, 71 percent for schistosomiasis, 97 percent for strongyloides, and 100 percent of investment into roundworm and whipworm.

The exceptions to this pattern (hookworm and onchocerciasis) are worth exploring. The high relative spend (70 percent, US$7.2 million) on vaccines for hookworm is directly linked to the presence of the Human Hookworm Vaccine Initiative, a PDP based at the Sabin Institute that is focused on new vaccine development. Likewise, 70 percent (US$4.1 million) of onchocerciasis funding is directed to drug development by two product development groups (a major drug company, and a small investment by the African Programme for Onchocerciasis Control). In other words, as with kinetoplastids, the presence of a dedicated product developer tends to encourage investment in applied research but, in their absence, funders lean strongly toward investing in basic research. The more promising investment pattern for hookworm and onchocerciasis should also not distract readers from the fact that in both cases funding is still far too small to generate the desired products in any reasonable timeframe.

Leprosy

Leprosy R&D was grossly underfunded in 2008, receiving only 0.3 percent of total global funding for neglected diseases and less than 3 percent of global funding for NTDs. All funding came from public and philanthropic organizations, with 12 organizations providing 99 percent of funds (see Figure A16-9). As with most other NTDs, NIH was the lead funder (32 percent of all investment); however, India and Brazil contributed 51 percent of global funding (just under US$5 million), reflecting the local leprosy burden in each of these countries.

Investment into new leprosy products was very modest, with well over half (58 percent, US$5.7 million) of all funding going to basic research. Development of new drugs to replace current 6–12-month multidrug treatment regimens received only US$0.7 million (8 percent of total leprosy funding) and investment into improved diagnostics was only US$0.5 million (5 percent) (see Figure A16-10).

These very modest investments partly reflect the fact that leprosy is targeted for eradication, with numbers of new leprosy patients declining from 763,000 in 2001 to 296,000 in 2005. Although a very positive outcome from the public health perspective, this disease trajectory means that investment into leprosy products for new and existing patients can be a far less compelling story for funders (and developers) than investment into NTDs with large and/or increasing burdens of mortality and morbidity.

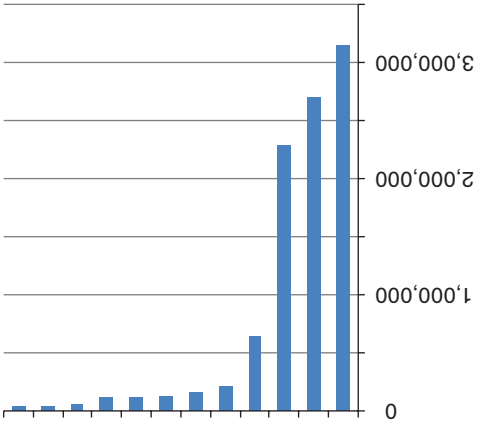
Trachoma

Trachoma is among the most neglected of the NTDs, receiving just over US$2 million in 2008 and having only five identified R&D funders, all public organizations (see Figure A16-11). The very modest industry contribution (US$96,000, 5 percent of total trachoma funding) reflects work on existing trachoma treatments rather than development of novel products.

As with leprosy, trachoma R&D suffers from a perception that a good treatment already exists, since face-washing and a one-off oral dose of azithromycin are highly effective. Yet the public health community has identified a need for new point-of-care trachoma diagnostics to replace current complex and expensive tests, or sometimes unreliable clinical diagnosis, as well as a trachoma vaccine. Neither of these products are likely to eventuate in the next 50 to 100 years if current investment patterns continue, with trachoma vaccines receiving only $99,000 in 2008 (typical vaccines cost several hundred million dollars to develop) and diagnostics only US$68,000 (diagnostics can typically be developed for $2 million to US$10 million) (see Figure A16-12).

FUNDERS	FY2008 (US$)
U.S. National Institutes of Health (NIH)	3,138,305
Indian Council of Medical Research (ICMR)	2,704,472
Brazilian Ministry of Health, Department of Science and Technology	2,287,212
American Leprosy Missions	642,100
Institut Pasteur	221,321
Undisclosed Funder	151,858
The Order of Malta Grants for leprosy research	131,165
The Hospital for Tropical Diseases (HTD)	112,003
Hospital and Homes of St Giles	108,131
Colorado State University	51,060
University College London Hospital	45,955
New York Community Trust	44,891
Subtotal Top 12 Funders	9,638,473
Leprosy Total Funding	9,769,250

FIGURE A16-9 Top 12 funders of leprosy R&D, 2008.



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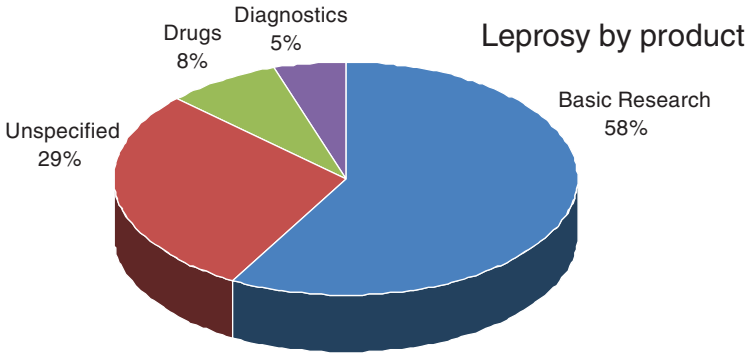

FIGURE A16-10 Leprosy funding by product area, 2008.

Buruli Ulcer

The most neglected of the 15 NTDs covered by G-FINDER was Buruli ulcer, with 2008 R&D funding under US$2 million. Of this, only a tiny sum was devoted to product development (US$310,000 in total for Buruli drugs, vaccines, and diagnostics), the majority of which came from industry (US$286,000, 91 percent of product development funding) (see Figure A16-13). Beyond this, only eight public and philanthropic organizations funded Buruli ulcer R&D, investing most of their funds into basic research (see Figure A16-14).

We note that a focus on basic research is necessary since one of the obstacles to developing new products is lack of knowledge of the cause, vectors, and epidemiology of Buruli ulcer. Nevertheless, even a modest investment in diagnostics would allow Buruli ulcer to be diagnosed sufficiently early to begin antibiotics, thus preventing development of the disfiguring ulcers that require surgical excision. Given the localized nature of Buruli ulcer, which occurs predominantly in Western Africa, and its predilection for children under 15 (WHO, 2007), development of a new vaccine could be an effective option, particularly because TB vaccines are already known to give short-term protection against the infection.

However, the chief obstacle to greater investment is that Buruli ulcer affects relatively few people compared to other NTDs, with WHO estimating around 7,000 (WHO, 2008) new cases of Buruli ulcer per year. These patients are also chiefly in sub-Saharan Africa rather than in middle-income countries, who could afford a greater R&D investment and can represent a more substantial market.

Discussion

The funding patterns above highlight several key points. Research and development of new products for NTDs is severely underfunded, the only exceptions being dengue vaccines and drug development for some of the kinetoplastid

FUNDERS	FY2008 (US$)
U.S. National Institutes of Health (NIH)	1,037,612
Statens Serum Institute (SSI)	703,674
Brazilian Ministry of Health, Department of Science and Technology	170,326
Aggregate Pharmaceutical and Biotechnology Company Respondents	96,339
Swedish Research Council	38,276
Institut Pasteur	27,432
Total Trachoma Funders	2,073,659

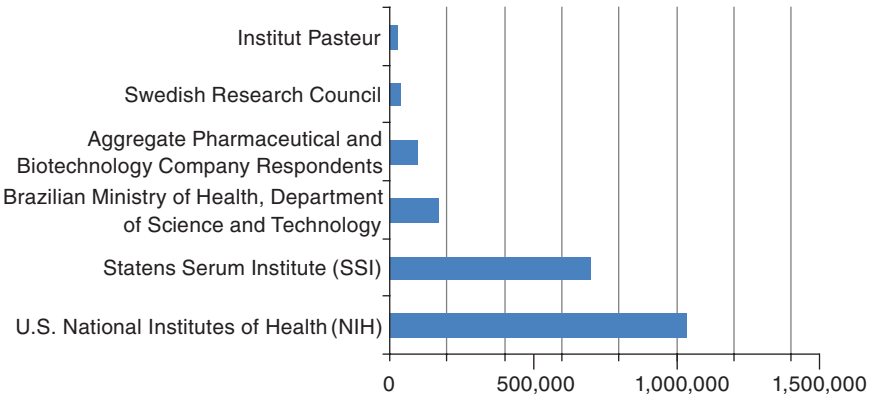

FIGURE A16-11 Top 12 funders of trachoma R&D, 2008.

diseases. Funding is not only insufficient but is generally poorly targeted, with investment patterns often bearing little relationship to identified product needs. Diseases for which expensive vaccine R&D is considered necessary, such as onchocerciasis, can receive less funding than diseases such as LF, which do not; funding in general is neither commensurate with nor matched to the product needs identified by the public health community.

The heavy reliance on public funding for many NTDs leads to a strong tendency toward investment in basic research rather than product development (which carries risks that many public funders are uncomfortable with); overreli-

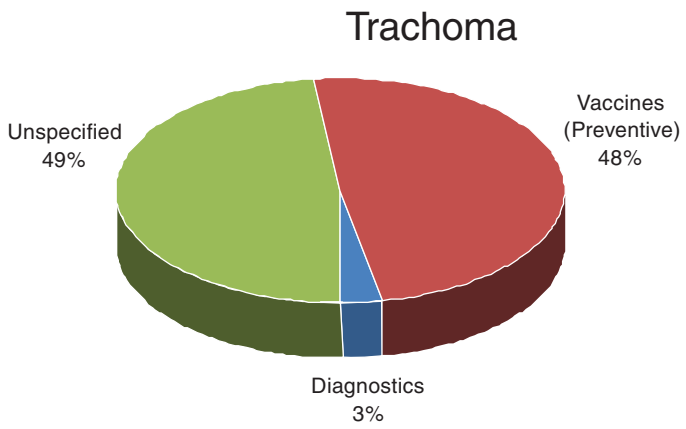

FIGURE A16-12 Trachoma funding by product area, 2008.

ance on a handful of public and philanthropic funders, particularly NIH and the Gates Foundation, for all diseases except dengue makes the situation even more tenuous.

Piecemeal funding, without a coherent and agreed strategy, is the hallmark of R&D funding for NTDs. However, there are noteworthy exceptions. These are diseases such as dengue and kinetoplastids, where active product development groups not only generate substantial funds (these two diseases now represent three-quarters of all NTD funding) but also focus these funds tightly onto R&D of the desired products. For dengue, this is chiefly due to industry groups and a PDP working on dengue vaccines, while kinetoplastids have benefited from the presence of an active drug PDP. A further positive trend is the role of IDC govern-

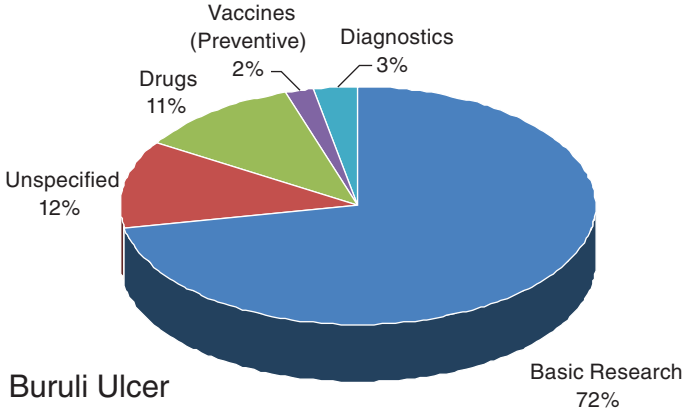

FIGURE A16-13 Buruli ulcer funding by product area, 2008.

FUNDERS	FY2008 (US$)
European Commission	625,656
U.S. National Institutes of Health (NIH)	403,924
Institut Pasteur	285,729
Aggregate Pharmaceutical and Biotechnology	285,685
UBS Optimus Foundation	140,246
Belgian National Fund for Scientific Research	84,402
Australian National Health and Medical Research	74,844
The Welcome Trust	40,862
Condazione Cariplo	13,116
Total Buruli Ulcer Funders	1,954,465

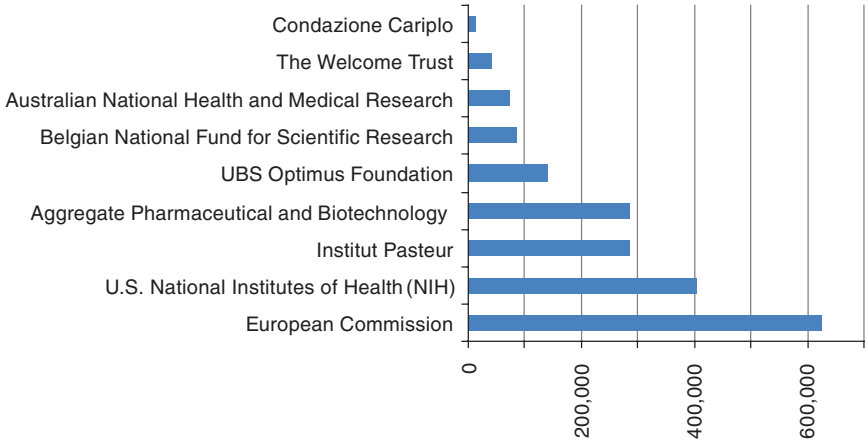

FIGURE A16-14 Top 12 funders of Buruli ulcer R&D, 2008.

ments, who now represent nearly 10 percent of global investment into R&D for NTDs and an even higher percentage in diseases areas of particular relevance to them, such as dengue or leprosy.

The outcome of these findings is crucial for public and philanthropic funders. A great deal of the nearly US$350 million spent each year on R&D for NTDs is unlikely to generate the products that patients need. Providing small amounts of funding across many diseases and product areas is likely to be wasteful and ineffective; and, even if more funding is provided, it is unlikely to generate new

NTD products unless the funding is targeted to the right areas, and those areas have product development groups in place who can successfully translate those funds into new products.

To ensure that current funding, and ideally significantly increased future funding, achieves its goal, we believe it is important that funders rethink the current approach. Funders and the global health community will need to decide what products should be prioritized, to create or identify groups able to develop these, and to provide sufficient funds to achieve their agreed objectives.

As a first step along this path, it will be important to create a methodology for assessing health return on R&D investment, so that funders can prioritize their valuable investments toward those diseases and products where they are likely to generate the greatest health impact. Pharmaceutical companies routinely assess likely market returns on investment to guide their decisions, while many governments also assess the cost-benefit of new health technologies before listing them on national health insurance schemes. However, there is no similar tool to guide investment decisions in the neglected disease R&D field.

Such a tool would need to take many factors into account, including the treatment gap, investment gap, and burden of disease in a given area, as well as the type of product needed, the state of the science (including the existence of relevant researchers and product developers), and the state of the existing product pipeline (see Figure A16-15). This task is complex but necessary because, in its absence, investment will in many cases continue to be ad hoc, inefficient, and targeted to areas where it is unlikely to deliver the desired outcomes.

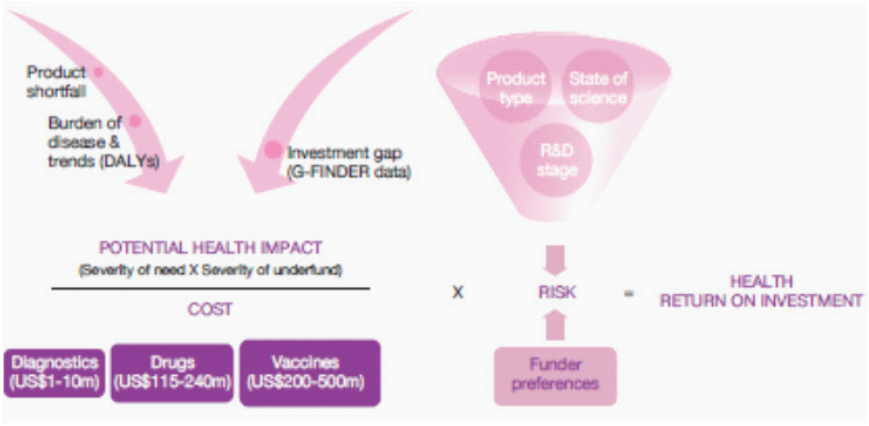

FIGURE A16-15 Assessing health return on investment.

By working together, the public, philanthropic, and private sectors can make a difference in the health outcomes for many millions of patients throughout the developing world.

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A17

THE GLOBAL PROGRAMME TO ELIMINATE LYMPHATIC FILARIASIS: HEALTH IMPACT AFTER 8 YEARS[31]

Eric A. ***Ottesen***[32,33]*, Pamela J. Hooper*[32]*, Mark Bradley*[34]*, and Gautam Biswas*[35]

Abstract[36]

Background: **In its first 8 years, the Global Programme to Eliminate Lymphatic Filariasis (GPELF) achieved an unprecedentedly rapid scale-up: 1.9 billion treatments with anti-filarial drugs (albendazole, ivermectin, and**

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Competing Interests: Dr. Mark Bradley currently works for GlaxoSmithKline.

diethylcarbamazine) were provided via yearly mass drug administration (MDA) to a minimum of 570 million individuals living in 48 of the 83 initially identified LF-endemic countries.

Methodology: **To assess the health impact that this massive global effort has had, we analyzed the benefits accrued first from preventing or stopping the progression of LF disease, and then from the broader anti-parasite effects ('beyond-LF' benefits) attributable to the use of albendazole and ivermectin. Projections were based on demographic and disease prevalence data from publications of the Population Reference Bureau, The World Bank, and the World Health Organization.**

Result: **Between 2000 and 2007, the GPELF prevented LF disease in an estimated 6.6 million newborns who would otherwise have acquired LF, thus averting in their lifetimes nearly 1.4 million cases of hydrocele, 800,000 cases of lymphedema and 4.4 million cases of subclinical disease. Similarly, 9.5 million individuals—previously infected but without overt manifestations of disease—were protected from developing hydrocele (6.0 million) or lymphedema (3.5 million). These LF-related benefits, by themselves, translate into 32 million DALYs (Disability Adjusted Life Years) averted. Ancillary, 'beyond-LF' benefits from the .1.9 billion treatments delivered by the GPELF were also enormous, especially because of the .310 million treatments to the children and women of childbearing age who received albendazole with/without ivermectin (effectively treating intestinal helminths, onchocerciasis, lice, scabies, and other conditions). These benefits can be described but remain difficult to quantify, largely because of the poorly defined epidemiology of these latter infections.**

Conclusion: **The GPELF has earlier been described as a 'best buy' in global health; this present tally of attributable health benefits from its first 8 years strengthens this notion considerably.**

Author Summary

Lymphatic filariasis (LF) is a vector-borne, chronically disabling parasitic infection causing elephantiasis, lymph-edema, and hydrocele. The infection is endemic in 83 countries worldwide, with more than 1.2 billion people at risk and 120 million already infected. Since 1998, the Global Programme to Eliminate Lymphatic Filariasis (GPELF) has targeted elimination of LF by 2020. In its first 8 operational years, the program has scaled-up to provide more than 1.9 billion treatments through annual, single-dose mass drug administration (MDA) to 570 million individuals living in 48 LF-endemic countries. Not only do the GPELF drugs prevent the spread of LF, they also stop the progression of disease in those already infected. In addition, since two of the three drugs used for LF elimination have broad anti-parasite properties, treated populations are freed from both intestinal worms and from skin

infections with onchocerca, lice, and scabies. To better understand the public health benefit of this ongoing global health initiative, we undertook an analysis of Programme data made available to WHO by participating countries. Our conservative estimates show that the GPELF has had an unprecedented public health impact on both LF and other neglected tropical diseases; it justly deserves the accolade of 'a best buy' in global health.

Introduction

In 1997, the Global Programme to Eliminate Lymphatic Filariasis (GPELF) was created in response to a specific resolution by the World Health Assembly (Molyneux and Zagaria, 2002). At that time the World health Organization (WHO), having recently devised a strategy aimed at achieving LF elimination through 'mass drug administration' (MDA) (Ottesen et al., 1997), received extraordinary pledges from two pharmaceutical companies (GlaxoSmithKline and Merck & Co., Inc.) for long-term drug donations of unprecedented size to jumpstart this nascent program.

The impressive programmatic progress made by the GPELF has been documented in a number of valuable reviews and updates (Molyneux and Zagaria, 2002; Ottesen, 2006; WHO, 2005, 2006, 2007, 2008) however, what is most needed now – for donors who are supporting this effort, for the Ministries of Health and health workers who are laboring on its behalf and for endemic communities who continue to invest their energies and resources towards its success – is to understand not just the technical achievements, but especially what difference it all has made to the health and welfare of the at-risk populations. What impact has 10 years of focus on LF – long recognized as one of the most debilitating and economically-draining of the neglected tropical diseases – really had?

To answer this question requires not just a tabulation of the GPELF's programmatic achievements in providing necessary drugs to the targeted at-risk populations, but also, importantly, a projection of the public health gain from this effort, using estimates based on the most accurate data and most reasonable assumptions available.

Methods

Data sources

Specific sources for the data are identified as they are presented; in general, however:

1) Numbers related to LF endemicity, populations at-risk (Table A17-1) and treatments delivered were derived from publications by WHO in the Weekly Epidemiological Record (WER) and WHO Annual Reports be-

TABLE A17-1 Population at Risk (WHO, 2006)

Region	# of endemic countries	At-risk population (*millions*)	Children at risk (*millions*)
Africa (AFRO)	39	394	176
Americas (AMRO)	7	8.87	3.39
Eastern Mediterranean (EMRO)	3	14.9	6.50
South-east Asia (SEARO)	9	851	297
Western Pacific (WPRO)	25	31.6	11.1
Total:	83	1,300	494

doi:10.1371/journal.pntd.0000317.t001

tween 2000 and 2008 (WHO, 2002, 2003, 2004, 2005, 2006, 2007, 2008); this information is also recorded at www.who.int/ lymphatic_filariasis.

2) Information on the quantities of albendazole, ivermectin (Mectizan) and diethylcarbamazine (DEC) used in the GPELF came from these same WER reports (WHO, 2005, 2006, 2007, 2008), from WHO's Annual Reports (available at www.who.int/ lymphatic_filariasis) and from records of GlaxoSmithKline and the Mectizan Donation Program.
3) Population demographic figures used to calculate age or gender subpopulations of the total at-risk populations were taken from the Population Reference Bureau (PRB, 2005-2006) and the World Bank Health, Nutrition and Population Statistics (World Bank, 2005).
4) Disability weights and formulas for calculating Disability Adjusted Life Years (DALYs) were derived from the Global Burden of Disease (Lopez et al., 2006).
5) Information on the clinical profiles and the effectiveness of treatment for both LF and soil transmitted helminth (STH) infections has been taken from scientific publications (Crompton, 2000; O'Lorcain and Holland, 2000; Ottesen et al., 1997; Stephenson et al., 2000).
6) Estimates of the epidemiology of STH infections (number and distribution of affected individuals worldwide) came from published information (de Silva et al., 2003).

Impact Projections

The assumptions made and the rationale behind the projections are outlined below and summarized in Tables A17-2 and A17-3.

Impact estimates: LF-related.

Babies protected from infection. To estimate the number of babies born into LF treatment areas between 2000 and 2007, demographic data from each country (births per 1,000 population discounted by infant mortality rates (US Census

TABLE A17-2 Projected Health Impact-LF Related

Impact #1	Individuals Protected	Disease Prevented	DALYs Averted
	6.6 million newborns	1.4 million cases of hydrocele	3.2 million DALYs
		800,000 cases of lymphedema	2.8 million DALYs
		4.4 million cases of subclinical disease	?

Assumptions and Reasoning

1) 66 million babies born into at-risk areas under MDA 2000-2007 (discounted for infant mortality) (PRB, 2005-2006)

2) LF infections occur in 10% of at-risk population (Ottesen, 2006)

3) 12.5% of LF infections result in lymphedema, 20.8% in hydrocele, 66.7% in subclinical damage (Ottesen, 2006)

4) Disability weights (based on Global Burden of Disease methods): 0.105 for lymphedema, 0.073 for hydrocele; onset at age 20; life span is Region-specific

5) LF transmission (estimated by mosquito infection rates) falls progressively to 50%, 25%, 12%, 6%, and 0% pre-MDA levels after each of the first 5 MDAs respectively

Impact #2	Individuals Protected	Disease Prevented	DALYs Averted
	9.5 million people	6.0 cases of hydrocele	14 million DALYs
		3.5 million cases of lymphedema	12 million DALYs

Assumptions and Reasoning

1) 570 million individuals (at minimum) treated under MDAs 2000-2007. The maximal number of individuals treated in any single MDA was determined for each country. The sum of these numbers indicates the minimum total number of individuals treated.

2) LF infections occur in 10% of at-risk (i.e., treated) population (Ottesen, 2006) (here 57 million) with 1/3 having clinical manifestations and 2/3 having subclinical disease (Ottesen, 2006) (here 38 million)

3) To maintain this 1/3:2/3 ratio 50% of those with subclinical disease must progress to overt disease (62.5% manifesting hydrocele [11.9 million] and 37.5%, lympehedema [7.1 million]) (Ottesen, 2006)

4) If treatment halts progression in only 50% of the subclinical cases (a conservative estimate [Shenoy et al., 2003]), 9.5 million people would have been protected from developing overt disease (6 million hydrocele; 3.5 million lymphedema)

5) Disability weights**: 0.105 for lymphedema, 0.073 for hydrocele; onset at age 20; life span, Region-specific

6) Treated individuals will not become re-infected in context of diminished LF transmission in MDA-covered areas

doi: 10.1371/journal.pntd.0000317.t002

TABLE A17-3 Projected Health Impact-Beyond LF

Impact #3	Individuals Reached	Target	Health Benefits
	56.6 million children *-minimal estimate-*	Soil-transmitted helminthes (intestinal parasites: hookworm, roundworm, whipworm)	Weight/height gain, learning ability, cognitive testing, school attendance, fitness, activity (Adams et al., 1994; Nokes et al., 1992; O'Lorcain and Holland, 2000; Stephenson et al., 1993)

Assumptions and Reasoning

1) 172 million treatments of albendazole given to children (age 2-15 in countries treated with DEC+albendazole; 5-15 in countries using ivermectin+albendazole) in 48 countries during MDAs 2000-2007 (WHO, 2005, 2006, 2007, 2008).

2) The maximal number of children treated *in any single MDA* was determined for each country. The sum of these numbers indicates the minimum total number of children treated (56.6 million) (WHO, 2005, 2006, 2007, 2008).

3) Uncertainty of STH prevalence estimates limits the specific quantification of health benefits despite their description in published studies (Adams et al., 1994; Nokes et al., 1992; O'Lorcain and Holland, Stephenson et al., 1993).

Impact #4	Individuals Reached	Target	Health Benefits
	44.5 million women of childbearing age (not pregnant) *-minimal estimate-*	Soil-transmitted helminthes (intestinal parasites: hookworm, roundworm, whipworm)	Decrease anemia (Crompton, 2000), maternal mortality, infant mortality; increased infant birth-weight (Christian et al., 2004)

Assumptions and Reasoning

1) 140 million treatments of albendazole given to non-pregnant women –of-childbearing-age (15-49 years old) in 48 countries during MDAs 2000-2007 (WHO, 2005, 2006, 2007, 2008; World Bank, 2005).

2) The maximal number of such women treated in any single MDA was determined for each country (WHO, 2005, 2006, 2007, 2008). The sum of these numbers indicates the minimum total number of women-of-childbearing-age treated (44.5 million).

3) Uncertainty of STH prevalence estimates limits the specific quantification of health benefits despite their description in published studies (Crompton, 2000; Stephenson et al., 1993; WHO, 1996).

continued

TABLE A17-3 Continued

Impact #5	Individuals Reached	Target	Health Benefits
	45 million people in Africa *-minimal estimate-*	Onchocerciasis, scabies, lice	Decreased physical, mental discomfort (severe itching) (Hengge et al., 2006); prevention of renal complications of streptococcacl superinfections (Lawrence et al., 2005)
	Assumptions and Reasoning		
	1) 149 million treatments of ivermectin given to communities in 12 African countries during MDAs 2000-2007 (WHO, 2005, 2006, 2007, 2008).		
	2) The maximal number of individuals treated in any single MDA was determined for each country. The sum of these numbers indicates the minimum total number of individuals treated (45 million) (WHO, 2005, 2006, 2007, 2008).		
	3) Uncertainty of prevalence estimates for each of these conditions limits the specific calculation of health benefits despite the descriptions reported in published studies (Boatin and Richards, 2006; Hengge et al., 2006; Remme, 2004).		

doi:10.1371/journal.pntd.0000317.t003.

Bureau, 2008) were applied to those populations living in areas targeted for LF treatments. Since LF transmission might not stop immediately after MDAs begin, changes observed in mosquito infection rates post MDA were used to estimate changes in LF transmission as progressively decreasing to 50%, 25%, 12%, 6%, and 0% of pre-MDA levels after each of the first 5 MDAs. These multipliers were used on a country-by-country and MDA-by-MDA basis to discount the number of surviving babies born into MDA areas, thereby allowing an estimate of the number of newborns protected from potential LF infection (66 million). Since LF infections are estimated to occur in approximately 10% of the at-risk population (Ottesen, 2006), 6.6 million newborn babies are therefore considered protected from contracting LF.

Cases of morbidity prevented in newborns. Globally, 12.5% of LF infections are estimated to result in lymphedema, 20.8% in hydrocele and the remainder, 66.7%, in subclinical disease (Ottesen, 2006). Cases of disease averted (hydrocele, lymphedema and subclinical) were calculated by multiplying these proportions by the number of LF infections averted in babies.

DALYs averted in newborns. The number of DALYs averted in newborns was calculated using methods outlined in Global Burden of Disease, utilizing

disability weights, the number of cases of clinical disease averted (hydrocele and lymphedema), an estimated onset of disease at age 20 and region-specific life spans (Lopez et al., 2006). Since disability weights are not available for subclinical LF disease, DALYs associated with this manifestation were not estimated.

For all of the calculations associated with the prevention of LF disease, it was assumed, based on available information, that treated individuals will not become re-infected in the context of diminished LF transmission in MDA-covered areas.

Infected individuals protected from progression of subclinical disease to clinical disease. For each country the number of individuals treated in each MDA is known, but since it is not known how many unique individuals have received treatment in a program with multiple MDAs, the conservative approach to identifying this number of unique individuals treated in any one country is to identify the maximal numbers of individuals treated in any single MDA for each country. These numbers were then summed for all countries and used as the minimum total number of individuals already treated (570 million). Since LF infections are estimated to occur in approximately 10% of the at-risk population (Ottesen, 2006), 57 million would be expected to be infected with LF. Approximately two-thirds of infected individuals have subclinical disease (Ottesen, 2006) (38 million), with 50% of those expected to progress to overt disease (19 million). Approximately 62.5% of individuals with overt disease manifest hydrocele (11.9 million) and 37.5% manifest lymphedema (7.1 million). If it is assumed that treatment halts disease progression in only 50% of subclinical cases (a conservative estimate (Shenoyet al., 2008), 9.5 million people would have been protected from developing overt disease (i.e., 6 million cases of hydrocele and 3.5 million cases of lymphedema averted).

DALYs averted through halting progression of disease. The number of DALYs averted through progression of disease was calculated using methods outlined in Global Burden of Disease, utilizing disability weights, the number of cases of clinical disease averted (hydrocele and lymphedema; calculated as described above), an estimated onset of disease at age 20 and region-specific life spans (Lopez et al., 2006).

Impact estimates: 'Beyond-LF' benefits. Because individual country estimates of the prevalence and distribution of soil transmitted helminthiases are generally not available, it was not possible to estimate directly the number of STH infections, either in children or women of child bearing age, that have been treated as a consequence of LF MDA activities. However, since it is widely accepted that the common STH infections are distributed throughout the pan-tropical belt where lymphatic filariasis is endemic (de Silva et al., 2003), we recognize that a proportion of the albendazole and ivermectin treatments delivered for LF will have had a beneficial impact for children and women of child bearing age who harbor in-

testinal helminth infections. The number of individual children less than 15 years of age treated with albendazole was estimated by multiplying demographic data (children under the age of 15 years, for each country (PRB, 2005-2006) by that country's total treatment figures, then summing the maximal number of children treated in any single MDA for each country between 2000 and 2007 (the conservative estimate of the number of unique individuals treated; see above). Since age is an exclusion criterion for LF treatment, the annual estimates thus derived were discounted depending on the therapeutic regimen applied as follows: in ivermectin and albendazole areas of Africa and the Yemen, data for children 5 to 15 years of age only are included, whereas for the rest of the world where DEC and albendazole are utilized, data for children 3 to 15 years of age are included.

Women between 15 and 49 years were considered to be of childbearing age, and the number of individuals treated in this age class was calculated by multiplying demographic data (PRB, 2005-2006) for each country by that country's total treatment figures, then summing the maximal number treated in any single MDA for each country between 2000 and 2007 (the conservative estimate of the number of unique individuals treated; see above). Since pregnancy is an exclusion criterion for LF treatment, the annual estimates thus derived were discounted by subtracting the estimated percent of the female population that is pregnant at any given time: the total fertility rate for each region was multiplied by a nine month gestational period and divided by 408 months (representing the estimated average number of reproductive months in a woman's lifetime).

Whilst the beneficial outcomes of treating STH infections in these population groups are listed, we do not attempt to quantify the accumulated health impact because of the uncertainty surrounding the prevalence estimates. The same rationale and argument adopted for soil transmitted helminth infections were applied when we considered the impact of ivermectin treatments on skin diseases of various etiology in Africa.

Results

Programmatic Achievements of the GPELF 2000–2007

1. The Global Programme. One hundred twenty million people are affected with LF – 40 million with limb or genital damage recognized as either lymphedema/elephantiasis (15 million) or hydrocele (25 million), and twice that number with subclinical disease principally of the lymphatics or kidneys (Ottesen, 2006). These 120 million people live in 83 endemic countries of the tropics and subtropics where 1.3 billion people (1/5 of the world's population) comprise the total population considered 'at risk' for infection through their exposure to LF's mosquito-borne infective larvae (Table A17-1) (WHO, 2005). More than a third of these are children (PRB, 2005-2006).

Little more than a decade ago it was established that single doses of a 2-drug

regimen (either albendazole+ivermectin or albendazole+DEC) can effectively eliminate microfilariae from the blood of infected individuals for periods often in excess of a year (Gyapong et al., 2005). Once understood, this drug effectiveness permitted development of a strategy for LF elimination based on treating entire at-risk populations yearly with one of these two safe, effective 2-drug regimens in order to reduce microfilaremia (MF) below a 'transmission threshold' where future recrudescence would be unlikely even after population treatment was halted. From estimates of the life span of the adult parasites (Wuchereria bancrofti or Brugia malayi), from projections of the levels of 'drug coverage' that must be achieved in the targeted populations and from earlier experiences in countries targeting LF elimination, the average number of rounds of effectively conducted, yearly 'mass drug administrations' (MDAs) necessary to achieve success for national programs was estimated to be 4–6 (Ottesen et al., 1997). Recent experience from both program observations and specific research studies is consistent with this notion that in most instances between 2 and 6 rounds of effective MDA are able to clear microfilaremia (see below for sentinel site data). There are, however, specific situations where more than 6 rounds might be required, since the number of MDAs necessary appears to depend principally on the pre-treatment microfilaremia levels, programmatic drug 'coverage' and local vector parasite complex (Kyelem, 2008).

2. Treatments delivered. Since its official inauguration in 2000 the GPELF has seen the most rapid expansion of any drug delivery program in public health history; by the end of 2007 more than 1.9 billion treatments for LF had been delivered (WHO, 2008), almost *L* by the program in India (initially a program based on DEC alone; more recently, on albendazole+DEC) with the remainder distributed in the 47 other countries with active MDA programs (Figure A17-1). The amount of drug donated to support this Programme has been extraordinary: more than 740 million tablets of albendazole and more than 590 million tablets of ivermectin were provided between 2000–2007 by the Global Programme's partners in the pharmaceutical industry. The amount of the non-donated drug (DEC) that had to be purchased during this same period by countries that utilize DEC instead of ivermectin (which is used for LF only in Africa (Ottesen, 2006) was more than 4.7 billion tablets (Figures A17-2A and A17-2B).

3. Programme effectiveness in decreasing LF prevalence. The effectiveness of GPELF's strategy to reduce the prevalence of microfilaremia in an endemic population to levels below that believed necessary to sustain the parasite's life cycle has been substantiated by research teams in well-controlled, large-scale initiatives (e.g. in Egypt (Ramzy et al., 2006) and Papua New Guinea (Bockarie et al., 2002)). In addition, assessment of programmatically collected data available to WHO from another 20 countries shows similar progressive declines in mf prevalence in treated communities (Figure A17-3), with greater than 10-fold

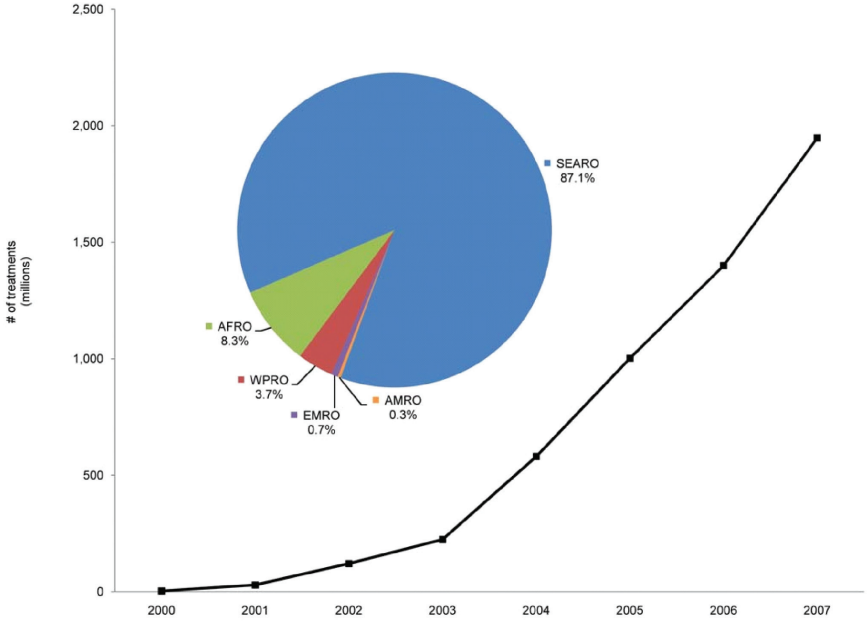

FIGURE A17-1 Cumulative treatments in GPELF. Progressive increase in number of treatments given through 2007; distribution by WHO region is depicted in pie-chart. doi:10.1371/journal.pntd.0000317.g001.

reduction in mf-prevalence levels seen in sentinel-site communities that have received 6 rounds of MDA and total clearance of mf (by inference, interruption of LF transmission) recorded in almost 2/3 of the communities after 5 MDA rounds (Figure A17-4).

Health Impact of the GPELF 2000–2007

As impressive as the record is for the number of treatments given, the number of albendazole and ivermectin tablets donated, the amount of DEC purchased, and the number of communities cleared of microfilaremia during the first 8 years of this Global Programme, still the most important Programme outcome is the overall health benefit that the GPELF has brought to populations at-risk for LF. This benefit must derive from projections based on the best data and most reasonable assumptions available (see below and Tables A17-2 & A17-3 for the assumptions and implications).

There are two principal sources of this health benefit:

1) LF-related benefits – i.e., those coming directly from the effects of the MDAs in preventing the acquisition of lymphatic filarial disease or in arresting its progression
2) 'Beyond-LF' benefits – i.e., those coming from ancillary benefits of the highly effective, broad-spectrum anti-parasitic drugs, albendazole and ivermectin, used in the Programme.

1. Projected health impact that is LF-related.

Protecting newborns from LF infection and disease. Since MDAs, by decreasing and then stopping LF transmission, will prevent uninfected individuals from becoming infected, the clearest measure of the Programme's long-term health impact is the amount of disease prevented over the lifetime of babies born into areas where their likelihood of acquiring infection has become much diminished or nil. To determine this impact requires an understanding of the number of babies born (and surviving) in areas covered by LF MDAs, the number who would have acquired infection (and disease) in the absence of GPELF, the 'disability weights' for different manifestations of LF disease and the rate at which

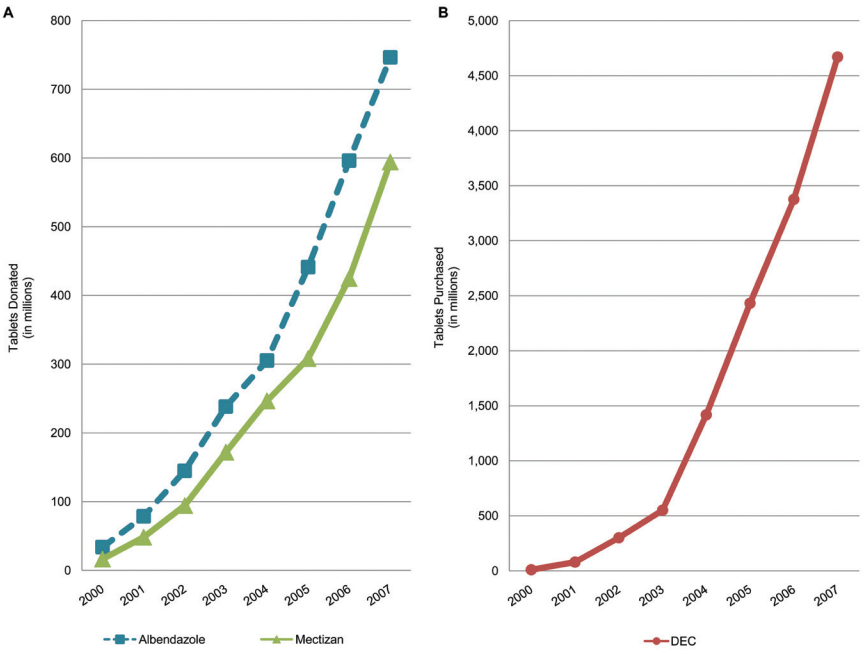

FIGURE A17-2 Cumulative totals of donated drugs (Panel A), albendazole and ivermectin (Mectizan), and purchased drug (Panel B) DEC, used in GPELF between 2000 and 2007. doi:10.1371/journal.pntd.0000317.g002.

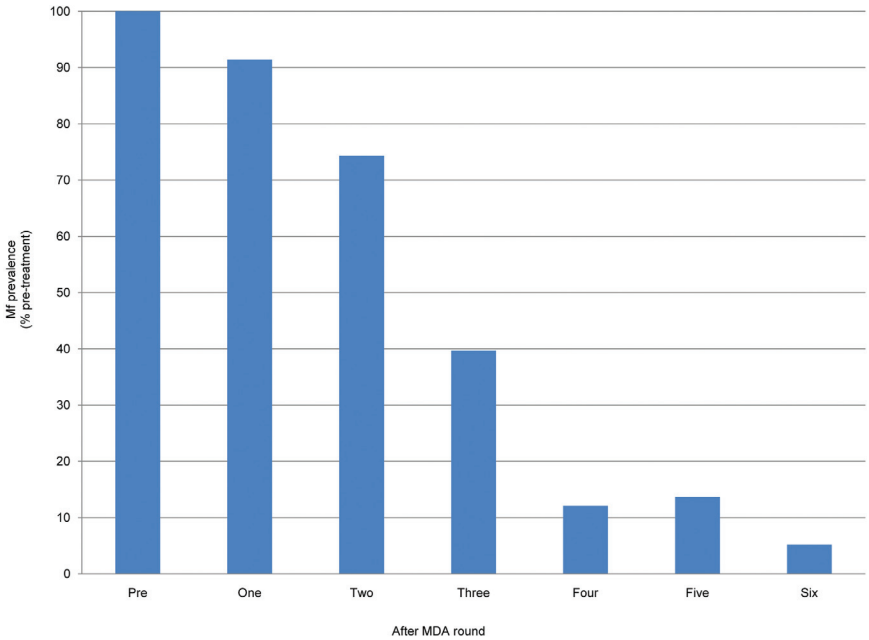

FIGURE A17-3 Effect of MDA on microfilaremia prevalence. Individuals in all of the sentinel sites (approximately 500 persons per site) reporting to the Global Programme were evaluated for microfilaremia. Progressive decline in prevalence among these individuals was recorded during yearly assessments (n = 131 sentinel sites for year 1; n = 124 for year 2; n = 139 for year 3; n = 148 for year 4; n = 68 for year 5; and n = 12 for year 6). doi:10.1371/journal.pntd.0000317.g003.

exposure to LF infection declines in treated populations. When these variables were assessed [see Discussion and Table A17-2 for fuller description], the following conclusions could be made:

- **Impact #1 - Prevention of LF infection (and disease):** Between 2000–2007, 6.6 million newborns (the fraction of all newborns who would have been expected to acquire LF) were protected by GPELF – thereby averting in their lifetimes nearly 1.4 million cases of hydrocele, more than 800,000 cases of lymphedema and 4.4 million cases of subclinical disease (Table A17-2).
  - Because of this disease prevention, 6.0 million Disability Adjusted Life Years (DALYs) have been averted (3.2 million from prevention of hydrocele and 2.8 million from prevention of lymphedema [Table A17-2]).

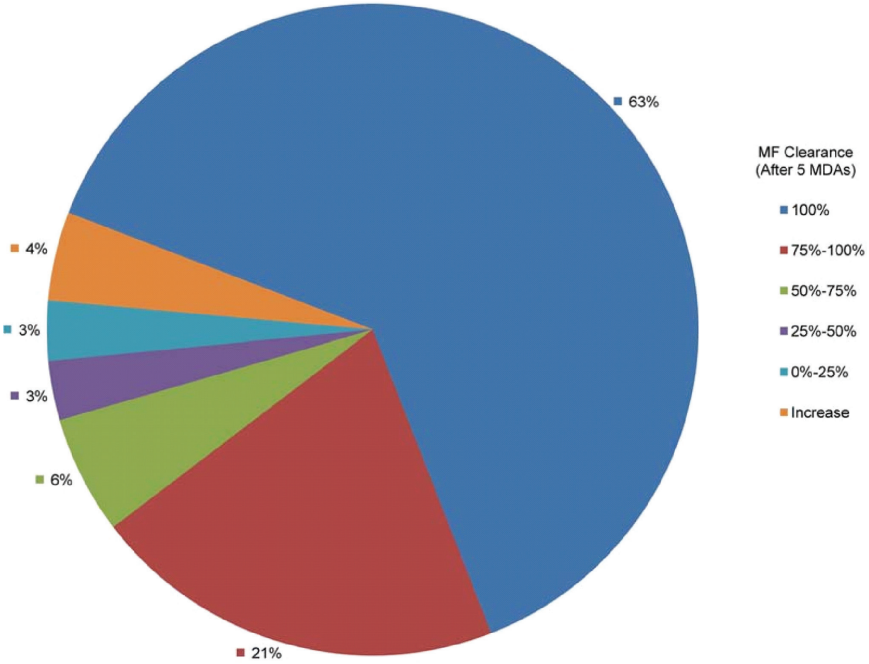

FIGURE A17-4 Clearance of microfilaremia from each sentinel site (approximately 500 persons per site) reporting to the Global Programme after 5 rounds of MDA treatment (n = 68). doi:10.1371/journal.pntd.0000317.g004.

Preventing the progression to overt disease in LF-endemic populations. With evidence now available that the MDA treatment regimens for LF can halt, or even reverse, the progression of subclinical to overt disease (Dreyer et al., 1992, 2001; Shenoy et al., 2008), it is clear that those already infected but having no overt disease also benefit directly from the yearly MDAs. To quantify this benefit requires understanding the number of individuals treated during the MDAs, the proportion of these individuals with subclinical LF disease, the number who would have progressed to each of the manifestations of LF disease and the 'disability weights' for each of these manifestations. When all of these were considered (see Discussion and Table A17-2), the following could be recognized:

- **Impact #2 - Prevention of LF disease:** Between 2000–2007, 9.5 million individuals – previously infected but without overt manifestations of disease – were protected by GPELF from developing hydrocele (6.0 million) or lymphedema 3.5 million).
  - This disease prevention translates into 26 million DALYs averted (14

million from hydrocele prevention and 12 million from lymphedema prevention).

2. Projected health impact from 'Beyond-LF' benefits. Preventing the consequences of intestinal parasite infections. The best drugs to control intestinal parasites (i.e., 'soil-transmitted helminths' [STH]: hookworm, roundworm and whipworm) are the same drugs (albendazole and ivermectin) used to eliminate LF (Gyapong et al., 2005; Ottesen, 2006). Though Mectizan (ivermectin) has formal regulatory approval only for lymphatic filariasis and onchocerciasis and is donated by Merck & Co., Inc. only for those indications, each year millions of children and women-of-childbearing-age are concomitantly treated for debilitating intestinal parasite infections (without additional cost or effort) while participating in their national programs to eliminate LF. To identify the impact of such treatment requires estimation of the number of children and the number of women-of-childbearing-age who received albendazole (with or without ivermectin) in all GPELF countries. Thus,

- **Impact #3 - 'Beyond-LF' benefit for children with intestinal parasites:** Between 2000–2007, more than 172 million treatments for intestinal parasite infections were given to 56.6 million children by GPELF (Table A17-3)
  - Based on earlier research studies, each infected child receiving treatment would be expected to develop increased appetite [26] (leading, in some settings, to 1 kg of extra weight gain and 0.6 cm extra growth in the first 5 months) (Stephenson et al., 1993); greater eye-hand coordination, learning ability and concentration (O'Lorcain and Holland, 2000); better school attendance, cognitive testing (20% improvement) (Noakes et al., 1992), fitness scores and spontaneous play activity (43% increase) (Adams et al., 1994; Stephenson et al., 1993).

- **Impact #4 - 'Beyond-LF' benefit for women-of-childbearing-age with intestinal parasites:** Between 2000–2007 more than 140 million treatments for STH were given to million women-of-childbearing age by GPELF (Table A17-3).
  - Repeated treatment of hookworm and other intestinal parasites improves both nutritional status and, most importantly, iron stores in women during their reproductive years (Christian et al., 2004; Crompton, 2000). Prior studies predict that such treatment can lead to an increase in infant birth-weights by more than 50 grams and a drop in infant mortality by as much as 40% (Christian et al., 2004). Maternal mortality should also decrease significantly in women receiving GPELF treatments, since iron deficiency anemia is a prominent cause of maternal mortality (WHO, 1996).

Prevention of debilitating skin diseases. Onchocerciasis, scabies, and pediculosis (lice) are all diseases of the skin caused by parasites common in resource poor communities and associated with appreciable mental and physical disability in affected populations. Ivermectin, one of the two drugs co-administered by the GPELF in Africa, is the best oral treatment for all of these debilitating skin diseases (Hengge et al., 2006; Heukelbach et al., 2004; Remme, 2004); it is also the mainstay drug for onchocerciasis control programs in Africa (Boatin and Richards, 2006). To gauge the GPELF impact on skin diseases it is necessary first to understand the number of individuals receiving ivermectin through GPELF activities in Africa. Thus,

- **Impact #5 - 'Beyond-LF' benefit for people with skin diseases in Africa:** Between 2000–2007, over 149 million treatments with ivermectin were administered by GPELF or APOC (African Programme for Onchocerciasis Control) to more than 45 million people in African communities (Table A17-3) where the prevalence of scabies skin infection may exceed 30% and the prevalence of onchocerciasis even more.
  - Ivermectin's long lasting impact on scabies can cause community prevalence to fall dramatically after 1 cycle of treatment and to disappear almost completely after 2 or more treatments (Heukelbach et al., 2004). Cured individuals show improvements in sleep patterns and overall wellbeing, but also importantly, treatment of scabies in childhood can prevent the post-streptococcal renal disease induced by group B streptococcus skin infections that often complicate chronic scabies infection (Lawrence et al., 2005).
  - Because of its broad geographic range, the GPELF has brought ivermectin treatment to additional millions of people living in onchocerciasis-endemic areas not previously targeted by onchocerciasis control programs (as these programs focus only on communities where the prevalence of onchocerciasis exceeds 40%) (Boatin and Richards, 2006).

Discussion

Since WHO's Global Programme to Eliminate Lymphatic Filariasis was officially launched in 2000, its programmatic achievements [recorded here through 2007] are unparalleled (Box A17-1): 1.9 billion treatments delivered through yearly MDAs to over 570 million people in 48 endemic countries. These accomplishments were made possible by the enormous drug donations of albendazole (over 740 million tablets from GlaxoSmithKline through 2007) and ivermectin (over 590 million tablets of Mectizan from Merck & Co., Inc.), by the willingness of National Programs to procure 4.7 billion tablets of DEC, and by the early sup-

BOX A17-1
The Global Programme to Eliminate LF—Its First 8 Years

Reach	Nearly 2 billion treatments delivered to more than 560 million people in 48 countries.
Dissemination	More than 50% of endemic countries actively involved in annual MDA programmes.
Child Protection	Nearly 176 million children already treated for LF, and over 66 million babies born into areas now protected by MDA.
Public Health Impact on LF	More than 6 million cases of hydrocele and 4 million cases of lymphoedema prevented, translating into more than 32 million DALYs averted.
Additional Health Benefits	More than 310 million treatments of albendazole delivered to women of child-bearing age and school-age children, providing sustained relief from the negative consequences of soil-transmitted helminth (STH) infections that include maternal anemia, low birth weight newborns, excess infant mortality, inhibited growth and development, diminished intellectual performance. Almost 150 million treatments of ivermectin delivered to African communities, providing sustained relief from onchocercal skin disease, scabies, lice and important STH infections.

port from numerous other organizations – most significantly the Bill and Melinda Gates Foundation, the Arab Fund for Economic and Social Development, the international development agencies of Japan and the United Kingdom and the Ministries of Health of endemic countries.

Though it is without question that this Programme has had a very great impact on global health, quantifying this impact still poses difficult challenges. Principally this is because all projections must be made not just from the numbers of people treated but also from the more-difficult-to-quantify effects of such treatment. Assumptions derived from current best understanding must be linked with the available data to formulate the health impact projections, and while making such assumptions is never entirely satisfactory, the present analysis does endeavor to identify clearly both the assumptions themselves and the sources of the data

used to generate the projections; it also has chosen to err on the conservative side in most estimations.

For the GPELF, health benefits lie in two domains: one related to the Programme's effects on lymphatic filarial disease and its consequences, and the other related to the outcome of treating LF-endemic populations with one or both of the very safe, broad-spectrum anti-parasitic drugs used by the Programme, albendazole and ivermectin.

LF-related impact

To gauge the LF-related impact, this analysis has considered quantitatively only what has been accomplished by: 1) preventing infection in those born into areas where GPELF is active and 2) stopping the progression to clinical disease in previously infected individuals whose disease has not yet expressed itself overtly.

1) To identify the amount of infection prevented, the number of babies born in areas under LF MDAs between 2000–2007 who survived infancy was first determined, by country (PRB, 2005-2006; World Bank, 2005). Estimation of how many of these newborns would have acquired LF during their lives and what manifestations they would have developed was based on the global prevalence figures available for LF and its clinical manifestations (Table A17-2) (Ottesen, 2006). Calculation of the DALYs attributable to that amount of disease during the lifetimes of those newborns assumed that clinical expression of disease (hydrocele and lymphedema) had its onset at an average age of 20 years and persisted throughout the life of the individual.

Since the risk of exposure of these infants to LF depends on the level of local transmission, it is necessary to estimate the rate of decline of transmission (here using vector infection in mosquitoes as a surrogate for transmission) as MDA programs progress. While programmatic evidence exists that effective transmission of LF might cease very soon after the initiation of MDA activities (Bockarie et al., 2002; Ramzy et al., 2006; Schlemper et al., 2000), entomologic studies linked with anti-filarial single-dose treatment regimens indicate that the decline in vector infection may be more gradual (Bockarie et al., 2000, 2002; Das et al., 2001; Grady et al., 2007; Kimura et al., 1992; Ramzy et al., 2006; Richards et al., 2005). Since the availability of such data is too limited (with respect to vector species, collection techniques, parasite assessments, LF prevalence, treatment regimens, and other variables) to give precise estimates of post-MDA changes in vector infection, data from available studies (Bockarie et al., 2000, 2002; Das et al., 2001; Grady et al., 2007; Kimura et al., 1992; Ramzy et al., 2006; Richards et al., 2005) were pooled, yielding a relationship that describes an 'average' rate-of-decline of vector infection; namely, declines to 50%, 25%, 12%, 6% and 0% of pre-treatment levels following each of the first 5 MDAs, respectively. (As these numbers were empirically defined, they already incorporate the influence of population 'coverage' on MDA effectiveness.) This information was then used

to estimate the effect that each MDA had for each treated population in each country in order to approximate the exposure to LF in infants born after initiation of GPELF activities.

2) Stopping the progression of subclinical to clinical disease in those already infected contributes appreciably to the calculations of LF-related health benefits from GPELF (Table A17-2). Evidence for such effectiveness of MDA regimens in halting disease progression is relatively recent and has focused particularly on children with subclinical or early-stage lymphatic disease (Dreyer et al., 2001; Shenoy et al., 2008). Because these effects are just now being studied comprehensively, and in order to be conservative in estimating GPELF's health impact, the present calculations are based on the conservative assumption (Shenoy et al., 2008) that the MDA programs would arrest subclinical disease progression in only 50% of the affected individuals (Table A17-2).

Though one cannot be completely certain of all of the calculations in Table A17-2, it is still hard to escape the conclusion that these values for GPELF's LF-related health impact are almost certainly gross underestimates – for at least 2 reasons. First, not considered at all in the assessments of GPELF's LF-prevention benefits are those related to any of the manifestations of LF disease other than hydrocele and lymphedema. Among those omitted, quantitatively most important would be the Programme's impact on subclinical LF disease (Dreyer et al., 1992; Dreyer et al., 2001; Chhotray et al., 2000) – especially microfilaremia, hematuria, lymphatic dilatation and lymphatic dysfunction – which affect a very large percentage of those with LF infection (Ottesen, 2006) but for which there are no 'disability weights' available for calculating DALYs or DALYs averted. Also overlooked are other extremely important, often debilitating overt clinical manifestations of infection – especially, the very common, recurrent acute adenolymphangitis episodes (ADL) and the progressive, crippling pulmonary disease, tropical pulmonary eosinophilia (TPE) (Ottesen, 2006). Excluding all of these important consequences of LF infection from the calculations of GPELF's health impact from preventing LF ensures that these calculations will significantly underestimate the Programme's impact.

Second, none of these quantitative calculations of GPELF's LF-related health impact has taken into consideration the direct effect that this Programme has had on arresting progression or ameliorating clinical disease of affected individuals. In addition to its delivery of essential anti-filarial drugs, the GPELF is also a program that advocates and initiates 'morbidity management' activities based on vigorous personal hygiene management of lymphedema or elephantiasis (WHO, 2004). Dramatic improvement in both physical state and mental attitude occurs in patients following the hygiene guidelines (Dreyer et al., 2002; WHO, 2004), but none of the health impact of this component of the GPELF has been quantified or captured in the calculations of Table A17-2. Similarly uncaptured is the potential direct improvement in both lymphedema and hydrocele now being reported by

patients following MDA treatment alone (i.e., even in the absence of hygiene management) (Bockarie et al., 2002).

'Beyond-LF' Health Impact

If the LF-related health impact of GPELF seems difficult to quantify, the 'beyond-LF' impact presents an even greater challenge. A major reason is that many of the 'beyond LF' benefits come from the impact that the GPELF drugs have on soil transmitted helminth (STH) infections in the treated populations. The quantitative epidemiology of these infections remains poorly characterized, albeit for good reasons: not only are STH infections caused by three distinct parasites (hookworm, roundworm and whipworm), but these three infections also occur in unequal proportions in different endemic regions and cause different diseases with varying severity and health consequences. Further, while the geographic overlap of STH infections with the LF at-risk areas is felt to be almost universal (Brady et al., 2006), it is rarely known which STH infections occur or with what abundance in which areas. Thus, while general estimates of overall STH prevalence can be approximated for areas where GPELF is active, the data itself is not certain enough to be used quantitatively to project GPELF's health impact from treating STH infections.

Despite such limitations, a number of very important studies have been carried out to document and measure the health consequences of STH infections – usually by monitoring changes in outcome indicators following treatment with albendazole or other drugs. These have shown, for example, that

1) Soil transmitted helminth infections exact a severe toll on the nutritional status and growth of infected children, but intervention with albendazole and ivermectin can make an extraordinary difference in their physical development, with spectacular gains in growth parameters quantified in a number of important studies (Crompton, 2000; O'Lorcain and Holland, 2000; Stephenson et al., 1993; Stephenson et al., 2000; Stolzfus et al., 1998).
2) Lethargy and lack of physical stamina often characterize children infected with intestinal worms, but within weeks of treatment significant increases can be found in physical activity and spontaneous play. Resting heart rates, physical fitness on the Harvard step test, and measurements of spontaneous play behavior all improved in children from Kenya and Indonesia after being treated for intestinal worms (Adams et al., 1994; O'Lorcain and Holland, 2000; Stephenson et al., 1993; Stoltzfus et al., 1998).
3) Children infected with intestinal worms are frequently seen to miss many more school days than their uninfected peers, as documented in Jamaica where children with intense Trichuris infections missed twice as many school days as their infection-free peers (Nokes and Bundy, 1993). Treat-

ment leads to significant reduction in school absenteeism; a 25% reduction was recorded in Kenya following school-based treatment for STH (Miguel and Kremer, 2004).

4) Children infected with intestinal worms perform poorly in learning ability tests, cognitive function and educational achievement, but treating school age children increases their ability to learn, as documented by improvement in children's short and long term memory, executive function language, problem solving and attention (Watkins and Pollit, 1997).

These STH infections that are treated by the GPELF MDAs are not just important for children. While their effect on the health and productivity of men remains poorly defined, in women-of-childbearing-age hookworm infection is recognized as a major cause of anemia, and this anemia significantly affects both maternal and newborn morbidity and mortality. Indeed,

1) WHO estimates that women in developing countries may be pregnant for half their reproductive lives and are at an increased risk of anemia during this time (WHO, 1996).
2) Anemia in pregnancy has been clearly associated with poor birth outcome, including low birth-weight (Allen, 2000; Rasmussen, 2001; Scholl and Reilly, 2000; Steer, 2000) and increased maternal morbidity and mortality (Guidotti, 2000; McDermott et al., 1996; WHO, 1996).
3) Hookworm-attributable anemia, induced by deficiencies in iron, protein and total energy, is a significant cause of intrauterine growth retardation and low birth weight (Stephenson et al., 2000). It might even exacerbate the sometimes fatal effects of malaria infection in infants and young children.
4) Treating STH infections in women-of-child-bearing-age improves both maternal health status and the status of infants born to infection-free mothers; therefore, WHO recommends that anthelminthic treatment be included in strategies to improve maternal nutrition wherever hookworm infection and anemia are prevalent (WHO, 1996). (GPELF, however, currently restricts its treatment to women who are not pregnant.)

In addition to its effect on certain of the STH infections, ivermectin – as GPELF's second drug with broad-spectrum antiparasite activity – is unsurpassed for the oral treatment of both onchocerciasis (Boatin and Richards, 2006) and ectoparasites (scabies and lice) (Heukelbach et al., 2004). While ivermectin has been the mainstay of onchocerciasis control programs for the past 2 decades, the control programs in Africa (where 99% of the onchocerciasis is found) have as their principal target only communities designated hyper- or meso-endemic (i.e., prevalence $40%), so that many communities endemic for onchocerciasis were left untreated until GPELF was initiated (Boatin and Richards, 2006). Since LF is

distributed very much more widely than onchocerciasis, and since almost all regions of Africa where onchocerciasis is endemic are also 'at risk' for LF, GPELF activity in those areas has resulted in the treatment of millions of additional individuals in these onchocerciasis-endemic areas who were not covered under the older control programs. These individuals are generally not those with blinding onchocerciasis but with severe onchocercal skin disease (OSD) and ''troublesome itching''; the burden of illness from this OSD, quantified in DALYS lost, is recognized as essentially equivalent to that estimated for onchocercal ocular disease and blindness (Remme, 2004). GPELF's impact on improving OSD is not yet quantified, but it can be defined once the number of individuals with onchocerciasis who live in the expanded treatment areas is more well understood (Boatin and Richards, 2006). On the other hand, for the very important skin diseases caused by scabies and lice, the significant health benefits that GPELF brings through its use of ivermectin in affected populations will be much more difficult to quantify, since so much less is known about the epidemiology of these widespread ectoparasite diseases, and no burden-of-illness estimates have yet been established (Hengge et al., 2006).

The Global Programme to Eliminate LF is not a static program; indeed, its reach continues to expand each year. In 2008 it is projected that .500 million people will be treated in that year alone. The effect on the calculated health benefits of the Programme that these progressively increasing numbers will have each year is enormous, since the number of protected children and cases of disease prevented will increase rapidly as new cohorts of treated individuals are added each year; in addition, of course, all of those benefits not currently quantified (both LF-related and beyond-LF effects) will continue to multiply as well.

Already the GPELF has been described as a 'best buy' in global health, and the present tally of health benefits only strengthens this contention. Even during its first 8 years, almost 2 billion MDA treatments have been given and 32 million DALYs-averted have been identified by considering (conservatively) just 2 of the 5 specific impacts attributable to the Programme Tables A17-2 & A17-3). Considering only these DALYs and estimating treatment costs at $0.10/person (a 'high' estimate given the fact that the preponderance of treatments were in countries where costs have been identified as being much lower [Ramaiah and Das, 2004]) suggests that, excluding the donated drug costs, $190 million will have been spent to effect the 1.9 billion treatments. If the 32 million averted DALYs were the only benefits achieved, each DALY averted by the Programme would have cost $5.90. This cost is extremely low compared to DALY averted costs of other programs (Laxminarayan et al., 2006), but even it is a gross overestimate of the true cost of DALYs-averted by GPELF activities, since so much of the Programme's benefit (Tables A17-2 & A17-3) remain unquantified and not included in this calculation. As this LF Elimination Programme continues to expand, its benefits will continue to accrue; as our ability to quantify these benefits improves, the Programme's true value will become progressively still more impressive.

Supporting Information

Alternative Language Abstract S1 Translation of the Abstract into French by P. J. Hooper
Found at: doi:10.1371/journal.pntd.0000317.s001 (0.06 MB PDF)

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Author Contributions

Conceived and designed the experiments: EAO PJH MB GB. Performed the experiments: EAO PJH MB GB. Analyzed the data: EAO PJH MB GB. Wrote the paper: EAO PJH MB GB.

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A18

THE ECONOMIC BENEFITS RESULTING FROM THE FIRST 8 YEARS OF THE GLOBAL PROGRAMME TO ELIMINATE LYMPHATIC FILARIASIS (2000–2007)[37,38]

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Abstract

Background: **Between 2000–2007, the Global Programme to Eliminate Lymphatic Filariasis (GPELF) delivered more than 1.9 billion treatments to nearly 600 million individuals via annual mass drug administration (MDA) of anti-filarial drugs (albendazole, ivermectin, diethylcarbamazine) to all at-risk for 4–6 years. Quantifying the resulting economic benefits of this significant achievement is important not only to justify the resources invested in the GPELF but also to more fully understand the Programme's overall impact on some of the poorest endemic populations.**

Methodology: **To calculate the economic benefits, the number of clinical manifestations averted was first quantified and the savings associated with this disease prevention then analyzed in the context of direct treatment costs, indirect costs of lost-labor, and costs to the health system to care for affected individuals. Multiple data sources were reviewed, including published lit-**

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erature and databases from the World Health Organization, International Monetary Fund, and International Labour Organization.

Principal Findings: **An estimated US$21.8 billion of direct economic benefits will be gained over the lifetime of 31.4 million individuals treated during the first 8 years of the GPELF. Of this total, over US$2.3 billion is realized by the protection of nearly 3 million newborns and other individuals from acquiring lymphatic filariasis as a result of their being born into areas freed of LF transmission. Similarly, more than 28 million individuals already infected with LF benefit from GPELF's halting the progression of their disease, which results in an associated lifetime economic benefit of approximately US$19.5 billion. In addition to these economic benefits to at risk individuals, decreased patient services associated with reduced LF morbidity saves the health systems of endemic countries approximately US$2.2 billion.**

Conclusions/Significance: **MDA for LF offers significant economic benefits. Moreover, with favorable program implementation costs (largely a result of the sustained commitments of donated drugs from the pharmaceutical industry) it is clear that the economic rate of return of the GPELF is extremely high and that this Programme continues to prove itself an excellent investment in global health.**

Author Summary

Lymphatic filariasis (LF), commonly known as 'elephantiasis', is one of the world's most debilitating infectious diseases. In 83 countries worldwide, more than 1.3 billion people are at risk of infection with an estimated 120 million individuals already infected. A recent publication reviewing the health impact of the first 8 years of the Global Programme to Eliminate Lymphatic Filariasis (GPELF) demonstrated the enormous health benefits achieved in populations receiving annual mass drug administration (MDA), as a result of infection prevented, disease progression halted, and ancillary treatment of coinfections. To date, however, no studies have estimated the economic value of these health benefits, either to the individuals or the societies afflicted with LF. Our study estimates that US$21.8 billion will be gained among individuals benefitting from just the first 8 years of the Global Programme, and an additional US$2.2 billion will be saved by the health systems of endemic countries. Treating endemic populations is possible at very low cost – particularly because of the generous drug donations from two pharmaceutical companies – but results in enormous economic benefits. Findings from this study yield a much clearer understanding the GPELF's full economic impact and strengthen the conviction that it is a 'best buy' in global health.

Introduction

As a leading cause of permanent and long-term disability worldwide, the parasitic infection lymphatic filariasis (LF) imposes a severe physical and socioeconomic burden on 1.3 billion at-risk persons in 83 endemic countries. An estimated 120 million people are already infected with LF, with about 40 million suffering from overt clinical disease manifested as painful severe swelling due to lymphedema (generally an accumulation of lymphatic fluid in the limbs) and hydrocele (fluid accumulation in the scrotal sac). To rid the world of this debilitating disease, the Global Programme to Eliminate Lymphatic Filariasis (GPELF) was begun in 2000 to guide endemic countries in implementing single-dose, once-yearly mass drug administration (MDA) using a combination of either albendazole+ ivermectin or albendazole + diethylcarbamazine (DEC) for an anticipated 4–6 years. Use of this effective strategy for LF elimination has become feasible because of the drug donations of albendazole and ivermectin from their pharmaceutical manufacturers, GlaxoSmithKline and Merck & Co., Inc, respectively.

Over the first 8 operational years of the GPELF (2000–2007), more than 1.9 billion MDA treatments were administered to approximately 570 million individuals in 48 countries. This significant programmatic achievement has resulted in a notably beneficial impact on the health of endemic populations (Ottesen et al., 2008). More than 6 million cases of hydrocele and 4 million cases of lymphedema have been prevented, resulting in over 32 million disability-adjusted life years (DALYs) averted and numerous quality-of-life benefits attained.

What remains relatively undefined, however, is the economic significance of these achievements. Specifically, how much financial cost and loss of income is prevented over the lifetimes of individuals protected from LF due to the first 8 years of the GPELF? And, what cost savings do national health systems realize from the reduction in LF infection and morbidity?

To date, few attempts have been made to examine LF from an economic perspective, particularly on a global level. Such data, however, is invaluable to policymakers, public health administrators, and program funders who may already be convinced that LF is a ‘best buy’ in global health but who lack precise estimates to support their conviction. This study offers such an economic analysis and estimates that following the first 8 years of the GPELF, US$21.8 billion of economic benefits will be gained by LF infected and non-infected individuals in MDA treated areas, in addition to US$2.2 billion in health systems savings. Furthermore, though this economic assessment has not included the value of the many ancillary benefits on other concurrent infections that are effectively treated by the anti-LF drug regimens, it still leads to a far better understanding of the GPELF’s true overall impact on one of society’s most debilitating and widespread tropical diseases.

Methods

Data Sources

Key data sources are listed below, though specific sources are cited throughout the paper:

1) *LF at-risk, infected, and treated population estimates* are taken from The World Health Organization's *Weekly Epidemiological Record* and WHO Annual Reports between 2000–2008 (WHO, 2002, 2003a, 2004, 2005, 2006a, 2007, 2008).
2) *Health impact estimates* are taken from *The Global Programme to Eliminate Lymphatic Filariasis: Health Impact after 8 Years* (Ottesen et al., 2008).
3) *Direct treatment costs* are based on published literature (cited as presented) in relation to medicine prices gathered from Health Action International and Management Sciences for Health (Health Action International, 2008; Management Sciences for Health, 2008).
4) *Indirect loss of labor estimates* are based on published literature as cited.
5) *Wage and income estimates* come from the International Labour Organization's *LABORSTA* database (International Labor Organization LABORSTA), the World Bank's *World Development Indicators Online* (World Bank), and minimum wage estimates from the International Labour Organization (International Labor Organization Minimum Wage Database) and the US Department of State's *Country Reports on Human Rights Practices 2008* (U.S. Department of State, 2008).
6) *Official currency exchange and inflation rates* are from the International Monetary Fund's *World Economic Outlook 2008* database (International Monetary Fund, 2008).

Population Groups Analyzed for Economic Benefits from the GPELF – the "Benefit Cohort Population"

For this analysis, two broad groups of individuals are recognized as economically benefitting from the MDA treatment given during the first 8 years of the GPELF:

- Those protected from acquiring infection (and subsequent disease [specifically, hydrocele and/or lymphedema]);
- Those already infected but protected from disease progression.

These two groups can be segmented into four sub-populations (detailed below and summarized in **Table A18-1**); together, they constitute the *"benefit cohort population"*.

TABLE A18-1 Sub Populations of the "Benefit Cohort Population"

Population Group	Subgroup	Definition
1. Individuals protected from acquiring infection (and subsequent disease)	a. Newborns	Babies born into MDA treated areas and whose entire lives are protected from potential LF infection and morbidity
	b. Other individuals protected from infection	Individuals who would have acquired infection but are protected because of interrupted transmission of LF resulting from MDA
2. Individuals infected with LF but protected from progression of the disease	a. Subclinical disease	Patients with subclinical infection at the time of MDA who are protected from progression to clinical disease as a result of MDA
	b. Clinical disease	Individuals with clinical disease at the time of MDA who are either protected from worsening of their disease or actually undergo improvement as a result of MDA

Population estimates for each sub-population were calculated using the same base figures and key assumptions as described previously (Ottesen et al., 2008); namely that 10% of the at-risk population is actually infected with LF, that this ratio would remain constant in the absence of MDA, and that the relative frequency of the clinical disease syndromes will also remain stable among those infected individuals.

Individuals protected from acquiring infection (and subsequent LF disease).

- **Newborns in MDA treated areas who are protected from infection over their lifetimes:** The number of babies born into LF treatment areas who likely would have become infected in the absence of MDA was calculated for *each country* covered by the GPELF between 2000–2007 based on the rates of surviving newborns, the levels of infection in at-riskpopulations, and the decreases in post-MDA infection exposure rates (Ottesen et al., 2008; Ottesen, 2006). These calculations resulted in the number of protected newborns being 6.6 million.

  Of all these babies who were protected from LF infection, an estimated 12.5% would have progressed to lymphedema and 20.8% to hydrocele; the remaining 66.7% would have had subclinical disease (Ottesen et al., 2008). *For this study, it is assumed that only individuals with clinical*

disease (lymphedema or hydrocele) would have incurred any economic burden. As previously published, an estimated 1.4 million cases of hydrocele and 0.8 million cases of lymphedema would have been averted in newborns between 2000–2007 in MDA treated areas (Ottesen et al., 2008).

- **Other individuals protected by MDA from acquiring LF infection:** In the absence of MDA, approximately 10% of the at-risk population is infected with LF (Ottesen et al., 2008). To maintain this steady-state proportion in a *dynamic* population, non-infected individuals must continue to acquire infection through LF transmission at a rate sufficient to 'replace' those who leave the population (i.e. through death) each year. The size of this benefit population group is therefore equal to the number of infected patient deaths in the year; this total was calculated by multiplying the number of infected individuals who either had clinical disease or were expected to progress to clinical disease by the age- and country-specific mortality rates derived from the World Health Organization's *Life Tables for WHO Member States* (WHO, 2006b).

  Between 2000–2007 in the populations covered by the GPELF, over 550,000 infected individuals who either had clinical disease or were expected to progress to clinical disease died; therefore, the same number of *replacement* infections would have been expected to occur over the same time-period to maintain the overall steady-state infection ratio in the at-risk population. However, because of MDA, these *replacement* individuals will be *protected* from acquiring infection and thus will accrue the benefits of averting clinical disease. As described elsewhere (Ottesen et al., 2008), the full protective benefits of MDA are likely not attained immediately after the first MDA, so calculations are based both on the numbers of people treated in each country each year and also on the assumption (derived from available transmission studies [Ottesen et al., 2008]) that only 50% would be protected after the first round of MDA treatment, 75% after the second, 87.5% after the third, 94% after the fourth, and 100% after the fifth. As a result, an estimated 480,000 individuals were protected from acquiring infection (and subsequent clinical disease) between 2000–2007.

All the protected individuals in these two 'benefiting populations' need not themselves have been directly treated during the MDA, as high MDA coverage in at-risk populations will drastically reduce the rate of transmission and, therefore, infection in untreated individuals as well (Stolk et al., 2003; Stolk et al., 2006). Indeed, reports from the World Health Organization do indicate high MDA coverage averaging more than 70% overall, with several regions and countries covering more than 90% (WHO, 2002, 2003a, 2004, 2005, 2006a, 2007, 2008).

Individuals already infected with LF but protected by MDA from progression of disease.

- **Individuals with subclinical disease at the time of MDA:** Previous studies have shown that approximately two-thirds of individuals infected with LF will have subclinical disease (Ottesen, 2006) and about half of these are expected to progress to overt clinical disease in their lifetimes (Ottesen et al., 2008). In order to remain conservative for the present analysis, it is estimated thatMDA halts disease progression in only 50% of *those who would have progressed to clinical disease* (Shenoy et al, 2009)—and that disease is apportioned as described previously: 62.5% being hydrocele, 37.5% being lymphedema.

Since this study assumes that the only individuals incurring economic costs due to LF are those with clinical disease, the only individuals with subclinical disease whose benefits from MDA are tallied in this analysis are those who would have been expected to progress to clinical disease. Previous estimates are that 9.4 million subclinical cases were prevented from progressing to hydrocele and lymphedema between 2000–2007 (Ottesen et al., 2008).

- **Individuals with clinical disease at the time of MDA.** Of the 10% of the at-risk population who are infected, approximately one-third has overt clinical disease—again, with the majority of those manifesting hydrocele (62.5%) and the remaining, lymphedema. It was previously estimated that between 2000–2007, approximately 570 million at-risk individuals, including 57 million with LF infection, received MDA (Ottesen et al., 2008); therefore, roughly 19 million individuals with overt clinical disease received MDA.

  It is still uncertain to what extent MDA improves morbidity in those already suffering from hydrocele or lymphedema, but recent studies provide preliminary evidence of the positive effects of repeated rounds of MDA on the progression or even reversibility of LF morbidity. Specifically, MDA has been shown to alleviate the number of acute ADL episodes associated with LF by 59–88% after just two rounds of annual MDA with DEC with and without albendazole (Partono et al., 1989; Casley-Smith et al., 1993). The effects of MDA on chronic disease, however, are more uncertain. A study in Papua New Guinea resulted in complete reversal of 87% of hydrocele and 69% of leg lymphedema cases after 5 annual rounds of DEC+ivermectin or DEC alone (Bockarie et al., 2002), and studies in Indonesia (Partono et al., 1981; Partono, 1985) and Tanzania (Meyrowitsch et al., 1996) using DEC, provide evidence of an improvement or complete disappearance of clinical manifestations by 62–90%

after 2–4 rounds of annual MDA. However, other studies have failed to show such significant clinical benefits from MDA (Ciferri et al., 1969; Fan et al., 1995; Das et al., 2003). While evidence of acute and chronic disease regression using a combination of ivermectin+albendazole or ivermectin alone is even less well documented, a recent report from Tanzania indicates that MDA (using albendazole+ivermectin) lessens the frequency and severity of ADL episodes by a significant degree. The same report also finds that approximately 15% of hydrocele cases and 98% of lymphedema cases had shown improvement after 4 annual rounds of MDA treatment using ivermectin+albendazole (Mackenzie et al., 2009).

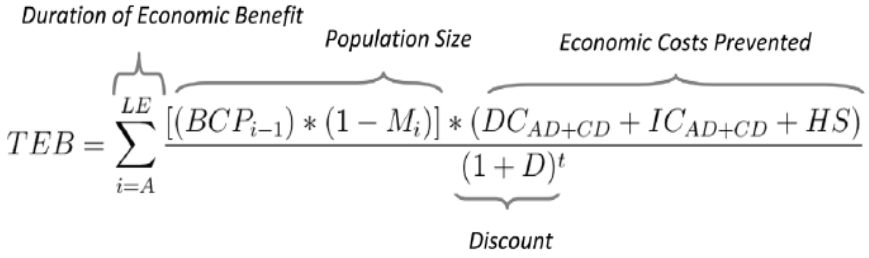
Because of these uncertainties, the base analysis of this study used a low-end estimate of 50% reversal in the frequency of acute ADL episodes. For chronic disease, a reasonably conservative estimate was used – 10% of hydrocele cases and 15% of lymphedema cases were considered reversible after 5 rounds of MDA involving either DEC or ivermectin in the treatment regimen. However, in order to take into account the uncertainties of the outcomes of MDA on pre-existing clinical morbidity, a sensitivity analysis was also conducted ranging from 0% reversal to 90% reversal as per the lower and upper boundaries cited by the literature.

Calculating the Total Economic Benefits of the GPELF

The previous section defined a 4-part *benefit cohort population* as the group of protected individuals who will realize economic benefits as a result of MDA activity between 2000–2007. The *total* economic impact of the GPELF, however, extends over a much longer period than these first 8 years because protection from LF infection or disease progression is a lifelong benefit. It is therefore necessary to aggregate the total economic benefit gained over the *projected remaining lifetime of the benefit cohort population*.

To estimate this total, a general formula (**Figure A18-1**) was applied and calculated independently for each country to accommodate country specific differences in several key variables (life expectancy, mortality rate, direct and indirect costs). All calculated costs and benefits are discounted to the base year of 2008.

Duration of economic benefits. The duration of economic benefits depends on the age of onset of clinical disease (assumed as 20 years old (Ottesen et al., 2008) in each country), the average life expectancy (differing by country), and the age at which an individual received MDA treatment. In this model, for each subgroup population, a *same single average age* for each country was used to encompass the entire age range of individuals within the *benefit cohort population* at the time of treatment, with the recognition that some of those receiving treatment will be younger than the average age and some older (**Figure A18-2**).



Where:

TEB	=	Total economic benefits (in *US$2005*)
LE	=	Average life expectancy (*years*)
A	=	Average age at time of MDA treatment (*years*)
BCP	=	Benefit cohort population (2000-2007) (*person-years*)
M	=	Annual mortality rate, age-specific
DC	=	Direct costs prevented (*US$2005*)
IC	=	Indirect costs prevented (*US$2005*)
AD	=	Acute disease
CD	=	Chronic disease
HS	=	Health system costs prevented (*US$2005*)
D	=	Annual discount rate (%)
t	=	Time (*Years beyond 2008*)

FIGURE A18-1 General formula for calculating economic benefits. The formula was applied and calculated independently for each country to accommodate country-specific differences in several key parameters (i.e., life expectancy, mortality rate, direct and indirect costs). All calculated costs and benefits are discounted by 3% per year to the base of 2008. doi: 10.1371/journal.pntd.0000708.g001.

- **Newborns** (Group 1a, **Table A18-1**) did not actually receive MDA treatment but are considered protected from the time of birth once transmission has been interrupted; thus their average age at the time of treatment is 0. However, because the average age of clinical disease onset is 20 years old (Ottesen et al., 2008), *benefits for newborns do not accrue until 20 years after birth* because on average, no clinical disease and hence, economic costs will be incurred before that age;
- For **other individuals protected from LF infection** (Group 1b), MDA treatment is estimated to occur at 20 years of age on average.
- **Infected individuals with subclinical disease** (Group 2a) are also estimated to be 20 years old on average when they receive MDA. Though

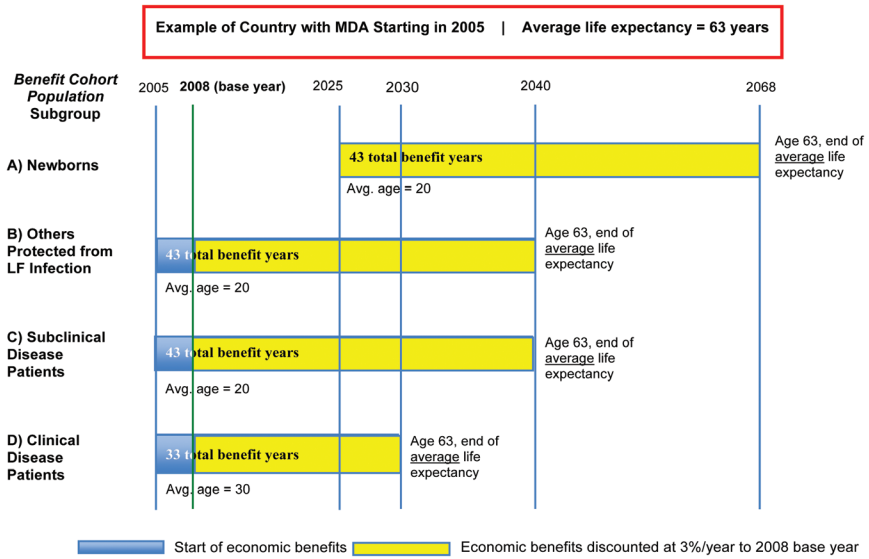


FIGURE A18-2 Duration of economic benefits. Economic benefits are calaculated ony for the *benefit cohort population* receiving MDA between 2000–2007; however, the benefits are gained until the end of their lifetime. For modeling purposes, single average ages were used to encompass the entire age range of individuals in each population subgroup, realizing that some individuals will be above this average age at the time of treatment, and some below. The size of each subgroup decreases each year based on country and age-specific mortality rates. doi: 10.1371/journal.pntd.0000708.g002.

subclinical infection is common in early childhood, this model assumes that the average age of treated (and thus protected) subclinical patients is 20 years.

- **Infected individuals with overt clinical disease** (hydrocele or lymphedema, Group 2b) are estimated to be 30 years old on average when they receive MDA. This estimate implies that clinical-disease patients have been living with their condition for an average of 10 years, since onset of clinical disease is taken as 20 years of age.

Population size. This study projects the total economic impact of the first 8 years of the GPELF by aggregating the economic benefits over the lifetime of the 2000–2007 benefit cohort population. To remain consistent with this study's goal of only estimating the GPELF's economic achievements following these 8 years, no projections are made for the growth of MDA treatments after 2007 or any resulting economic benefits to new individuals treated beyond the *benefit cohort population*.

TABLE A18-2 Benefit Cohort Population: Individuals and Person Years

Population Group	Population Subgroup	Benefit Cohort Population Size (2000–2007) (millions)	Average Age of MDA Treatment[1]	Average Years of Economic benefit[2]	Person-Years (Lifetime) (millions)[3]
1. Protected from acquiring infection and subsequent disease	a. Newborns	2.2	—	43	83.8
	b. Protected from infection	0.5	20	43	15.7
	Subtotal	2.7	—	—	99.5
2. Protected from disease progression	a. Subclinical morbidity	9.4	20	43	388.6
	b. Clinical morbidity	19.3	30	33	626.6
	Subtotal	28.7	—	—	1,015.3
Total		31.4	—	—	1,114.8

[1] Newborns, although not actually treated with MDA, are assumed to be protected from infection at the time of birth and protected from clinical disease from 20 years of age.

[2] Based on average life expectancy of 63 years, weighted by country specific rates and Benefit Cohort Population in each country.

[3] Sum of each year lived by each individual in the Benefit Cohort Population. Equal to (Benefit Cohort Population) × (Average Years of Economic Benefit), adjusted for annual mortality.

Year-to-year, the size of the *benefit cohort population* will decrease because of country-specific mortality and average life expectancy. Because the model assumes this non-static population over time, the economic-benefit denominator must be analyzed in person-years, which is the sum of each year lived by each individual in the benefit *cohort population*. **Table A18-2** shows that the first 8 years of the GPELF will provide over 1.1 billion person-years of economic benefit during the lifetime of the 31.4 million individuals in the *benefit cohort population*.

Economic costs prevented. Economic costs are comprised of *direct treatment costs and indirect labor costs*. Economic costs are further segmented in each sub-population group (**Table A18-1**) by disease type (acute or chronic) and morbidity type (hydrocele or lymphedema). Key model assumptions and estimates, weighted by country-specific rates, are summarized in **Table A18-3**.

- ***Direct treatment costs*** refer to costs (e.g., for medicines, consultation fees, transport, food, accommodation) that are incurred when an individual with clinical morbidity seeks treatment.

Patients seeking treatment for acute inflammatory attacks caused by LF usually receive pain relieving and anti-inflammatory medicines, with or without systemic antibiotics (Addiss and Brady, 2007). Chronic disease sufferers may also seek care following bouts of severe pain and swelling and receive a similar treatment package. Chronic patients may also purchase bars of soap in accordance with prevailing lymphedema management strategies (Addiss and Brady, 2007).

Median international reference prices for a course of amoxicillin, ibuprofen, and paracetamol were collected from Health Action International (Health Action International, 2008) and Management Science for Health (Management Science for Health, 2008) to approximate public and private sector costs of medicines across GPELF countries. Primary data show that for individuals seeking treatment at health facilities for LF, medicines, on average, comprise 50% of the total treatment cost, consultation fees 30%, and transport, food, and accommodation the remaining 20% (Babu et al., 2002; Krishnamoorthy, 1999; Nanda and Krishnamoorthy, 2003; Ramaiah et al, 1996; Rmaiah et al., 1999). For self-treatment individuals, only the medicine costs were attributed to total treatment costs.

Acute disease refers to periodic, recurring attacks of acute adenolymphangitis (ADL), defined by signs and symptoms of pain, tenderness, local swelling, and warmth in the groin or limbs with constitutional symptoms such as fever, nausea, and vomiting (Gyapong et al., 1996; Pani et al., 1995; Ramaiah et al., 1996).

Approximately 70% of hydrocele patients experience at least 1 ADL episode per year with an average of 2. For lymphedema patients, almost 95% experience at least 1 episode with an average of 4. The number of episodes for both morbidities, however, can be up to 7 or higher. Each ADL episode lasts on average 4 days although the duration can range to 9 or more days (Babu et al., 2005; Gasarasi et al., 2000; Gyapong et al., 1996; Kessel, 1957; Krishnamoorthy, 1999; Pani et al., 1995; Ramiah et al., 1996; Ramaiah et al., 2000a; Sebesan et al., 1992).

The proportion of individuals with ADL episodes who seek treatment – whether at a health facility, traditional healer, or through self-treating with medicine – ranges from 55% to 70% depending on the country and region. Similarly, the preferred treatment source and related costs are highly region-specific. In WHO-AFRO, self-treatment and traditional healers may be used in 70% of cases, leading to a weighted average cost across all sources of US$0.90 per ADL episode treated. In comparison, WHO-SEARO has an average weighted cost of US$1.40 per episode treated, largely due to the higher cost and proportion of treatment seeking in urban areas and private health facilities in India (Gyapong et al., 1996; Krishnamoorthy, 1999; Nanda and Krishnamoorthy, 2003; Ramaiah et al., 1996). WHO-WPRO has an even greater average weighted cost of $4.90

TABLE A18-3 Epidemiological and Cost Estimates Used in the Economic Benefit Model

Parameter Type	Acute or Chronic Disease	Associated Cost-Type	Rate or Proportion	Regional Variation	Hydrocele Avg. Estimate[1]	Lymphedema Avg. Estimate[1]	Sources, Key Assumptions
Epidemiological	Acute Disease	Direct and Indirect	% of clinical LF patients with ADL	Global estimate[2]	70% [45–90%]	95% [90–95%]	(Krishnamoorthy, 1999; Ramaiah et al., 1996, 2000; Pani et al., 1995; Babu et al., 2005; Gyapong et al., 1996; Kessel, 1957; Gasarasi et al., 2000; Sabesan et al., 1992)
			% of patients with ADL seeking treatment	Global estimate, India excepted[3]	65% [55–70%]	65% [55–70%]	(Krishnamoorthy, 1999; Nanda and Krishnamoorthy, 2003; Ramaiah et al., 1996; Gyapong et al., 1996)
			# of ADL episodes per patient (w/o MDA)	Global estimate[2]	2 [0–7]	4 [0–7]	(Krishnamoorthy, 1999; Ramaiah et al., 1996, 2000; Pani et al., 1995; Babu et al., 2005; Gyapong et al., 1996; Kessel, 1957; Gasarasi et al., 2000; Sabesan et al., 1992)
			% of ADL episodes prevented by MDA	Global estimate[2]	50% [15–88%]	50% [15–88%]	(Partono et al., 1989; Casley-Smith et al., 1993; Tisch et al., 2009), varies by MDA round
		Indirect cost	Avg. duration of ADL episode (days)	Global estimate[2]	4	4	(Krishnamoorthy, 1999; Ramaiah et al., 1996, 2000; Pani et al., 1995; Babu et al., 2005; Gyapong et al., 1996; Kessel, 1957; Gasarasi et al., 2000; Sabesan et al., 1992)

					[0–9]	[0–9]	
			% of work hours lost per day due to ADL	Global estimate[2]	75% [50–93%]	75% [50–93%]	(Ramaiah et al., 1998, 2000; Gyapong et al., 1996; Gasarasi et al., 2000)
	Chronic Disease	Direct and Indirect	% of Chronic Disease patients seeking treatment	Global estimate, India excepted[3]	40% [20–50%]	50% [30–55%]	(Nanda and Krishnamoorthy, 2003; Ramaiah et al., 1999; Babu et al., 2002; Gyapong et al., 1996)
			% of Chronic Disease patients benefiting from MDA	Global estimate[2]	10% [0–87%]	15% [0–69%]	[(Bockarie et al., 2002; Partono et al., 1981; Partono, 1985; Meyrowitsch et al., 1996; Ciferri et al., 1969; Mackenzie et al., 2009; Ramaiah et al., 1996), varies by MDA round
		Indirect cost	% of work hours lost per day due to chronic disease	Global estimate[2]	15% [13–17%]	20% [15–22%]	(Ramaiah et al., 1996, 2000; Babu et al., 2002)
Cost	Acute Disease	Direct cost	Avg. treatment cost per episode	Country-specific estimate[4]	$1.5 [$0.25–$5.20]	$1.5 [$0.25–$5.20]	(Health Action International, 2008; Management Science for Health, 2008; Krishnamoorthy, 1999; Nanda and Krishnamoorthy, 2003; Ramaiah et al., 1996, 1999; Babu et al., 2002)

continued

TABLE A18-3 Continued

Parameter Type	Acute or Chronic Disease	Associated Cost-Type	Rate or Proportion	Regional Variation	Hydrocele Avg. Estimate[1]	Lymphedema Avg. Estimate[1]	Sources, Key Assumptions
	Chronic Disease	Direct cost	Avg. treatment cost per year	Country-specific estimate[4]	$2.9 [$0.55–$10.05]	$4.3 [$0.85–$15.00]	(Health Action International, 2008; Management Science for Health, 2008; Krishnamoorthy, 1999; Nanda and Krishnamoorthy, 2003; Ramaiah et al., 1996, 1999; Babu et al., 2002)
	Acute and chronic disease	Indirect cost	Avg. wage per day	Country-specific estimate[4]	$1.05 [$0.30–$5.60]	$1.05 [$0.30–$5.60]	(International Labour Organization LABORSTA; World Bank Development Indicators Online; International Labour Organization Minimum Wages Database; U.S. Department of State, 2008)
	Chronic disease	Indirect cost	Work days per year	Global estimate[2]	300 [300–365]	300 [300–365]	Assuming 6 workdays per week

[1] Weighted Average over all GPELF countries.

[2] Global estimate indicates a standard rate or proportion was utilized for each GPELF country. This is primarily due to a lack of supporting country-specific data.

[3] Indicates a standard rate or proportion was utilized for each GPELF country with the exception of India where more primary data was available and suggested estimates differ from other GPELF regions.

[4] Estimates are country specific and gathered from public online international database sources.

due to higher wages and standard of living costs in this region. Across all GPELF countries, the overall weighted average of treatment seeking behavior and costs for ADL was 65% and $1.50 respectively.

Chronic disease refers to individuals with overt clinical disease in individuals with hydrocele and/or lymphedema. All population groups with economic benefits from MDA in this study are assumed to have (or would otherwise have acquired) chronic disease but only a proportion of these chronic disease patients incur acute ADL episodes.

The percentage of chronic disease patients who seek treatment is also highly dependent on the country/region, severity of disease, and availability of treatment. On average, this study conservatively assumes that 30% of hydrocele and 35% of lymphedema patients seek treatment, although in India these proportions are estimated at 60% and 65%, respectively, based on the available literature. These estimates are also weighted over time with the assumption that almost all chronic disease patients will seek treatment in the early years of disease morbidity but will reduce their frequency over the long-term. Chronic disease patients are assumed to seek treatment on average twice a year with lymphedema patients seeking and spending slightly more. On average, treatment seeking hydrocele patients will spend US$2.90 and lymphedema patients US$4.30 per year for their chronic conditions (Nanda and Krishnamoorthy, 2003; Ramaiah et al., 1999; Babu et al., 2002; Gyapong et al., 1996).

Hydrocelectomy (surgery to repair hydrocele) costs are included in the chronic disease direct cost calculation. The proportion of total direct costs related to hydrocelectomies, however, is very small because of the relatively low frequency of hydrocelectomies; hydrocele patients often have poor access to surgery facilities and are further deterred by the restrictive costs of the procedure.

- ***Indirect labor costs*** refer to income lost as a result of reduced work hours and economic activity due to LF morbidity. For women, economic activity also includes time spent on domestic chores because an opportunity cost of income-generating activity is implied. As in previous LF studies and burden of disease analyses, indirect cost estimates were calculated using the human capital approach, which presumes total cost and lost output are equal to the income foregone as a result of illness (Ramaiah et al, 2000b; Burton, 1961).

Approximating the income for individuals with LF is difficult because the majority of this population is comprised of subsistence farmers who do not participate in the formal labor market. A variety of methods in valuing working time have been incorporated in economic analyses of populations with similar tropical diseases (malaria, trachoma, onchocerciasis), including the examination of minimum wages (Onwujekwe

et al., 2000), average value added per agricultural worker (Frick et al., 2003), and proxies from prior studies in similar settings (McFarland et al., 2005). Based on these methods, the combination of 3 wage sources was used in this paper for best estimates of a fair market value of time for an agricultural worker with LF infection: (1) The International Labour Organization's *LABORSTA* database which lists average wages for agricultural field workers (International Labor Organization LABROSTA); (2) The World Bank's World Development Indicators Online which lists the average value added per agricultural worker (World Bank World Development Indicators Online); (3) The International Labour Organization's Minimum Wages Database and US Department of State's Country Reports on Human Rights Practices which list minimum wages by occupation including agricultural and low-skilled workers (International Labor Organization Minimum Wages Database; U.S. Department of State, 2008).

For countries listed by one or more sources, the lowest wage amount was used to ensure a conservative estimate. For countries not listed by any of the three sources, the lowest amount within the same region was used as a proxy. In this paper, it is assumed that all individuals with or at-risk of LF would have been economically active otherwise and would work 300 days per year.

Acute disease: Acute ADL episodes are severely debilitating, with studies in India showing total economic disability for the entire duration of the episode in 81–87% of cases versus 34–37% of controls (Ramaiah et al., 1998; Ramaiah et al., 2000a). Based on these and additional case-control studies, the present analysis assumes 75% of time spent on economic activity is lost due to acute disease during an ADL episode Gasarasi et al., 2000; Gyapong et al., 1996).

Chronic disease: Although LF chronic disease is less debilitating than acute ADL episodes, chronic disease patients still work fewer hours than equivalent non-LF workers. While the amount of disability is strongly correlated to the degree of disease, hydrocele patients are estimated to work 15% less time and lymphedema patients 20% less on average (Babu et al., 2002; Ramaiah et al., 1999; Ramaiah et al., 2000a).

- ***Health system costs:*** Comprehensive assessment of economic costs and benefits must also include the potential savings to the health system since decreased LF infections reduce medical treatments needed. To estimate these patient-service savings, country specific costs were gathered from the WHOCHOICE database, recording costs for a 20-minute visit to a primary health center having a 50% regional coverage (WHO-CHOICE, 2008). These costs were then multiplied by the number of individuals benefiting from MDA, the percentage that seek treatment in public health facilities, and the average number of visits per year.

Cost Standardization: To standardize the comparison of prices and wages over different time periods, all estimates when necessary were adjusted to 2005 values (to correspond to external supporting World Bank data) using national consumer price index (CPI) data (International Monetary Fund, 2008). Estimates were then converted from local currencies to U.S. dollars using official average 2005 exchange rates (International Monetary Fund, 2008).

Discount Calculation

For this study, 2008 was used as the base year for calculating economic benefits. When calculating future benefits, however, it is necessary to discount values to a net present value (NPV) under the economic principle that a dollar earned in the present is worth more than one earned in the future. Therefore, all annual accumulated cost savings beyond 2008 are discounted at 3% per year in accordance to guidelines set by WHO-CHOICE (WHO, 2003b).

Cost-Benefit Calculations

GPELF program costs can be compared with the economic benefits calculated in this study through a cost-benefit analysis to evaluate the efficiency and practicality of implementing the Global Programme. Estimating program costs, however, is not the intent of this study and such data was, therefore, sourced through our previously published work (Goldman et al., 2007). On a macro-level, no study has yet been conducted to estimate the total cost of the GPELF over its first 8 years and as a result, a broader programmatic cost-benefit analysis cannot be calculated. It is possible, however, to estimate the cost-benefit on an individual-level using per person costs calculated in a multi-country study of national MDA program costs for LF including training, mapping, mobilization, distribution, monitoring, and surveillance (Goldman et al., 2007). In this study, *Goldman et al.* analyzed both the average annual *economic* cost per person treated (i.e. including the implied costs of donated materials and drugs – set at US$0.19+$0.0019 for shipping per 400mg tablet of albendazole and US$1.50+$0.0018 per 3mg tablet of ivermectin) and also the *financial* cost per person treated (i.e. excluding the costs of the donated materials and drugs) from data collected through questionnaires and adjusted for LF-specific activities. Donated ivermectin is used in combination with donated albendazole in areas co-endemic for onchocerciasis in Africa plus Yemen. DEC, which is not donated, is used in combination with donated albendazole in all other countries and must be purchased by national programs.

In terms of per person economic benefits, the total economic benefits estimated over one year in this study was divided by the total number of people treated with MDA in that same year. For this analysis, per person economic

benefits were only calculated for the 7 countries whose program costs were also evaluated in *Goldman et al.'s* study. Cost-benefit was then measured using benefit-cost ratios (BCR), which is the per person treated benefit divided by the per person treated cost. For standardization purposes, the BCR reflects costs, benefits, and currencies adjusted to the year of the most recent MDA round in *Goldman et al.'s* study.

Results

Economic Benefits to the Benefit Cohort Population

During the first 8 years of LF MDA, the Global Programme delivered nearly 2 billion treatments and reached almost 570 million individuals in 48 of the 83 identified endemic countries (**Table A18-4**). As a result of these program achievements, 31.4 million individuals – defined in this study as the *benefit cohort population* – will gain economic benefits over their lifetime from averting direct treatment costs and indirect lost-labor costs. Of these 31.4 million individuals in

TABLE A18-4 GPELF MDA Treatments (2000–2007)

WHO Region	GPELF Countries (2000–2007)	Individuals Treated with MDA (Millions)	Treated Individuals Infected with LF (Millions)[1]	Benefit Cohort Population (Millions)
AMRO	Brazil, Dominican Republic, Guyana, Haiti	2.2	0.2	0.1
AFRO	Benin, Burkina Faso, Cameroon, Comoros, Ghana, Kenya, Madagascar, Mali, Niger, Nigeria, Senegal, Sierra Leone, Tanzania (incl. Zanzibar), Togo, Uganda	51.2	5.1	2.9
EMRO	Egypt, Yemen	2.7	0.3	0.2
WPRO	American Samoa, Cambodia, Cook Islands, Fed. States of Micronesia, Fiji, French Polynesia, Kiribati, Marshall Islands, Malaysia, Niue, Papua New Guinea, Philippines, Samoa, Tonga, Tuvalu, Vanuatu, Vietnam, Wallis and Futuna	17.4	1.7	1.0
SEARO	Bangladesh, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, Timor-Leste	494.4	49.4	27.2
All Regions	48 Total Countries	567.9	56.8	31.4

[1] Assumed that 10% of at-risk-population is infected with LF (Ottesen et al., 2008).

the *benefit cohort population*, 2.7 million (8.6%) would have acquired LF and subsequently progressed to clinical disease but were protected from infection altogether because of interruption of the transmission cycle by MDA. This group comprises the proportion of *newborns* (2.2 million) that are protected by virtue of being born in MDA-treated areas, as well as *other individuals in the general population* (0.5 million) protected because LF transmission has been interrupted.

The remaining 28.7 million (91.4%) individuals are those who were already infected at the time of MDA treatment but benefit from halted disease progression. This population group comprises individuals at the *subclinical* disease stage (9.4 million, [29.9%]) who avoid clinical disease altogether and individuals at the *clinical disease* stage (19.3 million [61.6%]) whose conditions may improve following MDA.

As seen in **Table A18-5**, the efforts in reaching and administering MDA to such a large population have produced extraordinary economic benefits over the first 8 years of the GPELF. An estimated US$21.8 billion will be saved over the lifetimes of the 31.4 million individuals who have or would have acquired clinical disease during this timeframe. This total amount results from summing the direct treatment costs ($1.4b) and indirect lost wages ($20.4b) prevented over the lifetime of each of the population groups under the assumptions and estimates previously outlined in **Table A18-3**. Direct costs for acute disease were calculated based on the aggregate number of ADL episodes expected in the absence of MDA and the average cost incurred per episode. Chronic disease direct costs were derived from the percentage and total number of patients seeking treatment multiplied by the average cost spent per treatment. Indirect costs for both acute and chronic disease were calculated by accruing the equivalent workdays lost to LF and multiplying this total by the average daily wage. All average costs and rate of disease estimates were weighted annually by countryspecific estimates and with respect to total number of person-years.

On average, each individual of the *benefit cohort population* will avoid nearly $700 in LF-associated costs that would have accrued over his/her lifetime. This equates to the amount earned for 19 working days per person-year, thus preventing the loss of approximately 6.3% of annual income (**Table A18-6**). These sums and averages are even greater when considered in a single year-to-year perspective, since beyond 2008, each year of economic benefit is discounted by 3% per year.

Table A18-6 also shows that the infected patient sub-population groups (i.e. *clinical and subclinical*) have the greatest total lifetime benefits based on their larger proportion of the total *benefit cohort population*. On a per person lifetime average, however, *subclinical* (Group 2a) and *'other protected individuals'* (Group 1b) benefits are larger.

Figure A18-3 highlights the total economic benefit segmented by cost, morbidity, and clinical presentation.

TABLE A18-5 Total Costs Prevented Over Lifetime of Benefit Cohort Population

Population Group	Population Subgroup	Benefit Cohort Population (millions)	Direct Costs Prevented		Indirect Costs Prevented		Total Costs Prevented (US$MM)
			Acute Disease (US$MM)	Chronic Disease (US$MM)	Acute Disease (US$MM)	Chronic Disease (US$MM)	
1. Protected from acquiring infection (and subsequent disease	a) Newborns	2.2	$71	$6	$207	$1,444	$1,727
	b) Protected from infection	0.5	$24	$2	$75	$532	$633
	Subtotal	2.7	$95	$8	$282	$1,975	$2,360
2. Protected from disease progression	a) Subclinical morbidity	9.4	$584	$49	$1,765	$12,146	$14,544
	b) Clinical morbidity	19.3	$528	$89	$1,596	$2,698	$4,911
	Subtotal	28.7	$1,112	$138	$3,361	$14,844	$19,455
Total		31.4	$1,207	$146	$3,643	$16,819	$21,815

TABLE A18-6 Total Costs Prevented per Individual in the Benefit Cohort Population

Population Group	Population Subgroup	Benefit Cohort Population (millions)	Total Costs Prevented (US$MM)	Lifetime Benefit per Individual	Avg. Annual Lost Work Days Prevented	Avg. % of Annual Lost Work Days Prevented
1. Protected from disease progression	a) Newborns	2.2	$1,727	$783	20	6.7%
	b) Protected from infection	0.5	$633	$1,319	39	13.1%
	Subtotal	2.7	$2,360	$879	23	7.7%
	a) Subclinical morbidity	9.4	$14,544	$1552	36	12.1%
	b) Clinical morbidity	19.3	$4,911	$255	8	2.5%
	Subtotal	28.7	$19,455	$679	19	6.2%
Total		31.4	$21,815	$696[1]	19[1]	6.3%

[1] Weighted Average of all Benefit Cohort Population subgroups

Identifying benefits by cost type. Approximately 94% of the total economic benefits were due to the prevention of indirect costs of lost working time and, therefore, output and income (**Figure A18-3, Section A**). The lower proportion of direct treatment costs (6%) was attributable to the low frequency of treatment seeking behavior and inexpensive medicine packages relative to the day-to-day accumulation of lost income from reduced economic activity.

Identifying benefits by morbidity type. Economic benefits accruing to populations protected from hydrocele are approximately equal to those from lymphedema (**Figure A18-3, Section B**). The estimated higher proportion of clinical disease patients with hydrocele (62.5%) compared to lymphedema (37.5%) offsets the greater average disability of lymphedema patients in terms of their ADL frequency, ADL duration, and percentage of work time lost due to disease.

Identifying benefits by clinical presentation. Preventing chronic disease accounts for about 78% of the total economic benefits – not unexpected given the long-term disabling nature of LF (**Figure A18-3, Section C**). Acute episodes generally affect individuals for only 8–12 days a year, whereas the chronic condition is a perpetual disability. Moreover, studies investigating the effects of DEC on individuals with overt clinical disease show greater evidence towards the lessening of ADL episodes than the reduction or reversal of the chronic condition. If

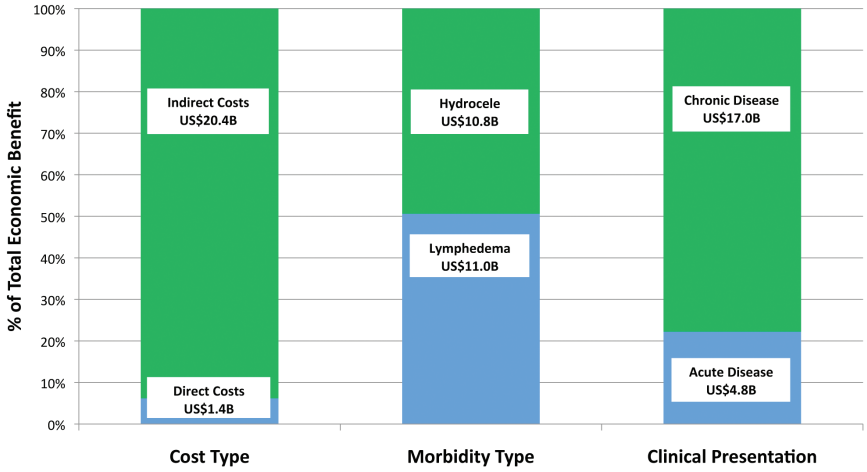


FIGURE A18-3 Total economic benefits by category. The total economic benefit for individuals (i.e., excluding health system savings) of US$21.8 billion can be further analyzed by cost type, morbidity type, and clinical presentation. doi: 10.1371/journal.pntd.0000708.g003.

future studies can demonstrate unequivocal benefits of MDA for chronic disease patients, its proportion of economic benefits will be even higher.

Identifying benefits per region. Table A18-7 highlights the regional variation in cost savings among GPELF programs. Much of the difference in per person benefits can be attributed to higher average costs and wages outside of the AFRO and SEARO regions. The total GPELF benefits, however, are heavily concentrated in SEARO and in particular in India, which comprised over 75% of all individuals treated during the 8-year period.

Economic Benefits to Health Systems

Economic benefits to national health systems resulting from reduced LF infections derive particularly from patient service costs averted in the public sector. Approximately US$2.2 billion in health system costs will be saved over the lifetime of the *benefit cohort population* (**Table A18-8**). Combined with the US$21.8 billion savings for individuals, the total economic benefit following the first 8 years of the GPELF is estimated at an extraordinary US$24.0 billion (**Figure A18-4**).

TABLE A18-7 Lifetime Economic Benefits per Region

WHO Region	Total Lifetime Benefit (US$MM)[1]	Lifetime Benefit per Patient	Avg. Annual Lost Work Days Prevented	Avg. % of Annual Lost Work Days Prevented
AMRO	$183	$1,446	20	6.7%
AFRO	$1,288	$439	23	7.5%
EMRO	$144	$922	20	6.6%
WPRO	$2,128	$2,186	18	6.0%
SEARO	$18,070	$665	19	6.2%
All[2]	$21,815	$695	19	6.3%

[1] Does not include health system benefit.
[2] Weighted average over all WHO regions.

TABLE A18-8 Health System Economic Benefits

WHO Region	Benefit Cohort Population (millions)	% Seeking Treatment at Gov't Primary Health Center[1]	Cost per 20 Minute Outpatient Visit to Government Primary Health Center[2]	Total 2008 Health System Cost Averted (US$MM)	Total Lifetime Health System Cost Averted (US$MM)
AMRO	0.1	52%	$3.7	$0.2	$4.3
AFRO	2.9	52%	$2.4	$2.7	$53.5
EMRO	0.2	52%	$2.1	$0.1	$3.8
WPRO	1.0	52%	$4.0	$1.4	$39.8
SEARO	27.2	52%	$2.2	$81	$2,085
All[2]	31.4	52%	$2.3	$85.5	$2,187.1

[1] Does not include health system benefit.
[2] Weighted average over all WHO regions.

Sensitivity Analyses

This overall economic analysis of the GPELF's first 8 years does have notable limitations due to the lack of regionalized primary data concerning both epidemiological and socioeconomic factors associated with LF. Indeed, two sections of the model remain with particular uncertainty: 1) *The degree to which MDA can reverse or return an individual with overt clinical disease to regular productivity, and* 2) *The relationship between hours lost and output/productivity lost due to disease*. The total estimated economic impact is particularly sensitive to these variables because of the large number of clinical disease patients receiving MDA and the high proportion of total prevented costs that come from indirect labor costs. As a result, sensitivity analyses were carried out to assess the range of economic benefits that can be achieved under varying estimates of each variable. Secondary sensitivity analyses investigating the frequency and duration of ADL episodes, and direct treatment costs indicated less variability of economic benefits when adjusting these parameters.

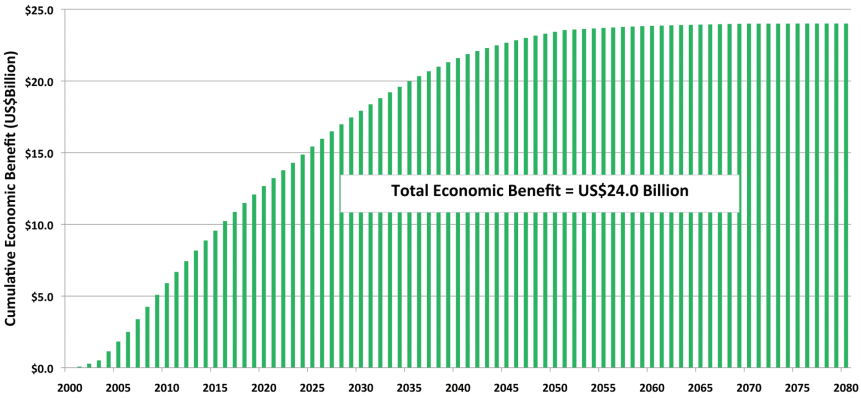


FIGURE A18-4 Cumulative economic benefits resulting from the first 8 years of the GPELF. Total economic savings to individuals and health systems accumulate through the *benefit cohort population's* lifetime. doi: 10.1371/journal.pntd.0000708.g004.

Chronic disease regression and reversal with MDA. As noted previously, there is considerable debate about the degree of regression of existing hydrocele and lymphedema following MDA treatment. Estimates range from no regression at all to complete reversal of 87% of hydrocele cases and 69% of leg lymphedema cases after 5 annual rounds of DEC with ivermectin or DEC alone (Bockarie et al., 2002). Other estimates from related studies also lie within this range (Partono et al., 1981; Partono, 1985; Ciferri et al., 1969; Mackenzie et al., 2009; March et al., 1960; Meyrowitsch et al, 1996), which is therefore used as the lower and upper boundaries for the sensitivity analysis. A linear relationship will also be assumed – i.e. that a 50% reversal of chronic disease would lead to an average 50% increase in the potential lost aggregate working hours for a chronic disease patient over his or her entire remaining lifetime.

Table A18-9 compares the degree of chronic disease reversal to the total economic benefit gained by the clinical disease population. In our model, US$21.8 billion would be saved based on 10% of hydrocele and 15% of lymphedema cases considered *curable* through MDA. If these estimates even double to 20% and 30%, respectively, the total amount rises to US$24.4 billion, equivalent to approximately 7.2% of annual income for inidividuals of the *benefit cohort population*. Under the maximum assumptions based on the data of Bockarie et al. (2002), total economic benefits would be a staggering US$37 billion or 11.0% of individual annual income. With such a varying degree of potential economic impact that is also likely dependent on parasite and MDA regimen type, a better understanding of the true relationship between antifilarial drug treatment and filarial morbidity is needed. In particular, prospective studies with rigorous case definitions, close clinical monitoring, control groups, and outcomes focused on

TABLE A18-9 Sensitivity Analysis for Chronic Disease Reversal Following MDA

Selected Studies	Hydrocele Reversal/ Improvement	Hydrocele Patients (n)	Lymphedema Reversal/ Improvement	Lymphedema Patients (n)	Estimated Economic Benefit Based on Study Parameters (US$MM)	Avg. % of Annual Lost Income (Work Days) Prevented
Ciferri 1960, Dunyo 2000, Das 2003[1]	0%	37	0%	26–48	$18,890	5.5%
Partono 1985	—	—	71%	49	$27,590	8.0%
Partono 1981	—	—	75%	20	$28,010	8.1%
Mackenzie 2009	15%	13	98%	62	$31,020	9.0%
Meyrowitsch 1996	67%	60	39%	26	$31,700	9.2%
Blockarie 2002	87%	105	69%	90	$37,390	11%
Base Model Estimates	10%	—	15%	—	$21,815	6.3%

[1] No change or results considered insignificant.

clinical morbidity rather than microfilaria prevalence alone (Addiss and Brady, 2007), would strengthen our understanding of this relationship. Nevertheless, that there exists scientific data supporting chronic disease regression and reversal remains uncontroversial and further studies in this regard will be essential to determining the full economic impact of MDA on the clinical manifestations of hydrocele and lymphedema.

Indirect productivity loss due to clinical LF. Our analysis calculates indirect costs based on the equivalent hours and resulting wages lost from economic activity. This approach, however, ignores how much *output and productivity* are actually lost as a result of fewer work hours. In a study of Indian weavers, the reported productivity gap between LF and non-LF individuals was 27% (Ramu et al., 1996), which is markedly higher than the 15–20% time difference used for measuring indirect costs from chronic disease in this study. In defense of the analysis, time valuation was utilized on its own because supporting primary data on productivity burden was absent from the literature. Moreover, *Ramu et al.'s*

study (1996) evaluated the productivity of weavers whereas compared to farmers, output is not predicated on seasonal and environmental factors that would cause increased correlation variation between time and output. Nevertheless, this distinction between *time* and *productivity* burden would likely only underestimate the true disability and loss of earning power for individuals with clinical disease.

At our base rate of 15–20% productivity loss averted, the total lifetime benefit for the *benefit cohort population* is US$21.4 billion. By increasing this rate to 30%, the total lifetime economic benefit rises almost 75% to US$36.4 billion, equivalent to 10.6% of individual annual income. This high sensitivity to chronic indirect costs indicates that additional research on the actual productivity and economic output burden of LF, rather than time alone, will bring significant value to developing a more precise economic benefit estimate in the future.

Similarly, chronic disease indirect costs are particularly sensitive to the average earnings of individuals with LF. This study chose to estimate conservatively by basing a wage on the minimum income amounts listed for agricultural workers using 3 separate database sources – the ILO's *LABORSTA* database (International Labor Organization LABORSTA), the World Bank's *World Development Indicators Online* (World Bank World Development Indicators Online), and minimum wage estimates from the International Labour Organization (International Labor Organization Minimum Wages Database) and the US Department of State's *Country Reports on Human Rights Practices 2008* (2008). If instead only World Bank wages were used, the average wage, weighted across all regions, would increase from $1.05 to $1.40 and the total economic benefit estimated in this model would rise from $21.4 billion to $28.8 billion, which is 8.4% of individual annual income. If only ILO wages were implemented in the model, the average wage would be $1.50 and the total economic benefit $30.7 billion or 9.0% of individual annual income. Additionally, LF patients may be employed in occupations earning more than subsistence farmers (e.g. weaving, mining, fishing) and therefore suffer a higher opportunity cost of illness. Average incomes are also generally higher in urban areas, where up to a third of the LF burden in India exists (Ramaiah et al., 2000b; Rao and Sharma; 1986). More socioeconomic research of LF patients will be necessary to yield greater accuracy of the opportunity cost of the disease and indirect economic benefits of the GPELF.

Acute episodes. Acute ADL episodes are notably debilitating and clearly inhibit economic activity. Therefore, the number and duration of annual ADL episodes prevented has an impact on both direct and indirect economic benefits. In this study's base model, it is estimated that individuals with hydrocele incur on average 2 ADL episodes per year and for lymphedema patients, 4 episodes per year. Previous studies have shown the annual incidence can vary from 1 to 8 (Krishnamoorthy, 1999; Pani et al., 1989; Sabesan et al., 1992), resulting in a range of total economic benefits of $19.0 billion to $25.6 billion (5.5% to 7.4% of individual annual income). The economic impact is also dependent on the average

duration of ADL episodes, which can last from 2 to 16 days. The upper end of this range would lead to economic benefits totaling $32.2 billion (9.4%) with a more modest increase in average duration of 6 and 8 days resulting in benefits of $23.3 billion and $25.0 billion, respectively (6.8%–7.3%). On the lower end, assuming ADL episodes last an average of only 2 days decreases the total economic benefit to $19.8 billion (5.8%).

Direct treatment costs. The results from **Figure A18-3** show that prevention of direct treatment costs constituted only 6.2% of the total economic benefit. Therefore, while previous research indicates a large variance in the cost, source, and frequency of treatment, the economic benefit outcome is not as sensitive to these variables as with chronic indirect costs. While there are reported cases of LF patients in private hospitals or using multiple treatment sources spending up to $40 per ADL episode (Mackenzie et al., 2009; Ramaiah et al., 1998) or $200 per year (Babu et al., 2002) for chronic disease treatment, these instances represent extreme outliers given that the mean costs associated with the reviewed literature typically range from $1–$5. If we were to double the average prevented costs of treatment for ADL episodes, hydrocele, and lymphedema, the total economic benefit would marginally rise to $22.9 billion (6.7% of individual annual income). Tripling the average treatment cost would result in an economic benefit of $26.2 billion (7.6%), which is a far less elastic outcome than when varying the parameters of chronic indirect costs or even the frequency of ADL episodes.

Cost-Benefit Analysis

Goldman et al. found the average annual *economic* cost per person treated (i.e. including the implied costs of donated materials and drugs – set at US$0.19+$0.0019 for shipping per 400mg tablet of albendazole and US$1.50+$0.0018 per 3mg tablet of ivermectin) ranged from US$0.40 in Philippines to $5.82 in Tanzania. The average annual *financial* cost per person treated (i.e. excluding the costs of the donated materials and drugs) ranged from US$0.06 in Burkina Faso to US$1.34 in Haiti (Goldman et al., 2007).

One-year economic benefits per person treated in this study ranged from US$1.00 in Burkina Faso to US$4.56 in the Dominican Republic. **Table A18-10** compares these economic benefit estimates with the economic and financial costs from *Goldman et al.'s* study to calculate country-specific BCRs. The *economic* cost BCR for the three African countries using the ivermectin+albendazole regimen are lower (0.21–0.37) than those in countries using DEC+albendazole (1.23–8.59). Since the drugs, however, are available at no cost to the GPELF, BCRs calculated using *financial* costs are more favorable, ranging from 1.64 in Egypt to 18.07 in the Philippines.

TABLE A18-10 Country-Specific Benefit-Cost Ratios

Country	Year	MDA Round	Avg. Economic Benefit per Person Treated (1-year)[3]	Economic Benefit / Financial Cost per Person Treated[4]	Financial Cost[1] / Benefit-Cost Ratio (1-year)	Economic Benefit / Economic Cost per Person Treated[4]	Economic Cost[2] / Benefit-Cost Ratio (1-year)
Burkina Faso*	2002	2	$1.00	$0.06	16.67	$4.82	0.21
Ghana*	2002	2	$1.82	$0.17	10.72	$4.88	0.37
Tanzania*	2003	4	$0.99	$0.26	3.81	$4.53	0.22
Dominican Republic	2003	2	$4.56	$0.87	5.24	$1.56	2.92
Egypt	2001	2	$1.64	$1.00	1.64	$1.34	1.23
Haiti (Leogane)	2002	3	$2.84	$1.30	2.18	n/a	—
Haiti (Milot)	2002	1	$3.60	$1.10	3.27	n/a	—
Phillippines	2003	3	$3.43	$0.19	18.07	$0.40	8.59

[1] Financial cost does not include the cost of ivermectin and albendazole, which are both donated. DEC must be purchased by national programs and is therefore included as a financial cost. Ivermectin is used in combination with albendazole in areas co-endemic for onchocerciasis in Africa plus Yemen. DEC, which is not donated is used in combination with albendazole in all other countries and must be purchased by national programs.

[2] Economic cost includes the implied cost of donated materials and druges (Source: Goldman et al. (2007)): US$0.19+$0.0019 for shipping per 400mg tablet of albendazole and US$1.50+$0.0018 per 3mg tablet of ivermectin.

[3] Includes both individual and health system benefits. Currency is adjusted to match year of MDA round.

[4] Source: Goldman et al. (2007).

* Countries receiving the albendazole+ivemectin drug regimen.

Discussion

LF is a pervasive, disabling disease whose importance is magnified by the fact that 1.3 billion people are at risk of infection in some of the poorest countries in the world. LF causes not only a severe physical burden on sufferers but also a considerable economic burden from both direct medical expenses and loss of income-generating activity. While precise data on the *economic burden* of LF morbidity have been scarce (Evans et al., 1993), it was the earlier estimate of disease impact resulting in US$1 billion in lost productivity each year in India alone (Ramaiah et al., 2000b) and another $1 billion combined for the endemic countries in Africa (Haddix, 1999) that contributed to the World Health Assembly's resolution for the elimination of LF and WHO's subsequent creation of the *Global Programme to Eliminate Lymphatic Filariasis* (GPELF) (WHO, 1997).

The present study constitutes the first attempt to quantify the principal *economic benefit* of the first 8 years of the GPELF and, as such, complements an earlier analysis on the health impact of these first 8 years (Ottesen et al., 2008).

It conservatively estimates that in 2008 alone, over US$775 million of direct and indirect patient costs were averted as a result of MDA in 48 endemic countries. Of the 570 million *individuals* treated in the MDAs, 31.4 million either had clinical disease or would have acquired clinical disease during these 8 years. In the *entire lifetimes* of these 31.4 million people, costs totaling of US$21.8 billion (an average of nearly US$700 per person) will be averted. On a per person-year basis, this translates to approximately 6.3% of one's average *annual* income after future discounting.

In the absence of MDA, much of the economic burden can be attributed to indirect costs in the form of lost labor time. ADL episodes exacerbate the chronic pathology of lymphedema and hydrocele, and can lead to total disability for the entire duration of 81–87% of acute attacks (Ramaiah et al., 1998, 2000a). The economic burden is also greater should ADL episodes occur more frequently during the critical planting seasons for agricultural workers, which evidence from some literature suggests is the case (Babu et al., 2005; Gasarasi et al., 2000; Rao et al., 1982; Ravindranathan et al., 1980).

Despite this greater severity and incapacitation of ADL, it is the lifelong disabling nature of the chronic conditions that makes LF such an economically crippling disease. In calculating the total indirect costs of chronic disease, this study estimated that over 1 billion working hours each year would have been foregone without MDA. At an estimated 15–20% reduction in daily work hours, approximately 6–8% of equivalent workdays are lost annually to chronic disease. Related studies from Ghana and India indicate 3.8% and 7.0% of all potential male labor inputs, respectively, were lost annually as a result of chronic LF (Gyapon et al., 1996; Ramaiah et al., 2000a).

Direct treatment costs, while much less than the indirect cost of lost labor, are still significant. Direct costs are especially burdensome because an acute or chronic disease patient may need to borrow money to pay for treatment or, more commonly, must avoid treatment altogether because it is unaffordable. Estimates from the literature suggest that only 60–70% of ADL and 40–50% of chronic disease sufferers on average, sought treatment (including self-treatment) – highlighting a tradeoff between financial and physical burden. In this study, the average treatment expense for an ADL episode is estimated at $1.40, which is almost 1.5 times greater than the estimated average daily income. Treatment in private facilities or using multiple treatment sources, however, can range up to 10 or more times this amount. In reality, costs can vary even more as some cases in India and Tanzania reported spending nearly $40 per ADL episode (Mackenzie et al., 2009; Ramaiah et al., 1998). The same extent of the range of direct costs can be found for chronic disease patients. A study in eastern India reported treatment costs upwards of $200 per year (Babu et al., 2002). While treatment seeking behavior is likely to be higher in a patient's early years with chronic disease, it is still reasonable to assume that direct treatment costs will be sustained in a patient's later years because the chronic manifestations themselves will progress

with age. Along with this progression, the need for other forms of treatment and pain management will remain.

LF is recognized as one of the most important neglected tropical diseases (NTDs), which are often characterized as diseases of poverty. Indeed, it is clear that the considerable losses in labor inputs from LF over a prolonged period of time make it all the more difficult for endemic areas to escape from such a poverty trap without MDA intervention. Although chronic disease patients may develop coping strategies to adapt to their condition and regain some time spent in economic activity, many do so at the expense of lower-earning jobs that require less physical activity (Gyapong et al., 1996; Muhondwa, 1983). In Tanzania, it is roughly reported that patients who were primarily fishermen lose about 53% of their income each month due to chronic LF disease (Ntuli et al., 2009). Those with severe morbidity may be confined to the home and forced to give up income-generating activity altogether.

Proponents of the friction-cost method of indirect cost calculation would argue that substitute labor could replace the lost inputs and outputs of an LF patient (Koopmanschap et al., 1995). However, with most LF patients working outside the formal economy, other family members would have to act as substitute labor, which often subtracts the same proportion of household income. For example, a study on the economic burden of malaria found household members more likely to care for the patient than act as substitute labor, particularly when skilled labor is involved; when substitution did happen, output was not perfectly replaced (Attanyake et al., 2000). Friction-cost theorists also argue that lost hours can be made up by extra productivity during non-sick hours; however, reduced labor inputs in time-sensitive activities such as agricultural planting cannot be so easily replaced later on. LF studies indicate that it may even be necessary for sick individuals to hire temporary workers to replace their labor, thus exacting an even greater indirect financial burden on the patient.

In analyzing the economic impact for the 31.4 million *benefit cohort population*, this study estimates that individuals receiving MDA before infection or at the subclinical disease stage have a much higher average lifetime and annual economic benefit than individuals already manifesting clinical disease (**Table A18-6**). With advanced stages of hydrocele and lymphedema posing even greater risks of physical and economic disability (Pani et al., 1995), MDA at the pre-infection or pre-clinical disease stage is critical, particularly in high-transmission areas. Furthermore, high coverage rates in areas undergoing MDA allow a subgroup of untreated individuals to be protected from infection, subsequent clinical disease, and the incurrence of economic costs as a result of reduced rates of LF transmission. The extension of benefits to individuals beyond those directly receiving MDA or infected with LF accentuates the wider community economic impact of the GPELF.

This broader impact also includes financial savings to national health systems as a result of decreased need for patient services associated with LF

morbidity. Using WHO-CHOICE's valuation of health center outpatient visits (WHO-CHOICE, 2008), MDA from 2000–2007 will lead to an estimated economic benefit of approximately US$2.2 billion over the same timeframe as calculated for the 31.4 million *benefit cohort population*. Such significant savings are particularly critical for resource constrained health systems and primary health centers operating beyond capacity. The economic benefits to health systems are arguably even greater than the estimate presented in this analysis. This model did not account for the effect of MDA on decreasing the need for hydrocele surgeries and lymphedema morbidity-support services because accurate regionalized data on the extent of averting these specific provider costs is limited. From the scarce literature available, hospitals in Tanzania, coastal Kenya, and northern Ghana have reported that 15–25% of all surgeries performed were for hydrocele (Wegesa et al., 1979; Mwobobia et al., 2000) and that establishing a single lymphedema treatment clinic in Haiti can cost the health system US$8,000 (Kanjilal et al., 2004). In India, the additional cost of implementing filariasis control programs at the primary health center (PHC) level was estimated at approximately US$800 per PHC per year (Krishnamoorthy et al., 2000). Limiting the future need for such services will bring sizable cost savings for both national filariasis control programs and health systems, which further underscores the GPELF's societal economic impact.

Cost-Benefit Calculations

In **Table A18-10**, the BCRs calculated with *economic* costs are low, particularly for the African countries using the ivermectin+albendazole regimen. In reality, however, the whole foundation of the GPELF is the long-term, sustained commitment of drug donations offered by GlaxoSmithKline for albendazole and Merck & Co., Inc. for ivermectin for as long as needed until LF is eliminated (WHO Press Office, Jan. 1998, Oct. 1998). Because of this commitment, governments and donors will never have to finance these costs themselves; indeed, without these commitments there would be no GPELF. Therefore, understanding the *financial* costs (i.e. excluding the costs of the donated materials and drugs) to the GPELF is more relevant for policy- and decision-making than is the analysis of economic costs. When comparing *financial costs* to *economic benefits*, then, **Table A18-10** shows very favorable BCRs, including up to 18.07 in the Philippines.

Whether examining financial or economic costs, the BCR becomes larger in the years beyond the recommended 5 rounds of MDA to achieve lifetime protection from LF. The *Goldman et al.* study (Goldman et al., 2007) showed strong evidence that costs decrease after the initial year of implementation and after 5 rounds of MDA, the drug costs and majority of program activities would arguably subside dramatically as well. In the Philippines for example, by conservatively extrapolating the initial year's annual economic cost over 5 years, the cost to *lifetime* benefit ratio indicates that a $1 investment leads to a sizable

return of $60 per individual treated. While this analysis does not account for costs following the 5th round of MDA (e.g. post-MDA surveillance), it can be reasonably assumed that the BCR would still remain very significant. Indeed, even if annual *economic* costs were to persist at an equivalent rate for an additional 10 to 15 years, the economic rate of return per person treated is still approximately $20–$30 for every $1 invested.

Comparing the cost-benefit of the GPELF to that of other NTD programs is difficult because there are few directly comparable analyses, particularly at a global level. A review of the African Programme for Onchocerciasis Control (APOC) projected an economic rate of return of 6% to 17% but did not factor in the implied economic cost of the donated drug (Benton, 1998). This finding is less than the drug-excluded LF cost-benefit estimate presented here, however, several economic benefits apart from onchocercal blindness prevention were not analyzed in the APOC review. Cost-benefit analyses for trachoma have focused almost exclusively on trichiasis surgery in a localized context (Frick et al., 2003). A broader array of cost-benefit studies has been carried out for malaria, although with differing scopes and outcome goals, making it challenging to compare results across the same disease, let alone between malaria and LF. In a review of several malaria costing studies, the BCR ranged from 1.9 to 17.1 using a variety of human capital and burden of disease methodologies (Mills et al., 2008). Other approaches assessing a more macroeconomic impact of malaria (Sachs and Malaney, 2002; Gallup and Sacks, 2001) have yet to be applied to NTDs but future research into such cost-benefit applications will be critical for validating the investment of the GPELF and stimulating likeminded investigations for related global NTD programs.

There has been considerable movement – particularly in Sub-Saharan Africa – toward integrating preventive chemotherapy programs to target multiple NTDs (e.g. LF, onchocerciasis, schistosomiasis, soil-transmitted helminths [STH], trachoma) together. Although there is no clear verdict yet on the benefits of integrated NTD treatments versus standalone vertical programs, early assessments indicate potential savings of 25–47% for the entire group of NTDs can be achieved in Sub-Saharan Africa by packaging MDA interventions together (Brady et al., 2006). These findings underlie an important concept of economic analysis, specifically that although an intervention (e.g. vertically integrated MDA programs for LF) may have a favorable BCR, there may be more *cost-effective* alternatives to achieving a similar *outcome* (e.g. the number of treatments administered, the total economic benefits of the GPELF). In this respect, the GPELF is well positioned to take advantage of synergistic opportunities with other disease program activities including vector control (malaria and dengue fever), surveillance (guinea worm, onchocerciasis), and distribution (integrated NTDs, Vitamin A) to maximize cost-effectiveness and economic impact (Molyneux, 2003). Joint efforts with the private sector and drug development projects addressing improved sanitation and housing facilities could also contribute to greater cost-

effectiveness for the GPELF (Haddix and Kestler, 2000). While this study is not positioned to analyze cost-effectiveness in details, it is abundantly clear that under any joint or standalone scenario, the GPELF indeed represents an excellent buy in global health.

Additional Economic Benefits of the GPELF

The prevention of LF infection and clinical disease has led to additional benefits that are difficult or impossible to quantify in monetary terms. The true economic value of the GPELF is, therefore, arguably much higher based on the numerous quality-of-life benefits achieved through clinical disease aversion, as well as the economic impact that MDA has on other diseases and syndromes related to LF.

Quality-of-life benefits. Quality-of-life benefits may relate only peripherally to the economic burden of the disease but may be equally as important as the costs included in the model due to their direct impact on patient livelihood. Social stigma is a very important consequence of LF morbidity. The ostracism and isolation that LF patients experience in their communities can lead to delayed treatment seeking; this results in faster progression to later stages of morbidity where the economic burden is even higher (Perera et al., 2007). In organized labor, employers may fire patients with obvious morbidity due to decreased productivity or misunderstanding of disease etiology. Female patients are often not considered suitable for marriage if they have lymphedema, which heavily impacts social and economic status (Coreil et al., 1998; Evans et al.,1993; Hunter, 1992). Similarly, males with hydrocele report difficulties in finding spouses, ridicule from community members, and various degrees of sexual dysfunction (Gyapong et al., 2000). Schoolchildren are expected to stay home to care for a family member with LF who is experiencing an acute attack, and infected schoolchildren frequently miss school or drop out due to ostracism (Ramaiah and Kumar, 2000). When LF impacts incomegenerating activity of the heads of households, children may be forced out of school and into labor at an early age. This absenteeism from school and eventual dropping out maintains the poverty cycle for affected families and has important implications for endemic communities as a whole (Perera et al., 2007). The efforts of the GPELF in eliminating these devastating consequences of clinical disease have created enormous quality of life benefits that have undoubtedly led to a tremendous economic impact through enhanced productivity and community welfare.

The GPELF must also be recognized as more than just a MDA-based distribution program As such, the GPELF's 'second pillar' is to provide care and initiate strategies for the control of clinical morbidity (Addiss and Brady, 2007). In particular, compliance to GPELF activities based on personal hygiene management of lymphedema has caused tremendous improvements in the physical

and mental wellbeing of chronic disease patients. These improvements surely produce an unquantifiable economic benefit and reinforce the notion that even if antifilarial drugs do not have a direct effect on clinical morbidity reversal, the GPELF has created other mechanisms for long-term increased productivity for overt clinical disease patients.

Economic impact on other LF syndromes and co-endemic diseases. MDA reduces the acquisition of other debilitating overt clinical LF manifestations such as chyluria and tropical pulmonary eosinophilia (TPE). While these other syndromes are less prevalent than hydrocele and lymphedema, their physical and resulting economic burden can be even more severe. Socioeconomic data concerning such LF-associated syndromes, however, is essentially absent and therefore currently unquantifiable. Also not considered quantitatively was the full economic impact of subclinical LF infection. By protecting individuals from *even reaching the subclinical level*, the GPELF will have garnered economic benefits from preventing the renal disease, lymphatic dilatation, and lymphatic dysfunction in subclinically infected patients (Chhotray et al., 2000; Dreyer et al., 1992).

The GPELF's drug regimens also result in decreased economic costs for other diseases *besides* LF – including river blindness and scabies in Africa and intestinal parasites globally. Considering the disease burden of these three infections and their geographic overlap with LF, it is certain that an important reduction in these diseases is found in MDA treatment areas, resulting in health and economic benefits from prevention and diminution of stunting, anaemia, renal disease, and other complications (Hengge et al., 2006; Laurence et al., 2005).

Study Limitations

A narrow range of country-specific primary data somewhat limits the breadth of economic analysis presented in this paper; however, much of the prevailing literature originates from India and Sub-Saharan African countries where over 75% of the *benefit cohort population* resides. Of significance, there is scarce regional data regarding treatment-seeking behavior for LF patients, but because this is a direct cost input, more exact data would result in only marginal changes to the overall economic impact. Similarly, LF disease-specific parameters (e.g. ADL frequency and duration, lost workdays) were attributed a global standardized estimate due to a lack of regional data. Sensitivity analyses conducted earlier in this study presented the resulting economic impact under differing degrees of pathology and indeed, a clearer understanding of regional variability would enrich future economic analyses. Other variables such as wages, health system costs, and direct treatment costs, however, were able to be made region- and country-specific with the aid of international databases from the ILO, WHO, and World Bank.

Economic Projections for the Future Impact of GPELF

Despite important limitations to our analysis, this study identifies a wide array of economic benefits that have resulted from the first 8 years of the GPELF – approximately US$21.8 billion of direct and indirect patient costs will be prevented in the lifetimes of more than 31 million individuals, US$2.2 billion of LF-associated patient services saved by national health systems over the lifetimes of the MDA-treated individuals, and additional quality-of-life benefits and treatment of co-morbidities such as STH that make the total economic value of the GPELF unquestionably far greater than the calculable estimate presented here.

These achievements notwithstanding, it is clear that the economic impact will be even greater when the GPELF reaches the remaining endemic countries and at-risk populations. Currently, the GPELF has extended to 48 of the 83 endemic countries and treated nearly 570 million individuals – approximately 44% of the,1.3 billion worldwide at-risk population (WHO, 2008). Extrapolating this proportion with the US$24 billion lifetime economic benefit already achieved, the full *potential* economic benefit of the GPELF could be in excess of US$55 billion distributed over each of the endemic WHO regions (**Figure A18-5**).

Reaching the remaining at-risk individuals presents notable challenges especially since much of the population not yet reached resides in some of the poorest countries in Africa. Additional resources and economic empowerment will be necessary to assist these countries in implementing programs for LF elimination (Bockarie and Molyneux, 2009). The expansion of the GPELF will therefore be a critical building block in this effort and also an important driver for increased attention to NTDs and the continuation of integrated NTD programs. The recognition of the sizable monetary benefit already achieved after 8 years provides new confidence that it is an investment well worth undertaking.

Supporting Information

Alternative Language Abstract S1 Translation of the abstract into French by PJH.

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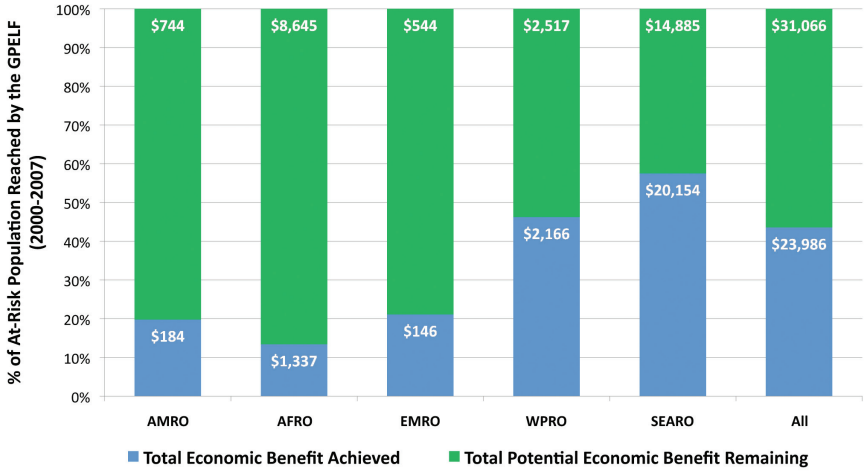

FIGURE A18-5 Potential economic impact of the GPELF. Indicates the economic benefit already achieved and the potential benefit remaining should the GPELF reach all endemic countries and at-risk populations. doi: 10.1371/journal.pntd.0000708.g005.

Author Contributions

Conceived and designed the experiments: BKC PJH MHB DAM EAO. Performed the experiments: BKC PJH MHB DAM EAO. Analyzed the data: BKC PJH MHB DAM EAO. Wrote the paper: BKC PJH MHB DAM EAO.

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A19

NEGLECTED TROPICAL DISEASES: THE DEVELOPMENT OF A BRAND WITH NO COPYRIGHT. A SHIFT FROM A DISEASE-CENTERED TO A TOOL-CENTERED STRATEGIC APPROACH

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A Paradigm Shift

In 2003, under the leadership of Dr. J. W. Lee, just appointed Director General, the World Health Organization (WHO) started a process of paradigm shift in the control and elimination of neglected tropical diseases (NTDs) (Box A19-1). The shift consisted of the adoption of a new vision that abandoned a purely academic approach to adopt one more responsive to the needs of affected individuals and communities. As a consequence, it entailed a strategic rethinking and a move away from a "theoretical," structural classification based on disease biology toward a "practical" one based on the available tools employed to control such diseases.

For a group of afflictions, mainly helminth infections, this shift generated a radical change in the public health control approach, which no longer consisted of the disease-specific implementation of isolated interventions but was now focused on a broader, person-centered concept involving large-scale provision of treatment in an integrated fashion. This paradigm shift was undertaken to ensure a more efficient use of the limited resources available and with the objective to help marginalized rural and urban population groups to pull themselves out of the vicious cycle of poverty and illness.

This paradigm shift toward integrated control of NTDs was a result of a long intellectual process that covered three major areas:

1. the *generation and acquisition of the necessary scientific knowledge*;
2. the *promotion and dissemination of the intervention strategies* to decision makers in endemic countries; and
3. the *building of the consensus* among the potential partners as a way to secure the financial and in-kind resources.

Table A19-1 illustrates the steps that were taken for the development of the scientific knowledge and evidence necessary to support the integrated control of helminth infections. This process covered a period of more than three decades, from the initial idea of a single tablet to treat schistosomiasis and soil-transmitted

BOX A19-1
NTDs and Their Common Features

The list of NTDs is vast and virtually open ended. For the time being, WHO's work is confined to a list of 17 selected helminth, protozoal, and bacterial diseases. There are 149 countries and territories where NTDs are transmitted, and at least 100 of them are endemic for 2 or more diseases and 30 are endemic for 6 or more (WHO, 2010d).

The NTDs are quite a diverse and heterogeneous group of diseases. However, they share a number of common features:

1. *The Hallmark of Poverty and Underdevelopment*

The most striking common feature of the NTDs is that they affect almost exclusively poor and marginalized populations (Hotez et al., 2009) living in settings where poverty is widespread and resources, or access to livelihood opportunities, are scarce. NTDs have an enormous impact on individuals, families, and entire communities in developing countries in terms of burden of disease, quality of life, loss of productivity, aggravation of poverty, and the high cost of long-term care. They constitute a serious obstacle to socioeconomic development and quality of life at all levels.

2. *Diseases of Non–Decision Makers*

Affected populations often live in remote rural areas, in conflict zones, or in urban slums and have little political voice. They cannot readily influence administrative and governmental decisions that affect their health and often seem to have no constituency that speaks on their behalf. Diseases associated with rural poverty may have little impact on decision makers in capital cities (Pecoul, 2005).

3. *Association with Stigma and Discrimination, Especially of Women*

Many NTDs produce disfigurement and disability, leading to stigma and social discrimination. Their impact disproportionately affects women, whose marriage prospects may diminish or who may be left vulnerable to abuse and abandonment (Hotez, 2008).

4. *Not Traveling*

Unlike influenza, HIV/AIDS, malaria, and, to a lesser extent, tuberculosis, NTDs generally do not travel and seem to present little threat to the inhabitants of high-income countries. Rather, the distribution of NTDs is restricted by climate and its effect on the distribution of vectors and reservoir hosts; there appears to be little risk of transmission beyond the tropics (Pecoul, 2005).

helminths (STHs) to the complete development of the necessary armamentarium of active drugs and strategies for distribution.

Table A19-2 presents the steps taken for the promotion of implementation of NTD control activities: this process took at least one decade from the leading article of Savioli et al. (1992) in the *Transactions of the Royal Society of Tropi-*

TABLE A19-1 Main Steps for the Development of Scientific Knowledge for NTD Control

Year	Step	Reference
1980	Suggestion of a single tablet of albendazole + praziquantel to treat both soil-transmitted helminthiasis and schistosomiasis	Rockefeller Foundation, unpublished report of Bellagio meeting 1980
1990	Proposal of an integrated system for helminth control	(Warren, 1990)
1992	The WHO publication: "Health of School Children: Treatment of Intestinal Helminths and Schistosomiasis" suggests combined drug delivery (coadministration) of albendazole/mebendazole and praziquantel	WHO/CDS/IPI/CTD 92.1
1994	Development of single dose of mebendazole 500 mg	(Albonico et al., 1994)
1999	Study on the possibility of concurrent administration of praziquantel and albendazole	(Olds et al., 1999)
2001	Development of the tablet pole for the administration of praziquantel	(Montresor et al., 2001)
2008	Test of the safety and effectiveness of triple drug administration (ivermectin, albendazole, and praziquantel) for treatment of lymphatic filariasis, soil-transmitted helminthiasis, and schistosomiasis	(Mohammed et al., 2008)

cal Medicine and Hygiene to the World Health Assembly resolution of 2001 and another 10 years to the recent launch of the first WHO report on neglected tropical diseases (2010d).

The donations and financial supports that made possible the scale-up of NTD control are presented in Table A19-3; the process starts with the first donation of ivermectin for the control of onchocerciasis in 1987, to the multiple and expanding donation from GlaxoSmithKline (GSK), Johnson & Johnson (J&J), and Eisai in 2010.

New Strategic Approaches

The main outcome of the NTD paradigm shift in the field of helminth infections was the definition and launch of the "new drug strategy" called preventive chemotherapy. The mainstay of the strategy is a population-wide, drug-based approach that supersedes the old disease-specific "compartments" that determined a scenario in which treatment of specific forms of helminthiasis was provided separately; preventive chemotherapy is rather centered on the best, coordinated use of the available medicines for a synergic action against a number of afflictions.

In 2006, *Preventive Chemotherapy in Human Helminthiasis* (WHO, 2006) recommended the integrated implementation of disease interventions against the four main helminth infections (schistosomiasis, soil-transmitted helminthiasis,

TABLE A19-2 Steps for the Promotion of Implementation of NTD Control

Year	Step	Reference
1992	Savioli et al.'s leading article: "Intestinal parasitic infections: a soluble public health problem" in the *Transactions of the Royal Society of Tropical Medicine and Hygiene*	Savioli et al. (1992)
2001	World Health Assembly resolution on schistosomiasis and soil-transmitted helminthiasis	WHA (2001)
2002	Establishment of a single Expert Committee for schistosomiasis and soil-transmitted helminthiasis	WHO (2002)
2002	Second Savioli et al. leading article "Schistosomiasis and soil-transmitted helminth infections: Forging control efforts" in the *Transactions of the Royal Society of Tropical Medicine and Hygiene*	Savioli et al. (2002)
2002	Establishment of the Partnership for Parasite Control	http://www.who.int/wormcontrol/en/
2003	Bali Declaration	Crompton et al. (2003)
2005	Berlin Meeting	http://whqlibdoc.who.int/hq/2006/WHO_CDS_NTD_2006.1_eng.pdf
2005	Establishment of the NTD department in WHO	
2006	WHO manual *Preventive Chemotherapy in Human Helminthiasis*	WHO (2006)
2007	Global Partners' Meeting on NTDs	http://whqlibdoc.who.int/hq/2007/WHO_CDS_NTD_2007.4_eng.pdf
2010	First WHO Report on Neglected Tropical Diseases	WHO (2010d)

lymphatic filariasis, and onchocerciasis) based on the coordinated use of a set of anthelminthic drugs, thereby expanding to two new diseases the integration efforts made previously for schistosomiasis and soil-transmitted helminthiasis. This strategy is made possible by the availability of powerful, safe, and easy-to-administer medicines that bring immediate, dramatic, and continued relief. Treatment can be extended to all at-risk populations through innovative delivery mechanisms put in place by nontechnical personnel, such as teachers and community-based volunteers. Regular treatment improves maternal health, reduces neonatal mortality, promotes childhood growth and development, increases school attendance and performance, and avoids chronic irreversible disease at a later stage in life. The major challenge for the implementation of preventive chemotherapy is to expand its coverage in order to provide all at-risk populations with regular treatment. In spite of logistic challenges, preventive chemotherapy

TABLE A19-3 Steps for the Building of Consensus Among Partners and Donors

Year	Step
1987	Donation of ivermectin from Merck & Co., Inc., for the control of onchocerciasis
1998	Expansion of the Merck & Co. donation for the control of LF
1998	GSK donation of albendazole for the control of LF
2002	The Bill & Melinda Gates Foundation grant Schistosomiasis Control Initiative
2007	J&J donation of mebendazole for the control of STHs
2007	Merck KGaA donated praziquantel for the control of schistosomiasis
2008	G8 declares in Hokkaido (Japan) that it will help to control and eliminate several NTDs
2008	President Bush announces New Global Program to Combat NTDs USAID began an integrated NTD control program, focusing initially on five countries in Africa
2008	DFID announces a commitment over the following five years to fight NTD
2009	The Bill & Melinda Gates Foundation grants US$34 million to Global Network for NTD
2010	Expansion of the GSK donation of albendazole for the control of STHs
2010	J&J quadruples mebendazole donation for the control of STHs
2010	Eisai announces donation of DEC for control of LF

NOTES: DFID, U.K. Department for International Development; GSK, GlaxoSmithKline; J&J, Johnson & Johnson; LF, lymphatic filariasis; STH, soil-transmitted helminth; USAID, U.S. Agency for International Development.

interventions are currently implemented on a worldwide scale and more than half a billion individuals are treated every year (WHO, 2010a, 2010b, 2010c).

The increasing success of this approach is boosted by a number of factors:

- the clear demonstration of the association of such infections with poverty and economic burden (Hotez et al., 2009);
- the geographical overlap existing among the four diseases targeted (Clements et al., 2010);
- the contribution of preventive chemotherapy not only to morbidity reduction but also to sustained decrease of transmission (Sinuon et al., 2007);
- its added benefits on a number of affections not specifically targeted by the intervention (such as scabies and lice) (Mumcuoglu and Gilead, 2008);
- its flexibility, which allows the expansion of its target to virtually any helminth infection, as shown by the case of fascioliasis and other food-borne trematode infections (Keiser et al., 2010); and

- the fact that drug delivery mechanisms in place for helminth control can be used as a platform to target other communicable diseases such as trachoma (Hu et al., 2010) paves the way for a further expansion of this public health approach which now shares, from an organizational and logistic perspective, many common features with immunization.

In the field of protozoan and bacterial diseases such as African sleeping sickness, leishmaniasis, Chagas disease, Buruli ulcer, and yaws, the main outcome of the NTD paradigm shift has been a new focus on improved and timely access to specialized care through a better case detection and an effective decentralization of clinical management, in an effort to preventing mortality and reducing morbidity and transmission (please refer to Appendix pages 310–323). Even if these diseases are tackled effectively, it requires the specific expertise of skilled personnel, and if dramatic and sustainable steps forward must await the development of better, safer, more affordable, and simpler-to-use diagnostics and drugs, it is clear that this group of infections could also immediately benefit from a more coordinated strategic approach if the focus of the intervention was shifted to a wider access to treatment for those in need, through an innovative and intensified case management aimed at optimizing the use of existing tools (WHO, 2010d).

Vector control was also rethought in light of the new, integrated strategic framework as a key crosscutting activity to be implemented in conjunction and coordination with both preventive chemotherapy and intensified case management. As such, integrated vector management was launched as an effective combination of different interventions as well as an intersectoral and interprogrammatic collaboration within the health sector and between this and other sectors, such as agriculture and the environment. Its aim is to improve the efficacy, cost-effectiveness, ecological soundness, and sustainability of disease control interventions implemented against those NTDs that are vector borne and that are in fact the majority (WHO, 2010d).

Rebranding

Following the development of the new strategic approaches, it was time for a change in name: in 2005, at the historical meeting in Berlin,[42] WHO formally rebranded this area of work, previously vaguely defined as "other communicable diseases" or "other tropical diseases," meaning other than malaria, tuberculosis, and HIV/AIDS, as neglected tropical diseases. The Berlin meeting also defined the NTDs as a set of infectious diseases—most of which are preventable and/or treatable—that remained among the primary causes of death and ill health among the poorest sectors of the population worldwide. In such a manner the international community recognized that many other chronically endemic tropi-

[42] Report of the WHO Strategic and Technical Meeting on Intensified Control of Tropical Diseases, available at http://whqlibdoc.who.int/hq/2006/WHO_CDS_NTD_2006.1_eng.pdf.

cal diseases, beyond the aforementioned "big three," were still much neglected in the global public health agenda and had to be moved out of the shadows. WHO convened this meeting with partners and experts to secure strategic and technical guidance and take this agenda forward.

On April 17 and 18, 2007, WHO convened the first Global Partners' Meeting on NTDs. Some 200 participants attended the meeting, including representatives of WHO Member States, United Nations agencies, the World Bank, philanthropic foundations, universities, pharmaceutical companies, international nongovernmental organizations, and other institutions dedicated to contributing their time, efforts, and resources to tackle neglected tropical diseases. Guests of honor included His Excellency Mr. Blaise Compaoré, President of Burkina Faso, and Mr. Samuel Eto'o, the Cameroonian footballer. This meeting declared to the world that the burden represented by NTDs is substantial and as such it deserves attention and high priority on the global public health agenda; that prevention, control, elimination, and eradication of these diseases is possible, but greater determination is required to achieve these goals through delivery of appropriate health care to the millions of poor people in need. "This event marks a turning point in the long and notorious history of some of humanity's oldest diseases," said WHO Director-General Dr. Margaret Chan in her opening address. "The burden imposed by these diseases, measured in terms of human misery alone, is unacceptable. We are committed to take action."

Lessons Learned and Successes Achieved

Even if only a few years have elapsed since the start of the NTD paradigm shift, it is already possible to appreciate some of its positive effects: overall, it has enabled Member States and partners to find innovative solutions enabling weak health systems to target the people most in need: the poorest sectors of the population with limited or non-existent financial means. Grouping several diseases together under the NTD framework has offered the opportunity to start recalculating the collective burden associated with this set of very diverse afflictions as well as their cumulative public health relevance and, consequently, to raise attention and mobilize resources for a world-scale implementation of disease control and elimination activities.

Despite the fact that many low-cost and effective interventions are available to tackle most of these diseases, the majority of affected populations do not yet have access to adequate treatment and care (WHO, 2010d). Nevertheless, where disease control interventions have been implemented, "hidden" but relevant successes have shown that these diseases can be effectively managed, and in certain instances elimination and eradication are undeniable possible outcomes (WHO, 2010d). Achieved successes have gradually come to light, offering an opportunity for expansion and generating interest by an increasing number of Member States, bilateral and multilateral donors, and new partners engaged in poverty alleviation.

The heavy burden imposed by NTDs on poor people is gaining wider rec-

ognition and prominence by countries and institutions with the capacity to release resources for prevention and control (Hotez and Kamath, 2009). Effective advocacy has successfully exploited the notion of neglect and stimulated health policy makers to work to overcome the burden associated with NTDs in harmony with the ideals and aims of the United Nations Millennium Development Goals (Boutayeb, 2007). Available tools for treatment intervention in communities are now reaching millions in need, offering evidence that, where interventions are implemented, results can be achieved with comparably limited investments.

Current Opportunities and Challenges

Experience shows that transmission of NTDs can decrease to the point of interruption, especially when treatment is complemented by improvements in safe water supply, housing, hygiene and sanitation, vector control, and veterinary public health measures (Huppatz et al., 2009; Sinuon et al., 2007). Control of NTDs is a highly cost-effective exercise with immediate benefits that are powerfully visible. These benefits, in turn, stimulate public demand for treatment, thus paving the way for community engagement.

The NTDs have the unique advantage of major donations from the pharmaceutical industry. Hundreds of millions of treatments are donated yearly to address the fight against both the "tool-ready" and the "tool-deficient" disease groups. This healthy relation between the public and private sectors answers the need for access to free treatment for the poorest in endemic countries.

Much has been accomplished, but more resources are needed, on the one hand, to expand treatment coverage of both preventive chemotherapy and case management, and on the other hand, to support the research and development required to develop, test, and produce new medicines and diagnostics. Such investments are crucial to progressively expand what is already working and to sustain the advancement and the progress in the control of the tool-deficient group of infections. The ultimate goal is to ensure that all populations in need have timely access to effective, simple, and safe single doses medications against any NTDs.

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A20

LOOKING BEYOND THE LAMP POST: ADDRESSING SOCIAL DETERMINANTS OF NEGLECTED TROPICAL DISEASES IN DEVISING INTEGRATED CONTROL STRATEGIES

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> "We cannot solve our problems with the same thinking we used when we created them."
>
> —Albert Einstein

There is an old story about the drunkard who insists upon looking for missing keys near a lamp post where "the light is better," even though the missing object had been dropped some distance away in darker terrain. Similarly, to someone who only has a hammer, everything can look like a nail. Such accounts remind us that the approaches that we rely upon to guide our problem solving are implicitly quite capable of undermining the effectiveness of our quest, especially if such orientations, or paradigms, may be founded on criteria that have more to do with particular interests, or predispositions, than with achieving desired outcomes. And in many cases, as Einstein famously observed (above), such biases in our thinking may well be contributing directly to the initial emergence of the problem itself.

The past decade has witnessed a host of new initiatives and funding (Buckup, 2008; Croft, 2005; Ravishankar et al., 2009; Yaich, 2009) to address devastating health concerns that affect the world's poorest people and are increasingly referred to as "neglected diseases." However, despite substantial increases in funding, the disease burden associated with these afflictions remains high (Hotez et al., 2008; Oprea et al., 2009). In some cases, such as Guinea worm, dramatic progress has been made; however, this has been achieved with relatively modest funding primarily through a comprehensive series of targeted public health interventions and in the absence of drug or vaccine breakthroughs (Barry, 2007).

As several colleagues and I recently argued (Spiegel et al., 2010), a key reason for persistence of a "neglected tropical diseases" disease burden may well be that efforts to address it predominantly by modifying the established drug development paradigm have inadvertently served to reinforce neglect of how social determinants of health (SDH) affect health equity. It is indeed curious that, while structural factors associated with alarming global health disparities have been receiving growing attention over the past decade as a counterbalance to a biomedical disease model that had tended to ignore such factors, highlighted by the 2007 report of the Commission on Social Determinants of Health, consideration of solutions for the populations most affected by neglected diseases seems to be

ignoring the implications of such reconceptualization. Indeed, a major debate has been concurrently pursued regarding whether "vertical" disease-specific funding itself has been counterproductive in diverting funds (Marchal et al., 2009; Ooms et al., 2008).

The focus of this paper is to explore the critical relevance of incorporating social determinants in measures being pursued for addressing neglected tropical diseases (NTDs), to take stock of the extent to which it is being incorporated in initiatives under way, and to consider how it can be more systematically integrated with other approaches to enable the pursuit of more effective control strategies.

Two Paradigms Passing in the Night

The era of globalization, characterized by increasingly intensified interactions, has been accompanied by an explosion in the production and sharing of knowledge regarding the characteristics of what is being experienced in recent decades. This has stimulated the development of new ways of understanding complexities and orienting what we can do about them.

From the perspective of global health, there have been two prominent tendencies to appreciating what is at stake. On the one hand, increasingly sophisticated bio-medical technologies have been developed to recognize, identify and diagnose relevant health/disease states and consider ways of intervening on individual and population levels, so as to be able to promptly address areas such as "emerging infectious diseases. On the other hand, there has been a growing recognition of the social disparities that have been aggravated by the patterns of globalization experienced over this period. Each of these orientations has prompted the explicit development of distinct new ways of looking at global health challenges, respectively emphasizing particular elements that were deemed to have been inadequately addressed and bringing forward new paradigms to consider in line with this perception:

- neglected diseases or NTDs, and
- social determinants of health (SDH).

Although the concept of *disease* is rooted directly in a biomedical definition of aberrant health states, its incidence and prevalence are no less related to social factors. *Neglect*, on the other hand, is by definition primarily a social construct, which points only in part to technical areas that require greater attention.

Recognition of this "neglected disease" crisis was heightened by attention drawn to the "10-90 Gap" paradigm popularized by the Global Forum for Health Research in 2000 (Global Forum for Health Research, 2002) to highlight the incongruity between disease burden and global health research efforts, although defenders of effectiveness of the basic "R&D paradigm" that is in effect to pro-

vide incentives for drug development (Stevens, 2004) posit that wealth creation remains fundamental to improving health, challenging the usefulness of the neglected disease characterization itself. Paradigms clearly play a major role in influencing our understanding and actions in health research (Rockhold, 2007), so the question remains: Can a paradigm focusing on "neglected disease" address today's persistent health equity challenges without an explicit consideration of broader contextual factors that affect health?

From the beginning, conceptualization of *neglected disease* as persistence in the prevalence of certain diseases affecting the poorest people in the poorest societies implicitly acknowledged association with social conditions. That being said, a particularly relevant expression of *neglect* was observed in the phenomenon that despite dramatic expansion of the pharmaceutical industry accompanying the expansion of globalization: "[S]ometimes there were simply no drugs at all because of the dearth of research and development (R&D) for neglected diseases. This understanding—and the drive to change the global paradigm—led Pécoul to set up DND*i* [Drugs for Neglected Diseases initiative] in 2003" (Shetty, 2010). In fact, as the focus has narrowed on designated sets of diseases in line with this sentiment, the concept of neglected tropical disease has itself received growing attention.

Table A20-1 illustrates how these trends have evolved in the past decade, reflecting the tremendous growth in attention that was experienced—triggering a 100-fold increase in explicit mention of "neglected tropical disease" in the scientific literature over this period. The potential bias of increased publication access is accounted for by comparison to tuberculosis, a disease of long-standing recognition that had itself experienced some stimulus in attention with increased funding available from the Global Fund to Fight AIDS, Tuberculosis, and Malaria.

In focusing on why the pharmaceutical industry had failed to develop products for diseases (of poverty) in the absence of market incentive (Love and Hubbard, 2003; MSF, 2001; Trouiller, 2004), it has been explicitly observed that the "economic paradigms, which have dominated international institutions, are being challenged by social ones" (Cohen-Kohler, 2007). Consideration of how to overcome *neglect* in relation to the prevalence of designated diseases has thus

TABLE A20-1 Trends in Journal Articles Incorporating Terms Related to "Neglected Disease," 1998–2009

	1998–1999	2003–2004	2008–2009	Trend Comparing 1998–1999 vs. 2008–2009
Neglected disease	126	237	805	+639%
Neglected tropical disease	3	2	303	+10,000%
Tuberculosis	68,000	50,700	106,000	+56%

NOTE: Articles identified in Google Scholar applying designated key terms (accessed December 7, 2009).

increasingly become narrowed to overcoming the specific *neglect* of drugs and vaccine development—reflecting how innovations and attention have become skewed to this orientation, something that is explored further following an introduction to alternative emphases that have emerged at roughly the same time.

In the context of attention to global disparities, and reinforced by the adoption of the Millennium Development Goals (MDGs) in 2000 as a way to establish international governments' commitment to addressing this phenomenon, attention increasingly was drawn to circumstances that could be driving these trends. In fact, building especially on the scope and insights of social epidemiology, and drawing on the work of a variety of "knowledge networks" established to support a comprehensive examination of factors deemed relevant to health equity, the World Health Organization established a Commission on Social Determinants of Health (Marmot, 2005) in 2005. In providing a comprehensive compendium of what was known about problems and related interventions, it has been observed that "the commission advocates a paradigm shift that would expand the current scope of analysis and action to include broader social factors: policies that are good for health, not just health care policies."

Long before the Commission on Social Determinants of Health, proponents of primordial and primary prevention have repeatedly questioned the "biomedical" paradigm, noting that social and environmental determinants of health play a major role in reducing disease burden, as was registered by Thomas McKeown in his examination of the factors underlying improved health in the United Kingdom, with particular reference to tuberculosis (Colgrove, 2002; McKeown and Record, 1962). In the early 20th century, for example, hookworm received ample funding from the Rockefeller Foundation to concurrently treat those infected *and* address health determinants via installation of sanitary facilities (Brown, 1976). This approach, which proved effective to virtually eliminate yellow fever, malaria, hookworm, and pellagra in the American South by 1950, seems to have vanished from sight in the contemporary era (Humphreys, 2009), although the success of the campaign to eradicate Guinea worm has indeed scored considerable success with a largely comparable orientation (Barry, 2007).

It is especially noteworthy to observe that growth in attention to the constructs of "determinants of health" and "social determinants of health" as new paradigms for approaching contemporary health challenges has been quite similar (Table A20-2), with an 11-fold increase in the latter concept experienced in its mention in scientific literature. This is all the more noteworthy in that the well-established construct of poverty in fact experienced an overall decline in its use in the scientific literature over this period, and even with the increased attention afforded by the MDGs and the global health discourse and disparity, its use in combination with health also experienced a slight reduction.

In recognition of the concurrent emergence of the new paradigms of "(tropical) neglected disease" and "(social) determinant of health," as vividly illustrated by Figure A20-1, and the fact that both of these paradigms were responses to

TABLE A20-2 Trends in Journal Articles Incorporating Terms Related to "Determinants of Health," 1998–2009

	1998–1999	2003–2004	2008–2009	Trend Comparing 1998–1999 vs. 2008–2009
Determinants of health	1,960	5,000	8,900	+354%
Social determinants of health	321	1,370	4,150	+1,193%
Poverty	200,000	213,000	176,000	−12%
Poverty and health	84,200	79,600	82,200	−2%

NOTE: Articles identified in Google Scholar applying designated key terms (accessed December 7, 2009).

the growing recognition of health concerns associated with poverty, it could be assumed that there would be considerable overlap between the communities undertaking associated work. To examine this, a more detailed breakdown of the published research was undertaken.

Table A20-3 reveals remarkably little overlap between the two currents! This is no doubt due in part to the different communities involved, who are accustomed to using different discourses and vocabularies. Although this is something that speaks to the challenge of pursuing interdisciplinary collaborations in the pursuit of common goals, there is evidence that the areas of focus of the two paradigms are indeed quite separate. Indeed, even though neglected diseases are fundamentally defined as diseases of "poverty," only a minority of research discussing this subject employed even this terminology. And the orientation of a new paradigm to encourage prevention in the burden of disease that is the driving force behind the increased use of the "social determinant of health" terminology seems to have not made much of a dent in the communities engaged with neglected diseases.

Table A20-4 confirms that the overwhelming majority of literature on neglected diseases has included consideration of drug and vaccine applications, but closer examination is called for to identify works from those that are focusing on development and implementation from those that are simply referring to this component of an integrated strategy. The unique 2003 article that did not include explicit mention of drugs or vaccines, titled "Integration of trachoma control into primary healthcare: The Tanzanian experience" (Mecaskey et al., 2003) draws attention to considering literature on specific diseases as an alternative strategy to examining how the "neglected disease" and "social determinants of health" discourses may be interacting, in the likelihood that more focused discussions may suggest that more integration exists in this context. Nevertheless, the absence of explicit acknowledgement in literature invoking the broader terminology of the two paradigms is indicative of a serious separation in the communities that are aligned with each; the net effect is that attention to nonmedical determinants of those suffering from neglected diseases seems to be ignored.

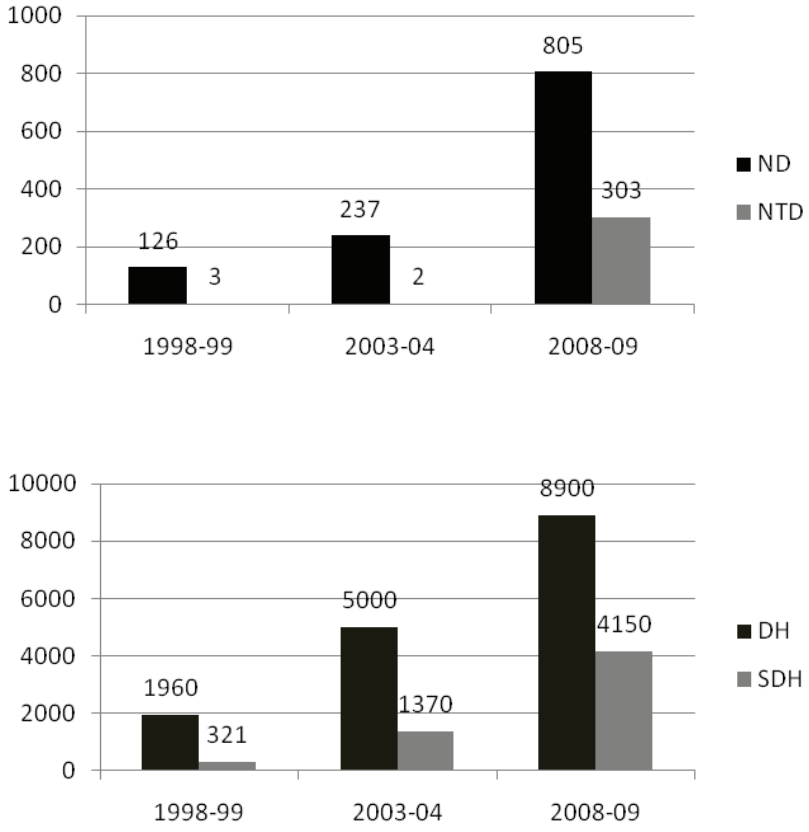

FIGURE A20-1 Concurrent growth in "neglected disease" and "determinants of health" discourse, 1998–2009.
NOTE: Articles identified in Google Scholar applying designated key terms (accessed December 7, 2009).

TABLE A20-3 Journal Articles Using Terms from Both Paradigms, 1998–2009

	Neglected Disease				Neglected Tropical Disease			
	All	+ DH	+ SDH	+ Poverty	All	+ DH	+ SDH	+ Poverty
1998–1999	126	0	0	9	3	0	0	0
2003–2004	237	4	0	43	2	0	0	0
2008–2009	805	14	7	194	303	8	3	128

NOTE: Articles identified in Google Scholar applying designated key terms (accessed December 7, 2009). DH, determinants of health; SDH, social determinants of health.

TABLE A20-4 Inclusion of Drug or Vaccine Mention in Literature on Neglected Diseases, 1998–2009

	Neglected Disease (ND)				ND + Poverty			
Year	All	With Drug	With Vaccine	Without Drug or Vaccine	All	With Drug	With Vaccine	Without Drug or Vaccine
1998–1999	126	68	41	0	9	6	5	0
2003–2004	237	155	100	0	43	35	28	1
2008–2009	805	568	327	28	195	157	132	1
	Neglected Tropical Disease (NTD)				NTD + Poverty			
Year	All	With Drug	With Vaccine	Without Drug or Vaccine	All	With Drug	With Vaccine	Without Drug or Vaccine
1998–1999	3	2	0	0	0	0	0	0
2003–2004	2	1	0	0	0	0	0	0
2008–2009	304	223	133	7	128	99	88	1

In conducting a bibliometric review of journal articles dealing with trachoma, a slightly higher proportion of articles citing "determinants" and "social determinants" of health is evident, but the extent to which this has been pursued is still marginal. However, in a circumstance where interventions such as improved water and sanitation management have an important role to play, it is encouraging to see a comparable growth in attention to terms such as "sanitation" and "poverty" in relation to the attention that remains primarily associated with "drugs" and "vaccines" (Table A20-5).

In summary, then, there seems to be ample evidence to suggest that the two paradigms that have emerged over the past decade to address global diseases of poverty are indeed "passing in the night" with little interaction. Whether this is a valid characterization of the literature in both areas can best be explored through more systematic knowledge synthesis review of this literature, going beyond this initial bibliometric scan to elaborate on the different currents. Of particular value would be the exploration of insightful works that tend to assess contributions to demonstrably benefit the health of vulnerable populations to reduce disease burden and, hence, can serve as a bridge to link the different approaches being pursued by the different communities.

Initiatives such as the Venice concluding statement on maximizing positive synergies between health systems and global health initiatives (Atun et al., 2009), which focuses on "the shared goal of saving lives and improving the health of all people," support an orientation of concentrating on impact. In this regard, as research funding has expanded over the past decade, there has been a timely

TABLE A20-5 Inclusion of Terms in Journal Articles on Trachoma, 1998–2009

Year	All	With Drug	With Vaccine	With Sanitation	With Poverty	With DH	With SDH
1998–1999	1160	463	358	183	147	9	0
2003–2004	1750	897	568	372	401	29	9
2008–2009	2150	1100	782	522	561	67	32

NOTE: DH, determinants of health; SDH, social determinants of health.

need to look beyond *where and toward what purpose research is being directed* to more explicitly consider impact. In this regard, it is indeed timely to develop a robust paradigm for how neglected diseases are addressed.

Approaches to Pursuing Integrated Control Strategies

As discussed earlier, the paradigm most frequently applied to consider the challenge of neglected disease has explicitly focused on new drug development. As Figure A20-2 illustrates, the disease burden associated with neglected diseases is a reflection not just of a failure to have brought forward biomedical innovations. Neglect is no less present in the weakness of local health systems that are unable to ensure access to the products that we have. And neglect of broader capabilities and infrastructure to improve health-affecting conditions has meant that disease burdens will remain prevalent even if treatment to those afflicted by disease can be undertaken. This is akin to the old Yiddish tale of the wise men of the mythical village of Chelm, who, after pondering what to do about repeated plunges into the valley because of a treacherous mountain road, decide to take action—by building a hospital in the valley!

If neglect of providing healthy living conditions has primarily contributed to the suffering of vulnerable populations, the displacement of possible measures to address these causes can be seen as a way of continuing to ignore the reproduction of circumstances that are producing illness in the first place. On the other hand, a balanced approach of providing treatment and pursuing possibilities of a breakthrough in this regard should certainly not be ignored either.

Our team at the University of British Columbia (UBC) is exploring ways to frame the neglected disease challenge in an integrated manner by considering the following four questions:

1. Are the social and environmental conditions that perpetuate the neglected disease being addressed?
2. Do we have economically viable health service systems in high-burden areas to provide diagnosis and treatment for this neglected disease?

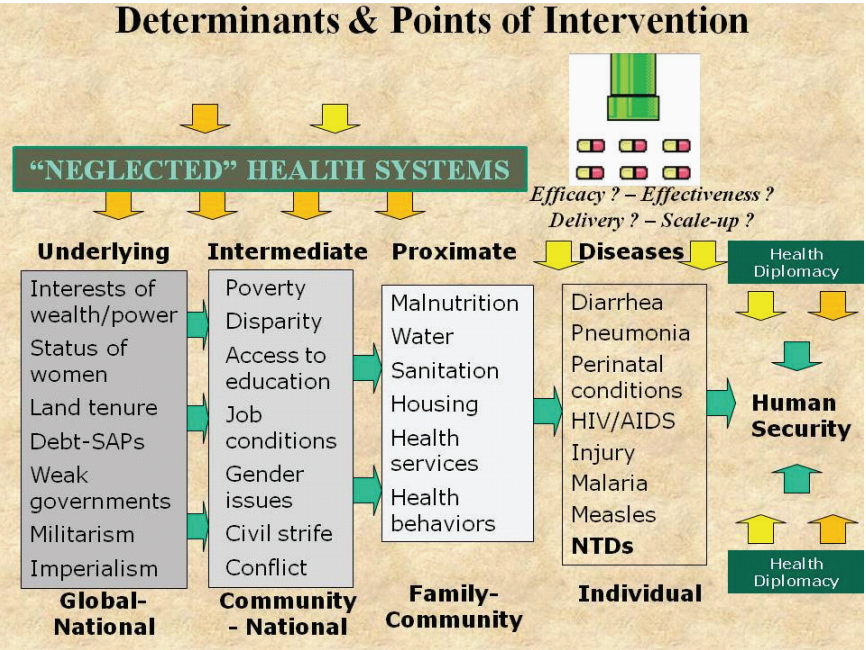

FIGURE A20-2 Overview of points of intervention to address disease and improve health security.

3. Have clinical trials shown treatment to be devoid of serious side effects and effective in practice?
4. Do we have efficacious treatment and diagnostic capabilities?

A key reason for why we are failing to adequately implement an integrated approach, which is increasingly agreed to be what is needed, may well be that proprietary interests have financial incentives that lean heavily toward addressing the fourth question and, to a slightly lesser extent, the third, with limited incentive to fund the second and virtually no incentive to conduct complex health intervention trials that take social and environmental conditions into account—arguably the most important area for intervention research.

The measured assessment of Franco-Paredes et al. (2009) regarding what is needed to control or eliminate the health impact of Chagas disease explicitly highlights the need for an integrated approach for this disease. Yet, despite an increase in social research, for example in the Tropical Disease Research Program (Manderson et al., 2009), such an orientation remains largely elusive with respect to the majority of neglected diseases.

The framework that our team works with in pursuing integrated control strategies is known as the "ecosystem approach to human health" (Lebel, 2003). This milestone public health innovation is a research paradigm that embraces transdisciplinarity, social justice, gender equity, multistakeholder participation, and sustainability:

> Recognizing that health is contingent on biophysical, social, economic and political environments (justice and sustainability) necessitates an approach that transcends disciplines (transdisciplinarity), takes into account various perspectives (multi-stakeholder participation) and is aware of systemic inequities and difference (social and gender equity). (Webb et al., 2010)

A vivid example of where we have applied the ecosystem approach to address a neglected disease was in preventing dengue transmission in Havana, Cuba, through the development of an integrated surveillance system built on three main subsystems (environmental, entomological, and clinical–epidemiologic), relying on extensive community involvement (Bonet et al., 2007). Indicators from each subsystem were selected and mapped using a GIS procedure that provided instant visualization by city block in the municipality. To elucidate the factors affecting control and prevention efforts, the perceived needs and risks, as well as knowledge, attitudes, and behaviors related to dengue, were assessed. Specific factors associated with the presence of mosquito breeding sites and risks of dengue were examined in a case-control study (Spiegel et al., 2007). An example of the insights that this generated was the identification of the spiritual vases of practitioners of the Afro-Caribbean religious practice of Santoria as sites of elevated risk. This prompted a series of meetings between religious leaders and the community with leaders of the dengue control campaign, so that improved preventive practices could be adopted.

It is essential that "bridges" to effective control and prevention must be built by facilitating participatory, community-based, and transdisciplinary approaches (Spiegel et al., 2005) so that the institutional barriers to effectively translating the knowledge that we possess and are expanding can be overcome. There is a growing movement and evidence base to support the fundamental change in vector control and dengue prevention, both in practice and in policy, to a community-based participatory model centered around an eco-bio-social approach (Caprara et al., 2009; Quintero et al., 2009). The ecosystems approach to human health (Eco-health) has been a successful eco-bio-social model employed in vector control programs at a local level (Boischio et al., 2009; Quintero, 2007; Spiegel et al., 2005).

The eco-health approach is particularly promising for dengue prevention and control as the presence of the vector and its density depends on the human population, human behavior and how these affect the surrounding environment (Vanlerberghe et al., 2009). Nevertheless, in many cases, eco-health interventions are short-lived, localized to particular communities, are undertaken without

provisions for scalability or involvement in the policy-making process, and the indices used to measure the impact of the projects do not accurately reflect dengue transmission risk (De Plaen and Kilelu 2004; Vanlerberghe et al., 2009). With the support of the WHO Tropical Disease Research Program, we are currently pursuing a cluster randomized trial applying an eco-health approach in Machala, Ecuador, so that we can strengthen the results of eco-health projects and interventions. This combined with the use of a pupa per person index for each cluster (in addition to or in lieu of the less accurate House, Container and Bretau indices) increases generalizability and improves the evaluation of efficacy of the programs (through a more accurate estimation of adult vector abundance) (Farrar et al., 2007; Vanlerberghe et al., 2009). By building on this knowledge, the evaluation of eco-health interventions in vector control and dengue prevention can be taken a step further; to the assessment of the feasibility of implementing eco-health intervention on a large scale in practice and policy and a cost comparison between the implementation of an integrated eco-health vector control and dengue prevention program and a traditional vertical insecticide-based program.

In this regard, eco-health pilot projects built on integrated surveillance linked to timely community-based interventions have suggested particular promise in considering how scaled-up interventions and supporting policy (i.e., re water management, solid waste removal, source-reduction campaigns, adequate housing) can be pursued, building on knowledge that exists regarding effective specific techniques (Kouri et al., 1998). Nonetheless, effective actions require capacity to be developed at the individual, technical, policy, and institutional level, and this remains a fundamental challenge to be met.

An Innovation to Strengthen Support of Integrated Control Strategies

As attention to ensure that neglected disease funding has increased, there is a risk that reliance on an outmoded drug development paradigm is creating a de facto opportunity cost by displacing innovative integrated approaches for reducing disease burdens. In addition to financial incentives militating against an integrated approach, lack of emphasis on social responsibility in scientific and medical education further contributes to the failure to focus on community or even individual health impact, and instead on treatment of disease (Spiegel et al., 2010). In this manner, the challenge of how to ensure synergy among these building blocks endures.

Interdisciplinary approaches to developing and validating a revised paradigm for better assessing research priorities for overcoming the burden of neglected diseases can play an important role in meeting this challenge. This could facilitate a more systematic addressing of barriers and provide concrete incentives for greater integration of effort from biomedical, clinical, health system, and socioenvironmental innovation. Inspired by the "15 by 2015" campaign call "that donor organizations allocate 15% of their vertical funding towards sustainable, acces-

sible, affordable comprehensive primary health care in all regions of the world" (15 by 2015 Campaign, 2009) our interdisciplinary team at UBC is promoting consideration of the feasibility of applying a similar orientation, beginning at the point of research program formulation. Specifically, we propose that research undertakings that thus far have been oriented primarily to areas such as "drug development and delivery" become refocused on "reducing the burden" of the specific neglected disease.

To promote this change in mindset, we propose the consideration of a simple way of financing multifaceted innovation implementation trials, drawing from examples where redirections of investment have taken place through adoption of measures to compensate for market imperfections (Department of Economic and Social Affairs of the United Nations Secretariat, 2009). Just as the concept of "carbon offsets" has become widely adopted to provide a counterbalance to activities that introduce negative impacts by shifting investment to activities that produce compensatory benefits (e.g., carbon sequestration; Ovandoa and Caparrós, 2009), we feel that "social offsets"[43] be introduced to (1) systematically consider a wider range of effective intervention options, including population health interventions; and (2) sustainably channel incentives for supporting such innovation. This innovation can ensure that a proportion of funding (not only from public-sector research-granting agencies but also in public–private partnerships and the private sector itself) is targeted for this purpose.

Such an orientation is reflected in the recent proposals for creation of the Health Innovation Fund (Hollis, 2008; Hollis and Pogge, 2009), whose scope, while discussing impact, is still too narrowly bound to only value and incentivizing *biomedical* interventions. As a result of debates around the challenges involved in pursuing neglected disease research, our university has made a commitment to trialing a broader approach and has extended its neglected diseases focus from "drug development" to "effective interventions."

The approach we are advocating parallels to some extent what has occurred in evaluating the impacts of developments such as energy projects. Here, proponents have moved beyond just assessing financial costs and benefits of undertakings to take account of direct and indirect environmental impacts and ultimately consider the broader positive and negative social consequences, including the impact on the broad determinants of health of their development project on local,

[43] The concept of "social offsets" emerged recently in response to the need for affordable housing in some urban areas undergoing gentrification. When low-income residents became unable to continue living in these neighborhoods, developers were asked to pay a social offset, that is, contribute to a fund that invests in affordable housing for low-income people. As explained on page 4, the idea derives from the notion of "carbon offsets" (to compensate for carbon-producing activities such as air travel, one pays into a fund that mitigates carbon production by investing in clean energy technology or planting trees). In our proposal, we suggest that any investment in a narrow biomedical solution is offset by channeling a proportion of that investment into broader approaches for reducing health inequities (which may otherwise be exacerbated by biomedical investment). Our *PLoS Medicine* publication is the first peer-reviewed introduction of this concept.

regional, or national communities (Davenport et al., 2006). Similarly, it is time to extend the requirement that drug development not only affirm clinical safety and effectiveness in addition to laboratory-based efficacy, but also consider how health system strengthening and social health determinants needed to reduce the burden of the diseases in question can be reinforced, to increase the likelihood that the innovation will indeed positively impact the burden of the disease. Methodologies for planning and conducting complex health intervention trials (British Medical Research Council, 2006) and indeed systematically reviewing results from multicomponent research (Shepperd et al., 2009) are becoming more developed. Specifically, we propose to explore what we believe is a way of financing multifaceted innovation implementation trials.

In this regard, we wish to extend the kind of innovative thinking that is being stimulated within the more narrowly framed "drug development" paradigm to consider even more effective ways of modifying incentives. For example, partnerships between pharmaceutical companies, nongovernmental organizations, and funders are becoming more common in an attempt to bridge the gap and make research and product development more attractive to drug makers. An example of this is the Mectizan Donation Program in which ivermectin, a drug against river blindness, is donated by a pharmaceutical company (Merck & Co.) and distributed in developing countries thanks to the support and network of the World Health Organization, the World Bank, and the United Nations Children's Fund (Peters and Phillips, 2004).

We were delighted to learn that researchers working with the African Programme for Onchocerciasis Control with extensive experience in community directed treatment with ivermectin projects shared this view that new approaches should be pursued, especially building on the successful engagement of communities, whereby "making control programmes people-centred should not mean thinking for the poor, but rather giving the poor the authority to make decisions" and that "a proportion of the 15% social offset suggested by Spiegel et al., should be used for education, not only of front-line health workers, but equally, if not more importantly, for education and engagement of target populations without whose active participation NTD control is not achievable" (Amazigo and Leak, 2010).

Summary

In order to ensure that scarce resources with multiple demands are used efficiently and effectively, we must incorporate innovative thinking in a common mission to address the burden of global disease—the "missing keys" in the story used to introduce this discussion. In doing so, we must be cognizant of both the nature of the challenges that must be overcome and the various incentives we have for pursuing the approaches that may be more appealing from the perspective of the actors involved. This necessarily means that an agile and flexible strategy should be facilitated.

Where efficacious treatments exist, we must concentrate on making this accessible and capable of being brought to scale. Where they do not, we should pursue their development, but not at a cost that may be harmful to achieving impact on the conditions that will lead to a persistent and aggravated disease burden, such as through integrated control strategies and improved infrastructure. There are many tools in the toolkit that can be applied to improve global health.

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A21

CHAGAS DISEASE IMPACT AND OPPORTUNITIES: BEYOND THE HISTORICAL DOGMA

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Abstract

The centenary in 2009 of the discovery of *Trypanosoma cruzi* and Chagas disease by Brazilian physician Carlos Chagas provided opportunities to revisit the history of this infection and initiated new calls for greater progress in combating this infection and the devastating disease that it causes. Unfortunately, the news on Chagas disease has not been good, as more than 100 years of research and clinical studies have failed to yield consistent and reliable diagnostics, dependable treatment therapies free of side effects, and even a hint of a useful vaccine to prevent infection. Consequently, the number of people infected remains largely a guess and most of these people go untreated due to, among other things, uncertainties about the relative benefits of treatment. Additionally, vector control—long

the mainstay of Chagas disease prevention efforts—suffers from underfunding and decentralization of facilities and manpower at the same time as reports surface of insecticide resistance in multiple regions. Undoubtedly, Chagas disease continues to earn the label of "the most neglected of the neglected diseases" (Anonymous, 2006)—understudied, often ignored by funders, and misunderstood by policy makers. Nevertheless, a reexamination of some of the historic dogmas in the field and consideration of new insights and opportunities suggest some bright spots and hope for progress in the future. This review attempts to critically address some of the beliefs that have dominated the Chagas field—and in some cases frustrated progress—in the past 101 years and to highlight some of the encouraging prospects for the near future.

General Background

Trypanosoma cruzi is a hemoflagelate parasite of wildlife, domestic animals, and humans and is the etiological agent of Chagas disease, a chronic affliction that often results in debilitating heart or gut disease. *T. cruzi* is found throughout much of rural as well as periurban and urban (Ramsey et al., 2005) areas of Latin America as well as in the southern United States. Transmission of *T. cruzi* is mainly via the contaminated feces left by blood-feeding triatomine insects that inhabit poor-quality housing in Latin America (Cohen and Gurtler, 2001). Infection can also occur congenitally, through blood transfusion or organ transplantation, and through the ingestion of contaminated food or liquids (Benchimol Barbosa, 2006). An oral/mucosal route of infection in humans and other animals is probably more common than is generally appreciated. It is also likely in most cases that infection is initiated with a relatively small number (fewer than hundreds) of parasites, which appear to spread rapidly throughout the host. There is no evidence for the restriction of parasites at the initial infection site or for a significant impact of the infection route on the overall course and outcome of infection.

In mammals, *T. cruzi* cycles between trypomastigotes that circulate in the blood and amastigotes, a replicative form that resides in the cytoplasm of infected host cells. Amastigotes complete eight or nine rounds of division over a four-to five-day period, eventually emerging from the compromised host cell as trypomastigotes that can reinfect other cells or be acquired by insect vectors during the course of their feeding. In the gut of the triatomine, these ingested trypomastigotes develop into rapidly dividing epimastigotes that move along the gut over several weeks. Upon reaching the hindgut, the parasites differentiate into metacyclic trypomastigotes, a stage similar to the blood-form trypomastigotes and capable of initiating infection in mammals.

Estimates of the impact of *T. cruzi* infection in the Americas range widely and are undependable because of the absence of routine surveillance and reporting and the relatively poor sensitivity of screening tests. It is likely that between 10 million and 20 million people in Central and South America are infected, making

T. cruzi infection the highest-impact infectious disease in this region with yearly losses of more than 50,000 lives and 0.586 million disability-adjusted life-years (Mathers et al., 2006). Bolivia is the most highly affected, with a countrywide infection rate of about 6 percent and reaching 40 percent is some settings (Hidron et al., 2010). At the other end of the spectrum, the United States is estimated to have ~300,000 *T. cruzi*–infected individuals; some of these autochronous cases are attributed to the presence of the complete transmission cycle (e.g., vectors, parasites, and infected mammals) in most of the southern United States (Beard et al., 2003; Bern and Montgomery, 2009; Dorn et al., 2007; Kjos et al., 2008). The potential for congenital, transfusional, and transplantational mechanisms of transmission have also made *T. cruzi* infection a significant risk globally, despite the absence of vector transmission outside the Americas (Gascon et al., 2010; Schmunis, 2007).

Because *T. cruzi* is zoonotic and naturally circulates in more than 100 mammalian species, it will never be eradicated. But its impact on humans can be managed and minimized. The upside of the ability of *T. cruzi* to infect many different host species is that there are excellent model systems for investigating the complexities of the infection and for testing control and treatment options.

Immunity and Disease

The vast majority of individuals infected with *T. cruzi* appear to control but not completely eliminate the infection. Severe acute infections may occur in those receiving a high infective dose (apparently the case in some oral infection outbreaks) or in the immunosuppressed. In these cases myocarditis and/or meningoencephalitis are common and may be lethal. Otherwise, acute-stage symptoms are generally rare or benign (e.g., fever, swollen lymph glands, and, occasionally, an inflammatory reaction at the bite site). The transition to a relatively asymptomatic chronic infection (also referred to as the "indeterminate phase") is marked by the generation of potent immune control of the infection and a consequent decrease in parasite levels. Parasites not only become less abundant in the face of the developing immune responses but also become confined to only certain host tissues (muscle, fat, and nervous system)—not inconsequentially, also the sites of eventual disease. There have been anecdotal reports of spontaneous cure of infection (e.g., a positive serologic response becoming negative over time), but there has not been a systematic study of this phenomenon.

The clinically quiet phase of the chronic infection ends when the cardiac or gastrointestinal complications of chronic Chagas disease start to manifest. The severity of clinical disease is highly variable; in the case of cardiac involvement, chronic *T. cruzi* infection may result in arrhythmias, apical aneurysm, congestive heart failure, thromboembolism, and sudden death. Chagas cardiomyopathy is the most common cause of cardiomyopathy in South and Central America and the leading cause of cardiovascular death in disease-endemic regions. The fraction

of infected individuals who develop clinical symptoms as a result of chronic *T. cruzi* infection has been estimated to be 30 to 40 percent, although these figures are not well documented and may vary between regions because of the genetic backgrounds of the humans and parasite populations as well as other factors (population age, nutritional status, socioeconomic conditions, exposure to super-infection or co-infections, etc.).

Immune control of *T. cruzi* infection in most hosts is multidimensional and highly potent (Tarleton, 2007). The numbers of intracellular amastigotes and extracellular trypomastigotes in mammals are tightly controlled by abundant cytolytic $CD8^+$ T cells and ample antibody responses, respectively, both assisted by $CD4^+$ T helper cells that also enhance macrophage-mediated parasite-killing mechanisms. Studies in various immunodeficient mouse strains suggest that the absence of any one of these immune mechanisms results in an uncontrolled, high parasitemic and eventually lethal infection (Tarleton, 2007). One of the persistent dogmas of *T. cruzi* infection is that it is "immunosuppressive" and fails to generate protective immune responses. However, multiple lines of data do not support this assumption, including (1) the measurement of exceptionally robust antibody and T cell responses in infected hosts, (2) the maintenance of firm control of parasite levels, over a period of decades in humans, and the loss of that control upon chemical or biological immunosuppression, and (3) the ability to transfer relative protection to naïve hosts via immune antibodies and T cells. Despite this strong and effective immune response and its ability to limit the parasite load to nearly undetectable levels, the infection persists in most cases. Like other persistent pathogens, *T. cruzi* may utilize a number of immune escape mechanisms that make long-term persistence possible. Additionally, long-term persistence itself appears to result in a gradual dwindling of immune function over time because of immune exhaustion (Albareda et al., 2006, 2009).

The origins of clinical disease in human *T. cruzi* infection are still debated, but it is clear that the decades-long persistent parasitization of the affected muscle tissue is the key element determining disease severity (Tarleton, 2003). Tissue damage probably accumulates slowly over the course of infection, as parasites and the immune responses to them create focal lesions that eventually compromise muscle integrity and function. Qualitative and quantitative aspects of the host immune response could also play an important role in the disease process (i.e., the more efficient the immune response is in controlling parasite replication, the lower the rate of tissue damage and the slower the development of clinical disease). Although highly efficient control of *T. cruzi* infection may limit disease severity, the associated absence of parasitologic cure raises a number of problems and questions:

- Detection of parasites—the direct evidence of infection—is often very difficult in the chronic phase of infection. This is a key challenge for diagnosis of the infection and an even greater problem for determining the benefits of treatment.

- Disease occurs despite maintenance of very low parasite numbers. An effective treatment or preventative is going to have to do better than the normal immune response (e.g., clear 100 percent of parasites).
- If cure is not possible despite highly effective immune responses, and if superinfection or re-infection following cure is common, what does this tell us about the chances for development of a vaccine that will prevent infection in humans?

The *priority issues* for Chagas disease include the following:

- Development of better diagnostics;
- Discovery, development, and testing of better treatment regimens, including new drugs;
- Development of better methods for assessing treatment efficacy; and
- Development of integrated, sustainable vector control protocols.

The problems and the needs for each of these issues are discussed in detail below.

Diagnosis

Diagnosis of *T. cruzi* infection is challenging for a number of reasons. The initial infection is often not detected except in the rare cases of high infective doses and severe acute symptoms (Aguilar et al., 2007; Benchimol Barbosa, 2006; Shikanai-Yasuda et al., 1991), or when inflammation occurs at the site of parasite entry (Nicholls et al., 2007). Although parasites may be visible in the blood during the one- to two-month acute phase, they are difficult to detect thereafter. Amplification techniques (e.g., hemoculture, xenodiagnoses, and polymerase chain reaction [PCR]) have been extensively evaluated as diagnostic tools with highly variable results (reviewed in Cooley et al., 2008). Most studies suggest that fewer than 50 percent of seropositive individuals have detectable parasites or parasite DNA, although numbers at both extremes of this average have been reported. In one of the more herculean attempts to assess the dependability of parasite detection in the chronic phase of *T. cruzi* infection, Cerisola et al. (1974) used xenodiagnosis (i.e., insect vectors as detectors of *T. cruzi*) to periodically sample 30 seropositive individuals as many as 21 times over several years, using 80 bugs per time point per subject. Only six subjects consistently had at least one infected bug at each sampling point but the remainder had one or more time points at which none of the 80 insects were positive. In the most extreme case, parasites were detected in only 2 of 18 sampling points (i.e., only 2 of 1,440 bugs fed on this individual were positive). This study firmly documents not only the low parasite levels in chronically infected subjects but also the between- and within-subjects variability in detecting those parasites. This type of sampling error carries over to

other amplification methods as well—including PCR—making these techniques instructive when positive but uninformative when negative.

Conclusive diagnosis of *T. cruzi* infection usually requires positive results on at least two out of three serological tests of different formats (e.g., ELISA, indirect immunofluorescence, hemagglutination, complement fixation, etc.); sera that are positive on only one of three tests are termed "discordant" and these donors are rarely evaluated further or treated. Studies from different geographic regions have documented the undependability of current diagnostics (Avila et al., 1993; Caballero et al., 2007; Castro et al., 2002; Gutierrez et al., 2004; Marcon et al., 2002; Picka et al., 2007; Pirard et al., 2005; Salomone et al., 2003; Silveira-Lacerda et al., 2004; Wincker et al., 1994; Zarate-Blades et al., 2007). For example, Pirard et al. (2005) screened nearly 400 randomly selected blood samples from a Bolivian blood bank and found that 33 percent were positive by all seven of the serological tests employed. However, nearly 20 percent of samples were positive on one or more, but not all seven, tests. Thus, depending on the tests used in a standard "best two-out-of-three" approach, the same individual could be judged to be infected, not infected, or unknown.

This poor state of affairs with respect to diagnosis is in many ways not surprising, given the approaches used in the production of these tests. Many of these serological tests, including one approved for blood screening in the United States (Tobler et al., 2007), use crude or semipurified parasite preparations, often derived from epimastigotes, a stage of *T. cruzi* present in the invertebrate vector but not in vertebrate hosts. Other tests have incorporated more defined parasite components, including multiple fusion proteins containing epitopes from various parasite proteins, which individually have shown some promise as diagnostics (Caballero et al., 2007; Chang et al., 2006; da Silveira et al., 2001). In the absence of a true gold standard for determining infection status, new tests are usually evaluated using only sera that are positive on multiple other serologic tests, and not sera that are borderline, equivocal, or "discordant." This approach virtually ensures that the test being evaluated is no worse, but not necessarily any better than, other tests with known limitations.

The acute need in diagnostics is for a rigorously validated test that can conclude positive or negative serological status on the basis of a single assessment and thus without "discordant" results. The format of the test is not crucial; it need not be a rapid or point-of-care test because initiation of treatment following a positive diagnosis is very rarely time-sensitive. The bulk of current screening is done in reference laboratories where speed and simplicity are not the most crucial parameters. It is much more important that the test be accurate, dependable, and preferably quantitative, so that changes in serologic status can be monitored over time, particularly posttreatment. The author's lab has put forward one candidate for an improved diagnostic test for *T. cruzi* that measures antibodies to a panel of more than a dozen recombinant *T. cruzi* proteins (Cooley et al., 2008). The proteins included in this multiplex formatted test were selected from nearly 400 can-

didates using a broad panel of patient sera and includes proteins that are unique to *T. cruzi* (i.e., not present in other kinetoplastids) as well as proteins that are likely to be highly conserved among parasite isolates from different geographic regions and of different genetic types.

Drug Discovery, Testing, and Use

Two nitroaromatic heterocycle compounds are currently available for treatment of *T. cruzi* infection: benznidazole (BZ, Rochagan®, Roche Pharmaceuticals) and nifurtimox (NX, Lampit®, Bayer Healthcare). NX acts via the reduction of the nitro group to a nitroanion radical that reacts with oxygen to produce toxic superoxide anions (Docampo and Stoppani, 1979; Docampo et al., 1981). The mechanism of action of BZ also appears to involve nitro reduction, but the reduced intermediates are thought to act by covalently modifying various biomacromolecules (Docampo, 1990; Moreno et al., 1982). Both drugs have significant side effects that limit their use and effectiveness.

Another unfortunate but widely accepted dogma of Chagas disease is that these drugs "cure" most acute infections but are ineffective in treating the chronic phase infection. This conclusion is based upon evidence of posttreatment conversion to negative serology (and in some cases, negative parasitemia) in acute and shorter-length infections and the relative lack of such evidence in chronically infected adults. Additionally, the fact that some of these results come from randomized, placebo-controlled trials in the case of children and adolescents (Andrade, 1996; Sosa Estani, 1998), but that such trials have not been conducted in adults (although several such studies are nearing completion; Marin-Neto, 2008) is often cited as evidence of the ineffectiveness of these drugs in longer-term infections. The latter is clearly an instance of "absence of proof" not being "proof of absence." In reality there is little direct proof of "cure" resulting from treatment in either children or adults. As already noted, a reduction in the detection of parasites or parasite products in the circulation is not proof of cure. Conversion to negative serology is a reasonable and accepted, though unproven, surrogate for cure. That conversion to a negative serology is more common following treatment of acute or shorter-term infections is not surprising because the B cell memory and antibody levels achieved during a chronic infection would be expected to be slower to decline as compared to that of an acute or shorter-term infection in younger subjects. Furthermore, the multiplex serological test mentioned above detects declines in antibody levels in BZ-treated adults that are rarely evident using conventional serology, suggesting that better tools may provide better data on the outcome of treatment (Laucella et al., 2009). In short, clear and convincing evidence for treatment effectiveness is hardly any worse in adults than in children (or in chronic than in acute infections, as this is often interpreted), making the bias against treating those with chronic infection unfounded, at least based upon this body of evidence.

The biology of *T. cruzi* and the features of the infection also provide no support for a differential susceptibility to treatment during the acute and chronic phases; parasites are not quiescent in the chronic phase but rather continue to cycle in and out of host cells, to replicate and metabolize, and thus presumably are equally susceptible to antimicrobials irrespective of the length of the infection. Most important, the substantial evidence from observational studies of long-term posttreatment follow-up of chronic-stage treatment provides unequivocal verification of the ability of treatment to substantially impact disease progression (reviewed in Tarleton et al., 2007). Although these latter studies may be criticized for their nonrandomized design, their conclusions should not simply be discarded on this basis.

Despite the evidence for the efficacy of BZ and NX, these are far from ideal drugs. Both have substantial, although often manageable (Viotti et al., 2009), side effects, and treatment failure occurs in a variable number of cases. The biochemical basis of treatment failure is not fully understood; there are isolates of *T. cruzi* that are naturally more resistant to these compounds (both in vitro and in vivo) and in some cases this increased resistance is associated with decreased nitroreductase activity in these isolates (Wilkinson et al., 2008). The combination of misinformation about the efficacy of treatment in the chronic phase, the possibility of adverse effects from treatment, the lack of reliable methods to assess treatment efficacy, and the known variability in efficacy and the undependable supply of compounds virtually ensure that these drugs will continue to be profoundly underutilized, despite their effectiveness. Because drug treatment is the only effective means of preventing the development of clinical disease, it should be used in *all* acute and chronic infection cases where side effects or other aspects of the treatment do not put the patients at a greater health risk. It is unethical not to make better use of the tools that we already have in hand, and access to treatment, not only in Latin America but throughout the world, must be improved (Gascon et al., 2010).

There have been no new drugs developed for the treatment of *T. cruzi* infection in decades and the investigations of compounds as potential treatments nearly always stop well short of demonstration of parasitological cure in animals models. Fortunately, this is one of the areas that show real promise for rapid progress in the coming years. With respect to compound discovery, excellent systems are now available for high-capacity in vitro screening of compound libraries, rapid in vivo compound testing, and rigorous analysis of cure in both acute and chronic infections in experimental hosts (Figure A21-1) (Canavaci, 2010). High-throughput screens of large compound libraries (containing from 300,000 to more than 1,000,000 compounds) have been completed or are in progress. And plans have been announced to conduct two clinical trials of new compounds, the already licensed antifungal posaconazole by Merck and the ergosterol biosynthesis inhibitor ravuconazole pro-drug E1224 by the Drugs for Neglected Diseases Initiative (DNDi) and Eisai. This progress is being made possible by a combination of the

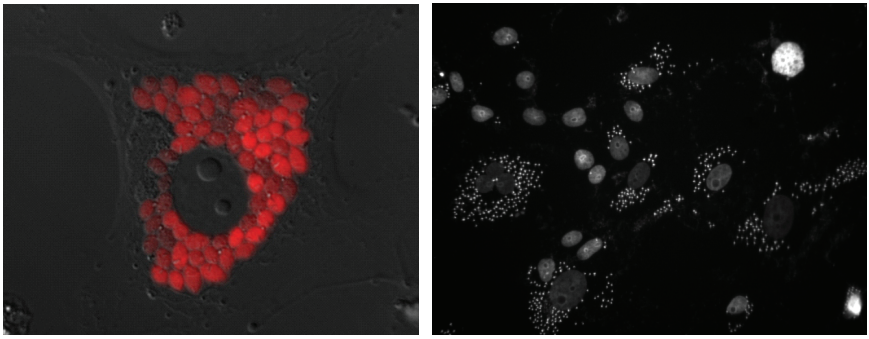

FIGURE A21-1 Amastigotes of *T. cruzi* within host cells. (left) CL strain parasites expressing the tandom Tomato red protein and useful for both in vitro and in vivo screening assays (Canavaci et al., 2010). (right) Example of high-content microscopic screening using DNA stains to detect *T. cruzi* replication within host cells.

persistence of individual investigators who have developed the testing protocols and provided the initial discovery data for the compounds going to clinical trials, large pharmaceutical companies who have the compound libraries, testing capacity, and chemical expertise, and public–private partnerships like DNDi that have helped coordinate some of these efforts.

The interest of the pharmaceutical industry in Chagas disease is exciting, but this interest could wane as quickly as it has come, especially if the initial clinical trials are not promising; there may be limited tolerance for failure. Funding for these efforts is also still tenuous; industry is donating resources but will likely need partners and other funders to get new compounds approved and to the clinic. Preclinical studies must rigorously evaluate efficacy using the best available model systems that also allow for definitive conclusions and comparative data between different candidate drugs. With these data in hand, the various entities can make coordinated and informed decisions, conserving resources by ensuring that only the best compounds go forward in development.

Assessing Treatment Efficacy

A principal consequence of the highly effective immune control of parasite load in *T. cruzi* infection is that detection of parasites or parasite products is challenging in the absence of treatment and totally unreliable as a measure of effectiveness following treatment; a positive parasitemia or PCR-indicated treatment failure but a negative test does not indicate successful cure. Given this fact, the development of a test that absolutely certifies parasitological cure following patient treatment is going to be difficult, if not impossible. However, this is not a situation that is unique to Chagas disease and is no justification for not treating

using the current drugs or for not developing and testing new treatments. Surrogates of cure will likely have to be the principal metric for treatment outcomes. Two measures have been used extensively to assess treatment success: decreases in the titers of anti–*T. cruzi* antibodies (Andrade, 1996; Sosa Estani et al., 1998) and the prevention of progression of symptomatic disease (Viotti et al., 1998). Both criteria are useful on a population basis to demonstrate the benefit of therapy and, on an individual basis, conversion to negative serology is a convincing indicator of parasitological cure. However, both outcomes take years (or even decades) of observation (e.g., the rate of progression to more severe disease is estimated at ~3 percent of subjects per year; Pinto Dias, 2006). A decade-long follow-up period is not an acceptable endpoint for the testing of new drugs.

Development of antipathogen immune responses is an accepted marker of infection—indeed the basis of diagnosis for many infections—including *T. cruzi*. A decline in these immune responses can also reflect the clearance of the infection. The maintenance of antipathogen T cell and antibody responses long after infection cure, an important characteristic of an effective immune response, considerably complicates the use of immunological parameters to monitor cure. However, careful examination of the characteristics of these responses during infection and following infection clearance suggests some distinctive aspects that may be useful in assessing cure. For example, by analyzing the antibody responses to multiple, individual *T. cruzi* proteins (Cooley et al., 2008), posttreatment changes that are not evident from conventional serological tests can be detected within one year after treatment (Laucella et al., 2009). Because these decreased antibody levels are not observed in untreated individuals and occur at a rate that is similar to the rate of cure as assessed by long-term follow-up of progression in clinical disease in drug-treated subjects (Viotti et al., 1994, 2006), this assay appears to be an excellent candidate for further evaluation as an indicator of treatment efficacy.

The attributes of antipathogen T cell responses also follow a predictable pattern after infection cure, with persisting T cells acquiring the phenotype of long-term (central) memory cells and with the loss of effector and shorter-lived effector memory T cells when antigen is no longer in the system (Wherry et al., 2004). A decline in effector T cells specific for *T. cruzi* has been documented in BZ-treated subjects and strongly correlates with decreasing antibody levels (Laucella et al., 2009). T cell responses are more cumbersome to measure than are serologic responses and are sometimes undetectable in subjects even before treatment (Laucella et al., 2009), making this a less dependable marker for cure. Nevertheless, these studies support further investigations of immunological parameters as possible markers of treatment efficacy in *T. cruzi* infection. These and other biomarkers of treatment success are likely to become the primary endpoints for clinical trials of new drugs for treating *T. cruzi* infection. None of these surrogate markers is likely to be directly confirmable as an indicator of cure (i.e., we cannot immunosuppress human subjects posttreatment to confirm cure, as is done in experimental models; Bustamante et al., 2008). Upcoming clinical trials, where

controlled follow-up and multiple endpoints and outcomes will be measured, should be used as opportunties to evaluate some possible surrogate markers.

It could be argued that drug treatment in Chagas disease could be efficacious simply by decreasing parasite load and, consequently, the level of inflammation and tissue damage, even if it fails to completely clear *T. cruzi* infection. Although treatment without cure could be beneficial, most data argue against this possibility. First, disease development is clearly linked to parasite persistence: as long as parasites are present, there is potential for more tissue destruction. Also, subjects with low and even undetectable parasite load still go on to develop clinical disease. Indeed, there is no evidence of an association between disease severity and parasite load (Hidron et al., 2010; Murcia, 2010). Finally, a drop in parasite load brought about by drug treatment would be expected to be only temporary and last only as long as the drug is being given. It is possible that a new, lower set-point of parasite load would be established after treatment, but this does not seem to be consistently the case in either human (Murcia et al., 2010) or experimental infections (Bustamante and Tarleton, unpublished). Also, the changing nutritional, general health, and especially immunological status of infected subjects would be expected to modify the efficiency of infection control overtime. In short, lowering parasite levels is not a dependable and acceptable goal for drug treatment in *T. cruzi* infection; the objective needs to be parasitological cure.

Vector Control

Without question, the biggest success story in the control and prevention of Chagas disease has been vector control. *Triatoma infestans* is the vector species responsible for the majority of *T. cruzi* transmission to humans in South America and is found almost exclusively in and around housing, living in the cracks and crevices of adobe, mud, and thatch constructions, and feeding at night on the animal and human inhabitants (Figure A21-2). Widespread, consistent, and highly effective insecticidal spraying campaigns in the 1980s and 1990s, focusing largely on this domiciliary vector species, dramatically reduced incidence of *T. cruzi* infection in the area known as the Southern Cone of South America. As a result, Brazil, Uruguay, and Chile were declared free of transmission by *T. infestans* (Moncayo and Silveira, 2009) and the Pan American Health Organization and the World Health Organization set their sights on "elimination" of *T. infestans*–mediated transmission of *T. cruzi* by 2010.

Such goals perpetuate another myth of *T. cruzi* infection—that vector transmission can be eliminated by insecticidal spraying alone. There is a long list of reasons that this is highly unlikely if not simply impossible. First, insecticidal spraying is time-consuming, labor-intensive, and expensive; multiperson crews must remove all belongings from structures before spraying the walls and roofs with residual insecticides. And this process has to be repeated every six months, perhaps forever, to eliminate reinfestations. The well-funded national campaigns

FIGURE A21-2 A setting of active transmission in the Gran Chaco region and the pyrethroid-resistant *Triatoma infestans* collected from the structure.

that made the Southern Cone Initiative successful have now been largely dismantled, and the responsibility of vector control has fallen to underfunded, underequipped, and understaffed local governments (Gurtler et al., 2008). Second, *T. infestans* is not the only vector for *T. cruzi* and is not exclusively domiciliary. A dozen or more species of reduviid bugs are likely capable of vectoring *T. cruzi* infection, and these species each have unique behaviors and distribution patterns and thus distinctive ways of interfacing with humans. Discovery of sylvatic foci of *T. infestans* indicates that this species will not be eliminated as a transmis-

sion threat even if it is removed from all domestic dwellings by insecticide use (Noireau et al., 2005). Additionally, new settings for transmission in and near cities are making it clear that *T. cruzi* transmission is not restricted solely to rural settings (Bowman et al., 2008). Third, and the least surprising facet, resistance to insecticides is being reported in multiple settings (Figure A21-2) (Picollo, 2005). Whether this resistance is due exclusively to the decades of house spraying or if the agricultural use of insecticides is also contributing is not known. There are alternative insecticides, but these are often more expensive and are too noxious to the inhabitants of houses to be widely accepted.

Thus, although vector control by insecticide use has been an unqualified success, it is not a long-term solution, particularly when applied in isolation from other vector transmission and infection control tools. The unique behavioral characteristics of various vector species and the increasing variety of settings in which transmission is being reported emphasizes that one size does not fit all when it comes to dealing with the vectors of *T. cruzi* and with transmission control in general. For example, in the Grand Chaco region of Northern Argentina, companion animals, not humans, have been identified as the major infection source of bugs that subsequently transmit the infection to the human residents of the house (Cohen and Gurtler, 2001). Recent outbreaks resulting from apparent oral transmission are often presented as evidence of a "new" route of transmission (Aguilar et al., 2007; Benchimol Barbosa, 2006; Shikanai-Yasuda et al., 1991). More likely, oral transmission is a common, if not the dominant, route of transmission in humans that is just now being more widely recognized. The transmission characteristics in different environments have to be better studied, and integrated plans for each specific local situation must be designed. In this process, there needs to be better use of simple tools where effective (e.g., bug collars on domestic animals and insecticidal screens and nets on houses and beds), along with the evaluation of more innovative approaches, such as the vaccination or intermittent treatment of companion animals to prevent them from being sources of infection. The identification and aggressive treatment of parasitemic humans, especially the minority of "supertransmitters" who are highly infective for insects, is needed (Cerisola et al., 1974). The development of cheap house construction methods and materials that discourage infestations is a clear long-term solution to permanently decrease the opportunities for human infection. Finally, an improved infrastructure for and commitment to supporting vector and transmission control in all countries of the Americas is needed.

Summary: Leadership and Policy Making

Although the problems are many, the outlook for making an impact on Chagas disease is nonetheless bright. This is not a difficult infection to understand; the vectors are large insects that primarily feed within a house and that transmit the infection indirectly and inefficiently via their feces, not their bite. Infection

rarely kills acutely, so there is plenty of time to treat the infection and the goal of treatment—to eradicate, not manage the infection—is obvious, even if difficult to certify. Current diagnostics are usable but need improvement, particularly with respect to assessing treatment efficacy. Drugs are available that are effective in many cases. Because these are the only option for the 20 million individuals already infected and for those who will become infected in the future, these should be more widely used despite their potential side effects. The explosion in interest in new drug development in the past few years and announced plans for clinical trials are extremely encouraging that safer drugs are on the horizon. Vector control has already shown its utility; it just needs to be conducted more intelligently and with better integration with other treatment and preventative programs. Not discussed above are the opportunities for a human vaccine for Chagas disease; the jury is still out on this possibility. Given the perceived requirement that elimination and not simply better control of an existing infection is the goal, prophylactic or therapeutic vaccines would have to totally prevent infection or promote complete parasite clearance in those already infected. This is a big task for a vaccine. Until such abilities can be demonstrated in experimental infections, vaccines for *T. cruzi* will likely remain just a hope.

A particularly vexing problem in Chagas disease is in the areas of leadership and policy. National (including in the United States) and international policies have been ineffective at best, harmful at worst. Perpetuating the myths that chronic Chagas disease cannot be treated with current drugs and that transmission can (or has) been largely eliminated does not accurately reflect the bulk of the data. Policies that rely almost exclusively on insecticidal spraying and speak of eradication/elimination within years when this is impossible, no matter what the time frame, is careless. These practices minimize the severity of the problem, obstruct the use of current drugs and the development of new ones, encourage the elimination or decentralization of vector control programs, and discourage the involvement of large nonprofit funders in new or continuing control and prevention efforts. A policy of "more of the same" will not achieve the progress that is necessary and possible. National and international policy makers have to do a much better job at honestly assessing the problems and the realistic opportunities and coordinating the effort to build upon these. Establishment of research and development priorities based upon rigorous and educated evaluations and developing the funding mechanisms to move beyond planning to implementation is crucial for making real progress. Success will require not only funding but also political will and local buy-in. Scientists must execute the appropriate studies and provide the data and clear interpretations that can guide policy development and implementation. *T. cruzi* infection and Chagas disease are manageable problems—there is a success story waiting to be written here if the job is done carefully and correctly.

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B

Agenda

The Causes and Impacts of Neglected Tropical and Zoonotic Diseases: Implications for Global Health and Opportunities for Novel Intervention Strategies

September 21–22, 2010
Keck Building, Room 100
500 Fifth Street, NW
Washington, DC

DAY 1: Tuesday, September 21, 2010

8:00–8:30: Registration and Continental Breakfast

8:30–8:45: Welcoming Remarks
David Relman, M.D., Chair, and James Hughes, M.D., Vice-Chair, Forum on Microbial Threats

8:45–10:15: Keynote Remarks
David Relman, Moderator

8:45–9:30 Opportunities for medical diplomacy: The Global Health Initiative
Ezekiel Emanuel, M.D., Ph.D., White House Office of Management and Budget

9:30–10:15 NTDs slated for elimination and eradication
Donald Hopkins, M.D., M.P.H., The Carter Center

10:15–10:45: Discussion

10:45–11:00: Break

Session One: An Overview of the NTDs

James Hughes, Moderator

11:00–11:30: Neglected infections of poverty in the United States
Peter Hotez, M.D., Ph.D., The George Washington University

11:30–12:00: NTDs in the setting of conflict
Chris Beyrer, M.D., M.P.H., Johns Hopkins University

12:00–12:30: Parasite prevalence and the worldwide distribution of cognitive ability
Christopher Eppig, University of New Mexico

12:30–1:00: Discussion of Session One

1:00–1:45: Lunch

Session Two: Global Burden of Disease/Opportunities for Control

Mary Wilson, Moderator

1:45–2:15: The social and environmental context of infectious diseases occurrence in Brazil: Interventions, policies, and research needs
Mauricio Barreto, M.D., M.P.H., Ph.D., Federal University of Bahia in Salvador, Brazil

2:15–2:45: Neglected tropical and zoonotic diseases and their impact on women and children's health
Marian McDonald, Dr.P.H., M.P.H., M.A., Centers for Disease Control and Prevention

2:45–3:15: Addressing the social determinants of the NTDs in devising an integrated control strategy
Jerry Spiegel, Ph.D., M.A., M.Sc., University of British Columbia

3:15–3:30: Break

3:30–4:00: Reemergence of dengue in the United States?
Harold Margolis, M.D., Centers for Disease Control and Prevention

4:00–4:30: Chagas disease in the Americas: Health impacts and opportunities for control
Rick L. Tarleton, Ph.D., The University of Georgia and The Chagas Disease Foundation

4:30–5:00: Schistosomiasis
Charles King, M.D., M.S., Case Western Reserve University

5:00–5:30: Progress in the control and elimination of human African trypanosomiasis
Jean Jannin, M.D., World Health Organization

5:30–6:00: Integrated control of tropical diseases: Progress in the control and elimination of lymphatic filariasis
Eric Ottesen, M.D., The Task Force for Global Health

6:00–6:30: Discussion of Session Two; Open Discussion of Day One

6:30: Adjourn

DAY 2: September 22, 2010

8:00–8:15: Continental Breakfast

8:15–8:30: Summary of Day One: James M. Hughes, M.D., Vice-Chair, Forum on Microbial Threats

8:30–9:00: Keynote Remarks: **Christy Hanson, Ph.D.,** U.S. Agency for International Development
James M. Hughes, Moderator

9:00–9:15: Discussion

Session Three: Governmental and Nongovernmental Approaches to Integrated Disease Control

Kevin Russell, Moderator

9:15–9:45: Neglected zoonotic diseases
Lonnie King, D.V.M., The Ohio State University

9:45–10:15: Regional approaches to NTD control in the Americas
Steven Ault, Pan American Health Organization

10:15–10:45: The neglected tropical diseases in Africa and next steps for global control and elimination
Lorenzo Savioli, M.D., M.Sc., DTM&H, World Health Organization

10:45–11:00: Break

11:00–11:30: The U.K. commitment to NTD control
Alan Fenwick, Imperial College of London

11:30–12:00: The Gates Foundation commitment to NTD control
Julie Jacobson, M.D., DTM&H, The Bill & Melinda Gates Foundation

12:00–12:30: Discussion

12:30–1:15: Luncheon Remarks: Jesse Goodman, M.D., M.P.H., Chief Scientist, Food and Drug Administration
"Can we collaborate to develop new paradigms and approaches for public health product development and evaluation?"

Session Four: Unmet Needs: Development of Diagnostics, Drugs, and Vaccines to Control or Treat the Most Common NTDs

David Relman, Moderator

1:15–1:45: Public–private partnerships addressing diseases of the developing world: Lessons learned; current challenges; future opportunities
Mark Feinberg, M.D., Ph.D., Merck & Co.

1:45–2:15:	New drugs in clinical development **Shing Chang, Ph.D.,** DNDi
2:15–2:45:	Need for improved diagnostics **Patrick Lammie, Ph.D., M.S.,** Centers for Disease Control and Prevention
2:45–3:00:	**Break**
3:00–3:30:	R&D Investments **Mary Moran, M.D.,** Policy Cures, Sydney, Australia, London, UK
3:30–4:00:	Antihelminthic vaccines **Peter Hotez, M.D., Ph.D.,** The George Washington University
4:00–4:45:	Open Panel Discussion
4:45–5:00:	Closing Remarks James Hughes and David Relman
5:00:	**Meeting Adjourned**

C

Acronyms

AIDS	acquired immune deficiency syndrome
APOC	African Program for Onchocerciasis Control
BCG	Bacille Calmette-Guerin vaccine
CDC	Centers for Disease Control and Prevention
CMV	congenital cytomegalovirus
CNTD	Centre for Neglected Tropical Diseases at Liverpool University
DALY	disability-adjusted life-year
DDT	dichlorodiphenyltrichloroethane
DEC	diethylcarbamazine
DENV	dengue virus
DHF	dengue hemorrhagic fever
DNDi	Drugs for Neglected Diseases initiative
DRC	Democratic Republic of Congo
DSS	dengue shock syndrome
ELISA	enzyme-linked immunosorbent assay
FAO	United Nations Food and Agriculture Organization
FDA	Food and Drug Administration
FGS	female genital schistosomiasis
GAELF	Global Alliance to Eliminate Lymphatic Filariasis

GAVI	Global Alliance for Vaccines and Immunizations
GDP	gross domestic product
GHI	U.S. Global Health Initiative
GIS	geographic information system
GPELF	Global Programme to Eliminate Lymphatic Filariasis
GSK	GlaxoSmithKline
HAT	human African trypanosomiasis
HDI	Human Development Index
HHS	U.S. Department of Health and Human Services
HIV	human immunodeficiency virus
ICT	immunochromatographic card test
IDC	innovative developing country
IgG	immunoglobulin G
IgM	immunoglobulin M
IOM	Institute of Medicine
IQ	intelligence quotient
LAC	Latin America and the Caribbean
LF	lymphatic filariasis
MDA	mass drug administration
MDG	Millennium Development Goal
MDR	multidrug-resistant
MDR-TB	multidrug-resistant tuberculosis
NCC	neurocystercercosis
NECT	nifurtimox-eflornithine combination therapy
NGO	nongovernmental organization
NID	neglected infectious disease
NIH	National Institutes of Health
NTD	Neglected Tropical Disease
NZD	Neglected Zoonotic Disease
OIE	World Organization for Animal Health
PAHO	Pan-American Health Organization
PCR	polymerase chain reaction
PDP	product-development partnership
R&D	research and development
RNA	ribonucleic acid

RTI	Research Triangle Institue, RTI International
SAFE	surgery, antibiotics, face cleanliness, and environmental improvement
SCI	Schistomiasis Control Initiative
SEARO	World Health Organization Southeast Asia Regional Office
STH	soil-transmitted helminth
TB	tuberculosis
UNDP	United Nations Development Programme
UNICEF	United Nations Children's Fund
USAID	U.S. Agency for International Development
VL	visceral leishmaniasis
VPH	veterinary public health
WASHED	water supply, sanitation, hygiene, and education initiatives
WHO	World Health Organization

D

Glossary

Acute febrile illness: A type of illness characterized by a sudden onset of fever, which is an increase in internal body temperature to levels above normal.

Anthrax: An infectious disease caused by bacteria called *Bacillus anthracis*. Infection in humans most often involves the skin, the gastrointestinal tract, or the lungs.

Antibiotic: A class of substances that can kill or inhibit the growth of some groups of bacteria. Originally antibiotics were derived from natural sources (e.g., penicillin from molds), but many currently used antibiotics are semisynthetic and modified with additions of man-made chemical components.

Antibody (also known as **immunoglobulins**, abbreviated **Ig**): Antibodies are gamma globulin proteins that are found in blood or other bodily fluids of vertebrates and are used by the immune system to identify and neutralize foreign objects, such as bacteria and viruses.

Antigen: A molecule capable of eliciting a specific antibody or T-cell response.

Ascariasis: An infection caused by the parasitic roundworm *Ascaris lumbricoides*. It is perhaps the world's most common worm infection, affecting approximately 1 billion people worldwide. The infection occurs in people of all ages, though children are affected more severely than adults. It is found in association with poor personal hygiene, poor sanitation, and in places where human feces are used as fertilizer.

Asymptomatic infection: An infection where the patient does not have any apparent symptoms (also known as a subclinical infection).

Bacteria: Microscopic, single-celled organisms that have some biochemical and structural features different from those of animal and plant cells.

Bovine tuberculosis: Tuberculosis in cattle caused by infection with the bacterium *Mycobacterium bovis* that can be transmitted to other animals and to humans.

Brucellosis: An infectious disease caused by the bacteria of the genus *Brucella*. These bacteria are primarily passed among animals, and they cause disease in many different vertebrates. Humans become infected by coming in contact with animals or animal products that are contaminated with these bacteria, and the disease can cause a range of symptoms that are similar to the flu and may include fever, sweats, headaches, back pains, and physical weakness.

Buruli ulcer: A chronic, indolent, necrotizing disease of the skin and soft tissue caused by toxin-producing mycobacteria, *Mycobacterium ulcerans*. It is the third most common mycobacterial disease of immunocompetent hosts after tuberculosis and leprosy.

Chagas disease: A potentially life-threatening illness caused by the protozoan parasite *Trypanosoma cruzi*. Predominantly found in Latin America, *T. cruzi* is commonly transmitted to humans and other mammals by an insect vector.

Convenience sampling: A nonprobability sampling technique where subjects are selected because of their convenient accessibility and proximity to the researcher; see http://www.experiment-resources.com/convenience-sampling.html (accessed December 2, 2010).

Cysticercosis: A parasitic tissue infection caused by larval cysts of the pork tapeworm. These larval cysts infect brain, muscle, or other tissue and are a major cause of adult-onset seizures in most low-income countries. An individual acquires cysticercosis from ingesting eggs excreted by a person who has an intestinal tapeworm.

Cytomegalovirus (CMV): A common virus that infects people of all ages. Most CMV infections are "silent"; most people who are infected with CMV have no signs or symptoms. CMV can cause symptomatic disease in people with a weakened immune system and in babies infected before birth.

Dengue/dengue hemorrhagic fever (DHF): A vector-borne viral disease, dengue is transmitted between people by the mosquitoes *Aedes aegypti* and *Aedes albopictus*, which are found throughout the world. Dengue fever (DF) is caused by any of four closely related viruses, or serotypes, dengue 1–4. Infection with one serotype does not protect against the others, and sequential infections put people at greater risk for DHF and dengue shock syndrome (DSS).

Disability-adjusted life-years (DALYs): A metric used to measure the morbidity impact associated with a disease. One DALY can be thought of as one lost year of "healthy" life. The sum of these DALYs across the population, or the burden of disease, can be thought of as a measurement of the gap between current health status and an ideal health situation where the entire population lives to an advanced age, free of disease and disability; see http://www.who.int/healthinfo/global_burden_disease/metrics_daly/en/index.html (accessed December 2, 2010).

Disease burden: The impact of a health problem in a population measured by financial cost, mortality, morbidity, or other indicators.

Dracunculiasis: Also known as Guinea worm disease, dracunculiasis is caused by infection by the protozoan parasite *Dracunculus medinensis*. The disease affects poor communities in remote parts of Africa that do not have access to safe drinking water. There is no pharmaceutical or vaccine treatment for Guinea worm disease.

Echinococcosis: Often referred to as hydatid disease or echinococcal disease, echinococcosis is a parasitic disease that affects both humans and other mammals, such as sheep, dogs, rodents, and horses. There are three different forms of echinococcosis found in humans, each of which is caused by the larval stages of different species of the tapeworm of the genus *Echinococcus*.

Elimination: Cessation of transmission in a country, continent, or other limited geographic area; complete prevention of a clinical presentation of disease.

Endemic: The constant presence of a disease or infectious agent within a given geographic area; it may also refer to the usual prevalence of a given disease within such an area.

Eradication: Reducing the incidence of a disease to zero worldwide, such that further control measures are unnecessary; total interruption of transmission.

Feco-oral (or fecal-oral) infection: Infections that are spread by the ingestion of contaminated fecal material. Sometimes these types of infections are also spread by drinking water that is contaminated with infected fecal material.

Genomics: The study of genes and their associated functions.

Global Health Initiative: A U.S. government development initiative launched in 2009 that will invest $63 billion over six years to help partner countries improve health outcomes through strengthened health systems, with a particular focus on improving the health of women, newborns, and children through programs including infectious disease, nutrition, maternal and child health, and safe water.

Hookworm infection: The hookworm is a parasitic nematode that lives in the small intestine of its mammalian host. Two species of hookworms commonly infect humans, *Ancylostoma duodenale* and *Necator americanus*. Hookworm is a leading cause of maternal and child morbidity in the developing countries of the tropics and subtropics.

Human African trypanosomiasis (HAT): HAT is a protozoan parasitic disease of people and animals, caused by *Trypanosoma brucei* and transmitted by the tsetse fly. The disease is endemic in some regions of sub-Saharan Africa, covering about 36 countries and 60 million people.

Horizontal transmission: The spread of an infectious agent from one person or group to another, usually through direct contact with contaminated material, such as sputum or feces.

Hygroma: An accumulation of fluid in a sac, cyst, or bursa.

Hyperendemic: The condition in which a disease is present in a community at all times and with a high incidence.

Hypoendemic: A population or region in which the incidence of a disease is sufficiently low that the population has limited or no native immunity to it.

Incidence rate: The number of new cases of a specified disease during a defined period of time divided by the number of persons in a stated population in which the cases occurred.

Intelligence quotient (IQ): A measure of a person's intelligence as indicated by an intelligence test; the ratio of a person's mental age to their chronological age (multiplied by 100).

Kinetoplastid: A group of flagellated protozoa characterized by the presence of one or two flagella in the cell body and a "kinetoplast" within the mitochondrion. As human parasites, kinetoplastids are associated with Chagas disease, HAT, and leishmaniasis.

Leishmaniasis: A protozoan parasitic disease belonging to the genus *Leishmania*. These parasites are transmitted by the bite of a sand fly and can infect animals and humans. Cutaneous leishmaniasis is the most common form; visceral leishmaniasis is a more severe form, affecting vital organs of the body.

Leptospirosis: A bacterial zoonotic disease caused by spirochaetes of the genus *Leptospira* that affects humans and a wide range of animals, including mammals, birds, amphibians, and reptiles. Though recognized among the world's most common zoonoses, leptospirosis is a relatively rare bacterial infection in humans.

Longitudinal studies: A correlational research study that involves repeated observations of the same items over long periods of time—often many decades. It is a type of observational study. Longitudinal studies are often used in psychology to study developmental trends across the life span, and in sociology to study life events throughout lifetimes or generations.

Lymphatic filariasis (LF or elephantiasis): A parasitic disease caused by microscopic, threadlike worms. The adult worms only live in the human lymph system. The lymph system maintains the body's fluid balance and fights infections. Lymphatic filariasis is spread from person to person by mosquitoes. Lymphatic filariasis is a leading cause of permanent disability worldwide.

Microfilariae: The prelarval form of any filarial worm. Certain blood-sucking insects ingest these forms from an infected host, and the microfilariae then develop in the body of the insect and become infective larvae.

Morbidity: Disease, illness; any departure, subjective or objective, from a state of physiological or psychologic well-being.

Neglected tropical diseases (NTDs): A group of more than a dozen major chronic, mostly parasitic infectious diseases with high endemicity in the developing countries of Africa, Asia, and the Americas. NTDs are the most common infections of the world's poor, especially the bottom billion. Most are chronic and disabling parasitic infections, as well as selected bacterial and viral infections.

Neglected zoonotic diseases (NZDs): Diseases transmitted between animal and human hosts—sometimes by means of a vector, or carrying species—that are endemic in many developing countries of Africa, Asia, and South and Central America (e.g., anthrax, bovine tuberculosis, brucellosis, cysticercosis, and echinococcosis rabies). These diseases sicken and kill livestock and have direct and indirect effects on human health.

Onchocerciasis: A parasitic disease (also known as river blindness) caused by the filarial worm *Onchocerca volvulus*. It is transmitted through the bites of infected *Simulium* black flies, which breed in fast-flowing streams and rivers. Onchocerciasis is a major cause of blindness in many African countries.

Parasite: An organism living in, with, or on another organism.

Pathogen: A microorganism that causes disease.

Prevalence rate: The total number of persons sick or portraying a certain condition in a stated population at a particular time or during a stated period of time, regardless of when that illness or condition began, divided by the population at risk of having the disease or condition at the point in time midway through the period in which they occurred.

Protozoa and protozoan parasites: Protozoa are microscopic, unicellular organisms that can be free-living or parasitic in nature. They are able to multiply in humans, which contributes to their survival and also permits serious infections to develop from just a single organism. Transmission of protozoa that live in a human intestine to another human typically occurs through a fecal-oral route (for example, contaminated food or water or person-to-person contact). Protozoa that live in the blood or tissue of humans are transmitted to other humans by an arthropod vector (for example, through the bite of a mosquito or sand fly).

Proteomics: The large scale of proteins, especially their structures and functions.

Q fever: A disease caused by infection with *Coxiella burnetii*, a bacterium that affects humans and other animals. This organism is uncommon but may be found in cattle, sheep, goats, and other domestic animals. The infection results from the inhalation of endospores and from contact with the milk, urine, feces, vaginal mucus, or semen of infected animals.

Rabies: An often fatal viral zoonotic disease that causes acute encephalitis in warm-blooded animals.

Reservoir: Any person, animal, arthropod, plant, soil, or substance (or combination of these) in which an infectious agent normally lives and multiplies, on which it depends primarily for survival, and in which it reproduces itself in such manner that it can be transmitted to a susceptible vector.

Rickettsial disease: Infection caused by a variety of obligate intracellular, Gram-negative bacteria that are usually transmitted by ectoparasites such as fleas, lice, mites, and ticks.

Schistosomiasis: A parasitic disease (also known as bilharzias) caused by trematode flatworms of the genus *Schistosoma*. Although it has a low mortality rate, schistosomiasis often is a chronic illness that can damage internal organs and, in children, impair growth and cognitive development. Schistosomiasis is the second most socioeconomically devastating parasitic disease after malaria.

Subclinical infection: An infection where the patient does not have any apparent symptoms (also known as an asymptomatic infection).

Surveillance: The continuing scrutiny of all aspects of occurrence and spread of a disease that is pertinent to effective control.

Tapeworm: Parasitic flatworms or cestodes. Live tapeworm larvae (coenuri) are sometimes ingested by consuming undercooked food. Once inside the digestive tract, a larva can grow into a very large adult tapeworm. Cysticercosis is a disease of humans involving larval tapeworms in the human body.

Toxocariasis: The parasitic disease caused by the larvae of two species of *Toxocara* roundworms: *T. canis* from dogs and, less commonly, *T. cati* from cats.

Toxoplasmosis: Disease associated with a single-celled parasite called *Toxoplasma gondii*. Of those who are infected, very few have symptoms because a healthy person's immune system usually keeps the parasite from causing symptomatic illness.

Trachoma: An infectious eye disease, resulting from infection of the eye with *Chlamydia trachomatis*, that is the leading cause of the world's infectious blindness. Globally, 41 million people suffer from active infection, and nearly 8 million people are visually impaired as a result of this disease.

Trematode infections: Infections caused by parasitic flatworms (also known as flukes) that infect humans and animals. Infected individuals transmit trematode larvae in their feces.

Treponematoses: Bacteria that cause chronic infections (e.g., yaws [also known as framboesia, pian], endemic syphilis [bejel], and pinta), which often present as skin lesions.

Trichuriasis: Infection by a soil-transmitted helminth also known as whipworm. These parasitic worms live in the large intestine, and whipworm eggs are passed in the feces of infected persons.

Vaccine: A biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism, and it is often made from weakened or killed forms of the microbe. The agent stimulates the body's immune system to recognize the agent as foreign, destroy it, and "remember" it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters.

Vector: A carrier—especially an arthropod—that transfers an infective agent from one host (which can include itself) to another.

Vector-borne: Transmitted from one host to another by a vector.

Viremia: The presence of virus in the blood of the host.

Virus: A small infectious agent that can only replicate inside the cells of another organism. Viruses are too small to be seen directly with a light microscope. Viruses infect all types of organisms, from animals and plants to bacteria and archaea.

Water-based diseases: Diseases (e.g., schistosomiasis, Guinea worm disease) transmitted by a vector that spends part of its life cycle in the water and another part as parasites of humans and animals.

Water-washed diseases: Those diseases whose transmission is facilitated by insufficient quantities of water (regardless of its quality) for personal and domestic hygiene.

Yaws: An infection caused by *Treponema pertenue* that is a significant public health problem in three countries of the Southeast Asia region.

Zoonoses: Microbes that are naturally transmitted between animals and humans that cause disease in human populations but can be perpetuated solely in nonhuman host animals (e.g., influenza, rabies).

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Forum Member Biographies

David A. Relman, M.D. (*Chair*), is the Thomas C. and Joan M. Merigan Professor in the Departments of Medicine and of Microbiology and Immunology at Stanford University, and Chief of Infectious Diseases at the VA Palo Alto Health Care System in Palo Alto, California. He received an S.B. (biology) from Massachusetts Institute of Technology (1977), received his M.D. (magna cum laude) from Harvard Medical School (1982), completed his clinical training in internal medicine and infectious diseases at Massachusetts General Hospital, served as a postdoctoral fellow in microbiology at Stanford University, and joined the faculty at Stanford in 1994.

Dr. Relman's current research focus is the human indigenous microbiota (microbiome) and, in particular, the nature and mechanisms of variation in patterns of microbial diversity within the human body as a function of time (microbial succession), space (biogeography within the host landscape), and in response to perturbation, for example, antibiotics (community robustness and resilience). One of the goals of this work is to define the role of the human microbiome in health and disease. This research integrates theory and methods from ecology, population biology, environmental microbiology, genomics, and clinical medicine. During the past few decades, his research directions have also included pathogen discovery and the development of new strategies for identifying previously unrecognized microbial agents of disease. This work helped to spearhead the application of molecular methods to the diagnosis of infectious diseases in the 1990s. His research has emphasized the use of genomic approaches for exploring host–microbe relationships. Past scientific achievements include the description of a novel approach for identifying previously unknown pathogens; the identification of a number of new human microbial pathogens, including the agent of

Whipple's disease; and some of the most extensive and revealing analyses to date of the human indigenous microbial ecosystem.

Dr. Relman advises the U.S. government, as well as nongovernmental organizations, in matters pertaining to microbiology, emerging infectious diseases, and biosecurity. He is a member of the National Science Advisory Board for Biosecurity, a member of the Physical and Life Sciences Directorate Review Committee for Lawrence Livermore National Laboratory, and he advises several U.S. government departments and agencies on matters related to pathogen diversity, the future life sciences landscape, and the nature of present and future biological threats. He has served as Chair of the Board of Scientific Counselors of the National Institute of Dental and Craniofacial Research (National Institutes of Health [NIH]) and as a member of the Board of Directors, Infectious Diseases Society of America (IDSA). Dr. Relman is currently Vice-Chair of a National Academy of Sciences (NAS) study of the science underlying the Federal Bureau of Investigation investigation of the 2001 anthrax mailings, and he co-chaired a three-year NAS study that produced a widely cited report titled *Globalization, Biosecurity, and the Future of the Life Sciences* (2006). He is a Fellow of the American Academy of Microbiology and a member of the Association of American Physicians. Dr. Relman received the Squibb Award from the IDSA in 2001 and was the recipient of both the NIH Director's Pioneer Award and the Distinguished Clinical Scientist Award from the Doris Duke Charitable Foundation in 2006.

James M. Hughes, M.D. (*Vice-Chair*), is professor of medicine and public health at Emory University's School of Medicine and Rollins School of Public Health, serving as director of the Emory Program in Global Infectious Diseases, executive director of the Southeastern Center for Emerging Biological Threats, and senior advisor to the Emory Center for Global Safe Water. He is the senior scientific advisor for infectious diseases to the International Association of National Public Health Institutes funded by the Bill & Melinda Gates Foundation. Prior to joining Emory in June 2005, Dr. Hughes served as director of the National Center for Infectious Diseases (NCID) at the Centers for Disease Control and Prevention (CDC). Dr. Hughes received his B.A. and M.D. degrees from Stanford University and completed postgraduate training in internal medicine at the University of Washington, infectious diseases at the University of Virginia, and preventive medicine at CDC. After joining CDC as an Epidemic Intelligence Service officer in 1973, Dr. Hughes worked initially on food-borne and water-related diseases and subsequently on infection control in health care settings. He served as director of CDC's Hospital Infections Program from 1983 to 1988, as deputy director of NCID from 1988 to 1992, and as director of NCID from 1992 to 2005. A major focus of Dr. Hughes' career is on building partnerships among the clinical, research, public health, and veterinary communities to prevent and respond to infectious diseases at the national and global levels. His research interests include emerging and reemerging infectious diseases, antimicrobial resistance,

food-borne diseases, health care–associated infections, vector-borne and zoonotic diseases, rapid detection of and response to infectious diseases and bioterrorism, strengthening public health capacity at the local, national, and global levels, and prevention of water-related diseases in the developing world. Dr. Hughes is a fellow and Council Delegate of the American Association for the Advancement of Science (AAAS), a fellow of the American College of Physicians and IDSA, President of IDSA, Councilor of the American Society of Tropical Medicine and Hygiene, and a member of the International Board of the American Society for Microbiology (ASM). He is a member of the Institute of Medicine (IOM).

Lonnie J. King, D.V.M. (*Vice-Chair*), is the 10th dean of the College of Veterinary Medicine at The Ohio State University (OSU). In addition to leading this college, Dr. King is also a professor of preventive medicine and holds the Ruth Stanton Endowed Chair in Veterinary Medicine. Before becoming dean at OSU, he was the director of CDC's new National Center for Zoonotic, Vector-Borne, and Enteric Diseases (NCZVED). In this new position, Dr. King leads the Center's activities for surveillance, diagnostics, disease investigations, epidemiology, research, public education, policy development, and diseases prevention and control programs. NCZVED also focuses on water-borne, food-borne, vector-borne, and zoonotic diseases of public health concern, which also include most of CDC's select and bioterrorism agents, neglected tropical diseases, and emerging zoonoses. Before serving as director, he was the first chief of the agency's Office of Strategy and Innovation.

Dr. King served as dean of the College of Veterinary Medicine, Michigan State University, from 1996 to 2006. As at OSU, he served as the CEO for academic programs, research, the teaching hospital, the diagnostic center for population and animal health, basic and clinical science departments, and the outreach and continuing education programs. As dean and professor of large-animal clinical sciences, Dr. King was instrumental in obtaining funds for the construction of a $60 million Diagnostic Center for Population and Animal Health; he initiated the Center for Emerging Infectious Diseases in the college, he served as the campus leader in food safety, and he had oversight for the National Food Safety and Toxicology Center.

In 1992, Dr. King was appointed administrator for the Animal and Plant Health Inspection Service (APHIS), U.S. Department of Agriculture (USDA), in Washington, DC. In this role, he provided executive leadership and direction for ensuring the health and care of animals and plants, to improve agricultural productivity and competitiveness, and to contribute to the national economy and public health. Dr. King also served as the country's chief veterinary officer for five years, worked extensively in global trade agreements within the North American Free Trade Agreement and the World Trade Organization, and worked extensively with the World Animal Health Association. During this time he was the Deputy Administrator for Veterinary Services of APHIS, USDA, where he

led national efforts in disease eradication, imports and exports, and diagnostics in both Ames, Iowa, and Plum Island. He spent five years in Hyattsville, Maryland, in staff assignments in Emergency Programs, as well as Animal Health Information. While in Hyattsville, Dr. King directed the development of the agency's National Animal Health Monitoring System. He left APHIS briefly to serve as the director of the Governmental Relations Division of the American Veterinary Medical Association (AVMA) in Washington, DC, and served as the lobbyist for the AVMA on Capitol Hill.

Dr. King was in private veterinary practice for seven years in Dayton, Ohio, and Atlanta, Georgia. As a native of Wooster, Ohio, Dr. King received his B.S. and D.V.M. from OSU in 1966 and 1970, respectively. He earned his M.S. in epidemiology from the University of Minnesota and received his M.P.A. from American University in Washington, DC, in 1991. Dr. King is a board-certified member of the American College of Veterinary Preventive Medicine and has completed the Senior Executive Fellowship program at Harvard University. He served as president of the Association of American Veterinary Medical Colleges from 1999 to 2000 and was the Vice-Chair for the National Commission on Veterinary Economic Issues from 2000 to 2004. He has served on four NAS committees, including chairing the National Academies' Committee on Assessing the Nation's Framework for Addressing Animal Diseases. He is also Chair of the IOM Committee on Lyme Disease and Other Tick-Borne Diseases and for State of the Science, and he is also chairing the AVMA's Commission for AVMA Vision 2020. Dr. King is currently a member of the IOM Committee on Microbial Threats to Health, is a past member of the Food and Drug Administration's (FDA's) Board of Scientific Advisors, and is past President of the American Veterinary Epidemiology Society. He served as the Chair for the national One Medicine Task Force for the AVMA, which helped start the country's One Health Initiative. Dr. King was elected as a member of the IOM of the National Academies in 2004.

Kevin Anderson, Ph.D., serves as a Senior Program Manager in the Department of Homeland Security's (DHS's) Science and Technology Directorate, providing oversight and requirements for science programs focused on rapid detection and characterization of biological agents. Since joining DHS in 2003, Dr. Anderson has provided leadership for science program development, laboratory design and strategic planning, served as a subject matter expert and advisor to the Bioterrorism Risk Assessment and Biological Threat Characterization programs, and has participated in interagency working groups and assessments which provide guidance to medical countermeasure development, a key component of the nation's biodefense strategy. Prior to joining DHS, Dr. Anderson was a Principal Investigator at the U.S. Army Medical Research Institute of Infectious Diseases, leading research focused on understanding basic mechanisms of viral diseases causing hemorrhagic fever and development of medical countermeasures. He received postdoctoral training in molecular virology at the University of Alabama

at Birmingham and the University of North Carolina at Chapel Hill, performing basic research on human respiratory syncytial viruses, and earned Ph.D. and B.S. degrees in microbiology from Montana State University and the University of Maryland, College Park, respectively.

Ruth L. Berkelman, M.D., is the Rollins Professor and Director of the Center for Public Health Preparedness and Research at the Rollins School of Public Health, Emory University, in Atlanta. She received her A.B. from Princeton University and her M.D. from Harvard Medical School. Board certified in pediatrics and internal medicine, she began her career at CDC in 1980 and later became Deputy Director of NCID. She also served as a senior advisor to the Director of CDC and as Assistant Surgeon General in the U.S. Public Health Service. In 2001 she went to her current position at Emory University, directing a center focused on emerging infectious diseases and other urgent threats to health, including terrorism. She has also consulted with the biologic program of the Nuclear Threat Initiative and is most recognized for her work in infectious diseases and disease surveillance. She was elected to the IOM in 2004. Currently a member of the Board on Life Sciences of the National Academies, she also chairs the Board of Public and Scientific Affairs at the ASM.

Enriqueta C. Bond, Ph.D., is president emeritus of the Burroughs Wellcome Fund. Dr. Bond is currently a partner in QE Philanthropic Advisors, LLC, an organization that provides consulting services to foundations and nonprofits on matters of program, strategic planning, and capacity development related to medical sciences, international health, and science and math K–12 education. She received her undergraduate degree from Wellesley College, her M.A. from the University of Virginia, and her Ph.D. in molecular biology and biochemical genetics from Georgetown University. She is a member of the IOM and a fellow of the AAAS. Dr. Bond chairs the Academies' Board on African Science Academy Development and serves on the NRC Committee on the Future of the Research University. She serves on the board and executive committee of the Hamner Institute, the board of the Health Effects Institute, the board of the James B. Hunt Jr. Institute for Educational Leadership and Policy, and the NIH Council of Councils. In addition Dr. Bond serves on a scientific advisory committee for the World Health Organization (WHO) Tropical Disease Research Program. Prior to being named president of the Burroughs Wellcome Fund in 1994, Dr. Bond served on the staff of the IOM beginning in 1979, becoming its Executive Officer in 1989.

Roger G. Breeze, Ph.D., received his veterinary degree in 1968 and his Ph.D. in veterinary pathology in 1973, both from the University of Glasgow, Scotland. He was engaged in teaching, diagnostic pathology, and research on respiratory and cardiovascular diseases at the University of Glasgow Veterinary School from 1968 to 1977 and at Washington State University College of Veterinary Medi-

cine from 1977 to 1987, where he was professor and Chair of the Department of Microbiology and Pathology. From 1984 to 1987 he was Deputy Director of the Washington Technology Center, the state's high-technology sciences initiative, based in the College of Engineering at the University of Washington. In 1987, he was appointed Director of the USDA's Plum Island Animal Disease Center, a Biosafety Level 3 (BSL-3) facility for research and diagnosis of the world's most dangerous livestock diseases. In that role he initiated research into the genomic and functional genomic basis of disease pathogenesis, diagnosis, and control of livestock RNA and DNA virus infections. This work became the basis of U.S. defense against natural and deliberate infection with these agents and led to his involvement in the early 1990s in biological weapons defense and proliferation prevention. From 1995 to 1998, he directed research programs in 20 laboratories in the Southeast for USDA's Agricultural Research Service before going to Washington, DC, to establish biological weapons defense research programs for USDA. He received the Distinguished Executive Award from President Clinton in 1998 for his work at Plum Island and in biodefense. Since 2004 he has been CEO of Centaur Science Group, which provides consulting services in biodefense. His main commitment is to the Defense Threat Reduction Agency's Biological Weapons Proliferation Prevention Program in Europe, the Caucasus, and Central Asia.

Steven J. Brickner, Ph.D.,[1] is an independent consultant based in southeastern Connecticut. He received his Ph.D. in organic chemistry from Cornell University and completed an NIH postdoctoral research fellowship at the University of Wisconsin, Madison. Dr. Brickner is a synthetic organic/medicinal chemist with more than 25 years of research experience focused entirely on the discovery of novel antibacterial agents during his prior tenure at Upjohn, Pharmacia & Upjohn, and Pfizer. He is co-inventor of Zyvox® (linezolid), an oxazolidinone recognized as the first member of an entirely new class of antibiotic to reach the market in the more than 35 years since the discovery of the first quinolone. Approved in 2000, linezolid has annual worldwide sales of more than US$1 billion. He initiated the oxazolidinone research program at Upjohn and led the team that discovered linezolid and clinical candidates eperezolid and PNU-100480. While at Pfizer, he led the early development team that placed the oxazolidinone PNU-100480 into clinical trials, where it is being studied as a potential treatment for tuberculosis. Dr. Brickner received an honorary doctor of science degree from the University of Notre Dame in 2010, and he was a corecipient of the Pharmaceutical Research and Manufacturers of America 2007 Discoverers Award and the 2007 American Chemical Society Award for Team Innovation. He was named the 2002–2003 Outstanding Alumni Lecturer, College of Arts and Science, Miami University (Ohio). He is an inventor or co-inventor on 21 U.S. patents, has published more than 30 peer-reviewed scientific papers, and has given 25 invited speaker pre-

[1] Forum member until December 31, 2010.

sentations; he has been a member of the IOM Forum on Microbial Threats since 1997. In February 2009, he established SJ Brickner Consulting, LLC, which serves various clients in offering consulting services on all aspects of medicinal chemistry and drug design related to the discovery and development of new antibiotics.

Paula R. Bryant, Ph.D., is Chief of the Medical S&T Division, Chemical and Biological Defense Program at the Defense Threat Reduction Agency (DTRA) in Fort Belvoir, Virginia. As the Chief of the Medical S&T Division, Bryant interfaces with all levels of the Department of Defense and DTRA to plan, coordinate, integrate, and execute program activities necessary to provide timely and effective medical countermeasures against chemical, biological, and radiological (CBR) threats to U.S. interests worldwide. She also served as a Senior Scientist and Senior S&T Manager while at DTRA. Prior to joining DTRA, she was an Assistant Professor in the Department of Microbiology and The Ohio State University. She received her Ph.D. in microbiology and immunology from the Baylor College of Medicine.

John E. Burris, Ph.D., became president of the Burroughs Wellcome Fund in July 2008. He is the former president of Beloit College. Prior to his appointment at Beloit in 2000, Dr. Burris served for eight years as director and CEO of the Marine Biological Laboratory in Woods Hole, Massachusetts. From 1984 to 1992 he was at the National Research Council/National Academies, where he served as the executive director of the Commission on Life Sciences. A native of Wisconsin, he received an A.B. in biology from Harvard University in 1971, attended the University of Wisconsin, Madison, in an M.D.-Ph.D. program, and received a Ph.D. in marine biology from the Scripps Institution of Oceanography at the University of California, San Diego, in 1976. A professor of biology at the Pennsylvania State University from 1976 to 1985, he held an adjunct appointment there until going to Beloit. His research interests are in the areas of marine and terrestrial plant physiology and ecology. He has served as president of the American Institute of Biological Sciences and is or has been a member of a number of distinguished scientific boards and advisory committees, including the Grass Foundation; the Stazione Zoologica "Anton Dohrn" in Naples, Italy; the AAAS; and the Radiation Effects Research Foundation in Hiroshima, Japan. He has also served as a consultant to the National Conference of Catholic Bishops' Committee on Science and Human Values.

Peter Daszak, Ph.D., is President of EcoHealth Alliance (formerly Wildlife Trust), a U.S.-based organization that conducts research and field programs on global health and conservation. At Wildlife Trust, Dr. Daszak manages a headquarters staff of 35 and a global staff of more than 700, which conducts research and manages initiatives to prevent emerging pandemics and conserve wildlife

biodiversity. This includes research on zoonoses that spill over from wildlife in emerging disease "hotspots," including influenza, Nipah virus, SARS, West Nile virus, and others. Dr. Daszak's work includes identifying the first case of a species extinction due to disease; discovering chytridiomycosis, the major cause of global amphibian declines; publishing the first paper to highlight emerging diseases of wildlife; coining the term "pathogen pollution;" discovering the bat origin of SARS-like coronaviruses, identifying the drivers of Nipah and Hendra virus emergence, and producing the first ever emerging disease "hotspots" map.

Dr. Daszak is a member of the Council of Advisors of the One Health Commission, Treasurer of DIVERSITAS (ICSU), past member of the International Standing Advisory Board of the Australian Biosecurity CRC, and past member of the IOM Committee on Global Surveillance for Emerging Zoonoses and the National Research Council (NRC) committee on the future of veterinary research. He is Editor-in-Chief of the Springer journal *Ecohealth*, and past Treasurer and a founding director of the International Ecohealth Association. In 2000, he won the Commonwealth Scientific and Industrial Research Organisation medal for collaborative research in the discovery of amphibian chytridiomycosis. He has published more than 130 scientific papers and book chapters, including papers in *Science*, *Nature*, *PNAS*, *The Lancet*, *PLoS Biology*, and other leading journals. His work has been the focus of articles in the *New York Times*, *The Wall Street Journal*, *The Economist*, *The Washington Post*, *U.S. News & World Report, CBS, 60 Minutes*, *CNN*, *ABC*, *NPR's Talk of the Nation*, and *Morning Edition & Fresh Air with Terri Gross*. He is a former guest worker at the CDC, where he assisted in the pathology activity during the 1999 Nipah virus outbreak. His work is funded by the John E. Fogarty International Center of NIH, the National Institute of Allergy and Infectious Diseases (NIAID), the National Science Foundation (NSF), the U.S. Agency for International Development (USAID), Google.org, Rockefeller, and other foundations. To date, his group is one of the few to have been awarded three prestigious NIH/NSF Ecology of Infectious Disease awards, and it is one of four partners to share a recent multi-million-dollar award from USAID ("PREDICT") with the goal of predicting and preventing the next emerging zoonotic disease.

Jeffrey Duchin, M.D., is Chief of the Communicable Disease Epidemiology & Immunization Section for Public Health–Seattle & King County, Washington, and Associate Professor of Medicine, Division of Infectious Diseases (adjunct Associate Professor in the School of Public Health and Community Medicine) at the University of Washington.

Dr. Duchin trained in internal medicine at Thomas Jefferson University Hospital followed by a fellowship in general internal medicine and emergency medicine at the Hospital of the University of Pennsylvania. He did his infectious disease subspecialty training at the University of Washington. Dr. Duchin is a graduate of CDC's Epidemic Intelligence Service, assigned to the NCID. He

subsequently worked for CDC as a medical epidemiologist in the Divisions of Tuberculosis Elimination and HIV/AIDS Special Studies Branch before assuming his current position.

Dr. Duchin is a member of the IOM's Forum on Medical and Public Health Preparedness for Catastrophic Events and a current member of the CDC's Advisory Committee on Immunization Practices (ACIP). He is a Fellow of the Infectious Disease Society of America (IDSA) and of the American College of Physicians; a member of the IDSA's National and Global Public Health Committee and Pandemic Influenza Task Force; and is past-Chair of the IDSA's Bioemergencies Task Force. Dr. Duchin serves on the Editorial Board and Technical Advisory Group for Communicable Disease Alert and Response to Mass Gatherings for WHO and previously served as a member of the Department of Health and Human Services 2004 Tiger Team consulting with the Government of Greece on health preparations for the 2004 Olympics, in Athens, Greece.

Dr. Duchin's peer review publications and research interests focus on communicable diseases of public health significance, and he has authored text book chapters on the epidemiology of HIV/AIDS, bioterrorism, and outbreak investigations.

Jonathan Eisen, Ph.D., is a Professor at the Genome Center at the University of California (UC), Davis and holds appointments in the Department of Evolution and Ecology in the College of Biological Sciences and Medical Microbiology and Immunology in the School of Medicine.

His research focuses on the mechanisms underlying the origin of novelty (how new processes and functions originate). Most of his work involves the use of high-throughput DNA sequencing methods to characterize microbes and then the use and development of computational methods to analyze this type of data. In particular, his computational work has focused on integrating evolutionary analysis with genome analysis—so-called phylogenomics. Previously, he applied this phylogenomic approach to cultured organisms, such as those from extreme environments and those with key properties as they relate to evolution or global climate cycles. Currently he is using sequencing and phylogenomic methods to study microbes directly in their natural habitats (i.e., without culturing). In particular he focuses on how communities of microbes interact with each other or with plant and animal hosts to create new functions. Dr. Eisen is also coordinating one of the largest microbial genome sequencing projects to date—the "Genomic Encyclopedia of Bacteria and Archaea" being done at the Department of Energy (DOE) Joint Genome Institute, where he holds an Adjunct Appointment.

In addition to his research, Dr. Eisen is also a vocal advocate for "open access" to scientific publications and is the Academic Editor-in-Chief of *PLoS Biology*. He is also an active and award-winning blogger/microblogger (e.g., http://phylogenomics.blogspot.com and http://twitter.com/phylogenomics). Prior to moving to UC Davis he was on the faculty of The Institute for Genomic Re-

search (TIGR) in Rockville, Maryland. He earned his Ph.D. in biological sciences from Stanford University, where he worked on the evolution of DNA repair processes in the lab of Philip C. Hanawalt, and his undergraduate degree in biology from Harvard College.

Mark B. Feinberg, M.D., Ph.D., is vice president for medical affairs and policy in global vaccine and infectious diseases at Merck & Co., Inc., and is responsible for global efforts to implement vaccines to achieve the greatest health benefits, including efforts to expand access to new vaccines in the developing world. Dr. Feinberg received a bachelor's degree magna cum laude from the University of Pennsylvania in 1978 and his M.D. and Ph.D. degrees from Stanford University School of Medicine in 1987. His Ph.D. research at Stanford was supervised by Dr. Irving Weissman and included time spent studying the molecular biology of the human retroviruses—human T-cell lymphotrophic virus, type I (HTLV-I) and HIV—as a visiting scientist in the laboratory of Dr. Robert Gallo at the National Cancer Institute. From 1985 to 1986, Dr. Feinberg served as a project officer for the IOM Committee on a National Strategy for AIDS. After receiving his M.D. and Ph.D. degrees, Dr. Feinberg pursued postgraduate residency training in internal medicine at the Brigham and Women's Hospital of Harvard Medical School and postdoctoral fellowship research in the laboratory of Dr. David Baltimore at the Whitehead Institute for Biomedical Research. From 1991 to 1995, Dr. Feinberg was an assistant professor of medicine and microbiology and immunology at the University of California, San Francisco (UCSF), where he also served as an attending physician in the AIDS-oncology division and as director of the virology research laboratory at San Francisco General Hospital. From 1995 to 1997, Dr. Feinberg was a medical officer in the Office of AIDS Research in the Office of the Director of the NIH, the chair of the NIH Coordinating Committee on AIDS Etiology and Pathogenesis Research, and an attending physician at the NIH Clinical Center. During this period, he also served as Executive Secretary of the NIH Panel to Define Principles of Therapy of HIV Infection. Prior to joining Merck in 2004, Dr. Feinberg served as Professor of Medicine and Microbiology and immunology at the Emory University School of Medicine, as an investigator at the Emory Vaccine Center, and as an attending physician at Grady Memorial Hospital. At UCSF and Emory, Dr. Feinberg and colleagues were engaged in the preclinical development and evaluation of novel vaccines for HIV and other infectious diseases and in basic research studies focused on revealing fundamental aspects of the pathogenesis of AIDS. Dr. Feinberg also founded and served as the medical director of the Hope Clinic of the Emory Vaccine Center—a clinical research facility devoted to the clinical evaluation of novel vaccines and to translational research studies of human immune system biology. In addition to his other professional roles, Dr. Feinberg has also served as a consultant to, and a member of, several IOM and NAS committees. Dr. Feinberg currently serves as a member of the National Vaccine Advisory Committee and is a member of

the Board of Trustees of the National Foundation for Infectious Diseases. Dr. Feinberg has earned board certification in internal medicine; he is a fellow of the American College of Physicians, a member of the Association of American Physicians, and the recipient of an Elizabeth Glaser Scientist Award from the Pediatric AIDS Foundation and an Innovation in Clinical Research Award from the Doris Duke Charitable Foundation.

Jacqueline Fletcher, Ph.D., Regents Professor of Plant Pathology at Oklahoma State University, received a B.S. in biology from Emory University, Atlanta, Georgia, a M.S. in botany from the University of Montana, and a Ph.D. in plant pathology from Texas A&M University. She served as a postdoctoral associate at the University of Illinois before joining OSU in 1984, where she was appointed Sarkeys Distinguished Professor in 2001 and Regents Professor in 2008. She was named a fellow of the American Phytopathological Society (APS) in 2005 and a fellow of AAAS in 2007.

Dr. Fletcher is Director of the National Institute for Microbial Forensics and Food and Agricultural Biosecurity (NIMFFAB), a multidisciplinary OSU initiative that addresses high-priority national issues in research, teaching/education, and outreach with emphases in microbial forensics applications in plant pathology and produce safety. The NIMFFAB serves as a spoke laboratory for the Department of Homeland Security (DHS)-affiliated National Bioforensic Analysis Center, in the area of plant pathogen forensics. Dr. Fletcher's research focuses on mechanisms of virulence and insect transmission of plant pathogenic bacteria; on the relationships between human pathogens, such as *Salmonella* and *Escherichia coli*, and plants; and on the emerging disciplines of microbial forensics and agricultural biosecurity.

Dr. Fletcher served on the APS Council for 10 years, including the 4-year APS presidential sequence. In the months following September 11, 2001, Dr. Fletcher led APS responses and input to new national biosecurity initiatives. She has served for 9 years on the APS Public Policy Board (4 years as chair) and is currently on the APS Threatening Pathogens Advisory Committee. She also serves on several federal biosecurity advisory panels.

S. Elizabeth George, Ph.D.,[2] is director of the Biological Countermeasures Portfolio within the Science and Technology Directorate in DHS. Until it merged into the new department in 2003, she was Program Manager of the Chemical and Biological National Security Program in DOE's National Nuclear Security Administration's Office of Nonproliferation Research and Engineering. Significant accomplishments include the design and deployment of BioWatch, the nation's first civilian biological threat agent monitoring system, and PROTECT, the first civilian operational chemical detection and response capability deployed in the

[2] Forum member until December 31, 2010.

Washington, DC, area subway system. Previously, she spent 16 years at the U.S. Environmental Protection Agency (EPA), Office of Research and Development, National Health and Ecological Effects Research Laboratory, Environmental Carcinogenesis Division, where she was Branch Chief of the Molecular and Cellular Toxicology Branch. She received her B.S. in biology in 1977 from Virginia Polytechnic Institute and State University and her M.S. and Ph.D. in microbiology in 1979 and 1984, respectively, from North Carolina State University. From 1984 to 1986, she was an NRC fellow in the laboratory of Dr. Larry Claxton at EPA. Dr. George is the 2005 chair of the Chemical and Biological Terrorism Defense Gordon Research Conference. She has served as Councillor for the Environmental Mutagen Society and President and Decretary of the Genotoxicity and Environmental Mutagen Society. She holds memberships in the ASM and the AAAS and is an adjunct faculty member in the School of Rural Public Health, Texas A&M University. She is a recipient of the EPA Bronze Medal and Scientific and Technological Achievement Awards and the Department of Homeland Security Under Secretary's Award for Science and Technology. She is the author of numerous journal articles and has presented her research at national and international meetings.

Jesse L. Goodman, M.D., M.P.H., became Chief Scientist and Deputy Commissioner for Science and Public Health of FDA in 2009. He has broad responsibility for and engagement in leadership and coordination of FDA's crosscutting scientific and public health efforts. From 2003 to 2009, Dr. Goodman was Director of FDA's Center for Biologics Evaluation and Research, which oversees medical and public health activities critical to U.S. and global preparedness and the development, evaluation, safety, quality, and availability of biologics. A graduate of Harvard, Dr. Goodman received his M.D. from the Albert Einstein College of Medicine and did residency and fellowship training at the Hospital of the University of Pennsylvania and at the University of California, Los Angeles (UCLA), where he was also Chief Medical Resident. Prior to joining FDA, he was professor of medicine and chief of infectious diseases at the University of Minnesota, where he directed the multihospital infectious diseases research, training, and clinical programs, and where his NIH-funded laboratory first isolated and characterized *Anaplasma phagocytophilum*, the infectious agent causing a new tickborne disease, human granulocytic ehrlichiosis. Dr. Goodman has authored numerous scientific papers and edited the book *Tick Borne Diseases of Humans* (ASM Press, 2005). Dr. Goodman has been elected to the American Society for Clinical Investigation and to the IOM of the NAS, where he is a long-standing member of the Forum on Microbial Threats. He is an active clinician and teacher who is board certified in internal medicine, oncology, and infectious diseases and is staff physician and infectious diseases consultant at the National Naval and Walter Reed Army Medical Centers. Dr. Goodman is adjunct professor of medicine at the University of Minnesota.

Eduardo Gotuzzo, M.D., is Principal Professor of the Department of Medicine and director of the "Alexander von Humboldt" Institute of Tropical Medicine and Infectious Diseases, Peruvian University Cayetano Heredia in Lima, Peru, and head of the Department of Transmissible Diseases at the Cayetano Heredia Hospital. He is also an Adjunct Professor of medicine at the University of Alabama, Birmingham, School of Medicine. He is Director of the International Gorgas Course in Clinical Tropical Medicine, Universidad Peruana Cayetano Heredia, taught jointly with the University of Alabama, Birmingham. He is an adjunct faculty member of the William J. Harrington Training Programs for Latin America, University of Miami School of Medicine (since 1983); was associate to the International Health Department of the Johns Hopkins University (1986–1998); and was fellow of the Center for the Americas at Vanderbilt, Vanderbilt University. Dr. Gotuzzo is an active member in numerous international societies and has been President of the Latin American Society of Tropical Disease (2000–2003); the IDSA Scientific Program (2000–2003); the International Organizing Committee of the International Congress of Infectious Diseases (1994 to present); the International Society for Infectious Diseases (1996–1998); the PanAmerican Infectious Diseases Association; the International Federation for Tropical Medicine (2005–2008); and the Peruvian Society of Internal Medicine (1991–1992). He works on several research areas and teaches on subjects including emerging diseases, TB, HTLV-1, free-living amoebas, brucellosis, and parasites. He has published more than 290 articles and chapters as well as 6 manuals and 1 book. Recent honors and awards include being named an honorary member of the American Society of Tropical Medicine and Hygiene in 2002; an honorary member of the Society of Internal Medicine in 2000; and a distinguished visitor at the Faculty of Medical Sciences, University of Cordoba, Argentina (1999). In 1988, Dr. Gotuzzo received the Golden Medal for Outstanding Contribution in the Field of Infectious Diseases awarded by Trnava University, Slovakia. In 2007, Dr. Gotuzzo received the Society Citation Award from the IDSA. He was an honorary member of the Australian Society for Infectious Diseases (2008), the American Society of Tropical Medicine and Hygiene (2002), Academia de Medicina de México, Sociedad Nenzolana de Infectología, Sociedad Paraguaya de Infectología, and the National Academy of Medicine of Mexico (2010).

Carole A. Heilman, Ph.D., serves as director of the Division of Microbiology and Infectious Diseases (DMID) of NIAID, a component of NIH. DMID supports research to prevent and control diseases caused by virtually all human infectious agents (except HIV), including bacterial, viral, parasitic, and prion diseases. DMID supports a wide variety of projects spanning the spectrum from basic biology of human pathogens and their interaction with human hosts, through translational and clinical research, toward the development of new and improved diagnostics, drugs, and vaccines for infectious diseases. As director, Dr. Heilman

provides scientific direction, oversight, and management for an extramural research portfolio that encompasses 300 different organisms.

DMID supports the nation's biodefense as well as a solid research infrastructure that readily responds to public health challenges, such as emerging diseases. These resources were recently mobilized to respond to the emergence of 2009 H1N1 influenza by providing the first in-depth characterization of the H1N1 pandemic virus and conducting nine clinical trials that provided safety and efficacy data to inform public health practice.

Dr. Heilman has a Ph.D. in microbiology from Rutgers University. She did her postdoctoral work in molecular virology at the National Cancer Institute (NCI) and continued at the NCI as a senior staff fellow in molecular oncology. She later moved into health science administration, where she focused on respiratory pathogens, particularly vaccine development. Dr. Heilman has received numerous awards for scientific management and leadership, including three Department of Health and Human Services (HHS) Secretary's Awards for Distinguished Service recognizing her efforts on development of acellular pertussis vaccines, AIDS vaccines, and on accelerating biodefense research and development (R&D). Dr. Heilman serves as an infectious disease expert on the Board of Scientific Counselors for CDC. She also serves on the scientific board of the Fondation Mérieux's annual Advanced Course of Vaccinology and is a lecturer in this highly selective training program for decision makers in vaccinology. Throughout her career, Dr. Heilman has been a pioneer supporting the advancement of women in biomedical careers and serves as a mentor to a number of women within and outside of NIAID.

David L. Heymann, M.D., is currently Chair of the Health Protection Agency, United Kingdom; Professor and Chair, infectious disease epidemiology, at the London School of Hygiene and Tropical Medicine; and Head of the Global Health Security Programme at Chatham House, London. Until April 2009, he was Assistant Director-General for Health Security Environment and Representative of the director-general for Polio Eradication at WHO. Prior to that, from July 1998 until July 2003, he was Executive Director of the WHO Communicable Diseases Cluster, which included WHO's programs on infectious and tropical diseases, and from which the public health response to severe acute respiratory syndrome (SARS) was mounted in 2003. From October 1995 to July 1998, he was Director of the WHO Programme on Emerging and Other Communicable Diseases, and prior to that he was the Chief of Research Activities in the WHO Global Programme on AIDS. Dr. Heymann has worked in the area of public health for the past 35 years, 25 of which were on various assignments from CDC, and 10 of which have been with WHO. Before joining WHO, Dr. Heymann worked for 13 years as a medical epidemiologist in sub-Saharan Africa (Cameroon, Côte d'Ivoire, Malawi, and the Democratic Republic of Congo, formerly Zaire) on assignment from CDC in CDC-supported activities. These activities

aimed at strengthening capacity in surveillance of infectious diseases and their control, with special emphasis on the childhood immunizable diseases, including measles and polio, African hemorrhagic fevers, poxviruses, and malaria. While based in Africa, Dr. Heymann participated in the investigation of the first outbreak of Ebola in Yambuku (former Zaire) in 1976, then again investigated the second outbreak of Ebola in 1977 in Tandala, and in 1995 directed the international response to the Ebola outbreak in Kikwit for WHO. Prior to assignments in Africa, he was assigned for two years to India as a medical epidemiologist in the WHO Smallpox Eradication Programme. Dr. Heymann's educational qualifications include a B.A. from the Pennsylvania State University, an M.D. from Wake Forest University, a Diploma in Tropical Medicine and Hygiene from the London School of Hygiene and Tropical Medicine, and practical epidemiology training in the two-year Epidemic Intelligence Service of CDC. He is a member of the IOM; he was awarded the 2004 Award for Excellence of American Public Health Association, the 2005 Donald Mackay Award from the American Society for Tropical Medicine and Hygiene, and the 2007 Heinz Award on the Human Condition. In 2009 he was appointed an honorary Commander of the Most Excellent Order of the British Empire for services to global public health, and he was recently elected a fellow of the Academy of Medical Sciences in the United Kingdom. Dr. Heymann has been Visiting Professor at Stanford University, the University of Southern California, and the George Washington University School of Public Health; has published more than 145 scientific articles on infectious diseases and related issues in peer-reviewed medical and scientific journals; and has authored several chapters on infectious diseases in medical textbooks. He is currently the editor of the 19th edition of the *Control of Communicable Diseases Manual*, a joint publication of the American Public Health Association and WHO.

Philip Hosbach currently holds the position of Vice President of Immunization Policy and Government Relations at sanofi pasteur. The departments under his supervision are state government affairs, federal government affairs, medical communications, strategic advocacy, and immunization initiatives. His responsibilities include oversight of both public policy and immunization policy development. Mr. Hosbach acts as sanofi pasteur's principle liaison with CDC. He is currently coordinating sanofi pasteur's global efforts in responding to the emerging H1N1 pandemic. He is a graduate of Lafayette College (1984); shortly after that he began his professional career in the pharmaceutical industry with American Home Products. That career has now spanned 25 years, including the past 22 years focused solely on vaccines. Mr. Hosbach joined sanofi pasteur (then Connaught Labs) in 1987 in Clinical Research and held positions of increasing responsibility, including Director of Clinical Operations. While in Clinical Research, he also served as project manager for the development and licensure of Tripedia, the first diphtheria, tetanus, and acellular pertussis vaccine approved by FDA for use in U.S. infants. During his clinical research career at

sanofi pasteur, he contributed to the development and licensure of seven vaccines. Following his work in clinical research, Mr. Hosbach took a position in the commercial operations area of sanofi pasteur and quickly moved through the ranks on the business administration side of the vaccine division. During that time, Mr. Hosbach led a number of departments within sanofi pasteur, gaining valuable business experience within U.S. Commercial Operations. The departments he led during that time included Public Health Sales and Marketing, Public Relations, Public Affairs, New Product Marketing, and Business Intelligence. He has been a member of the IOM Forum on Microbial Threats since 2005 and has been a Steering Committee member of the Influenza Summit, which is jointly sponsored by CDC and the American Medical Association, since its inception. Since 2000 Mr. Hosbach has served on the Board of Directors for Pocono Medical Center and Pocono Health Systems, located in East Stroudsburg, Pennsylvania. He also serves as Chairman of the Compensation Committee.

Stephen A. Johnston, Ph.D., is currently director of the Center for Innovations in Medicine in the Biodesign Institute at Arizona State University. His center focuses on formulating and implementing disruptive technologies for basic problems in health care. The center has three divisions: Genomes to Vaccines, Cancer Eradication, and DocInBox. Genomes to Vaccines has developed high-throughput systems to screen for vaccine candidates and is applying them to predict and produce chemical vaccines. The Cancer Eradication group is working on formulating a universal prophylactic vaccine for cancer. DocInBox is developing technologies to facilitate presymptomatic diagnosis. Dr. Johnston founded the Center for Biomedical Inventions (also known as the Center for Translation Research) at the University of Texas, Southwestern, the first center of its kind in the medical arena. He and his colleagues have developed numerous inventions and innovations, including the gene gun, genetic immunization, the tobacco etch virus protease system, organelle transformation, digital optical chemistry arrays, expression library immunization, linear expression elements, synbodies, immunosignaturing diagnosis, and others. He also was involved in transcription research for years, first cloning *Gal4* and later discovering functional domains in transcription factors and the connection of the proteasome to transcription. He has been Professor at the University of Texas Southwestern Medical Center at Dallas and Associate and Assistant Professor at Duke University. He has been involved in several capacities as an adviser on biosecurity since 1996 and is a founding member of BioChem 20/20.

Kent Kester, M.D., is currently the commander of the Walter Reed Army Institute of Research (WRAIR) in Silver Spring, Maryland. Dr. Kester holds an undergraduate biology degree from Bucknell University (1982) and an M.D. from Jefferson Medical College (1986). He completed his internship and residency in internal medicine at the University of Maryland Hospital/Baltimore VA Medical

Center (1989) and a fellowship in infectious diseases at the Walter Reed Army Medical Center (1995). A malaria vaccine researcher with more than 50 authored or coauthored scientific manuscripts and book chapters, Dr. Kester has played a major role in the development of the candidate falciparum malaria vaccine known as RTS,S, having safely conducted the largest number of experimental malaria challenge studies ever attempted to date. Dr. Kester's previous military medical research assignments have included Director of the WRAIR Malaria Serology Reference Laboratory; Chief, Clinical Malaria Vaccine Development Program; Chief of the WRAIR Clinical Trials Center; and Director of the WRAIR Division of Regulated Activities. He currently is a member of the Steering Committee of the NIAID/Uniformed Services University of the Health Sciences Infectious Disease Clinical Research Program, as well as multiple NIAID Safety Monitoring Committees. He also serves as the consultant to the U.S. Army Surgeon General in Medical Research and Development. Board certified in both internal medicine and infectious diseases, Dr. Kester is also a fellow of both the American College of Physicians and the IDSA. He holds faculty appointments at both the Uniformed Services University of the Health Sciences and the University of Maryland School of Medicine.

Gerald T. Keusch, M.D., is Associate Provost and Associate Dean for Global Health at Boston University and Boston University School of Public Health. He is a graduate of Columbia College (1958) and Harvard Medical School (1963). After completing a residency in internal medicine, fellowship training in infectious diseases, and two years as an NIH research associate at the Southeast Asia Treaty Organization Medical Research Laboratory in Bangkok, Thailand, Dr. Keusch joined the faculty of the Mt. Sinai School of Medicine in 1970, where he established a laboratory to study the pathogenesis of bacillary dysentery and the biology and biochemistry of Shiga toxin. In 1979 he moved to Tufts Medical School and New England Medical Center in Boston to found the Division of Geographic Medicine, which focused on the molecular and cellular biology of tropical infectious diseases. In 1986 he integrated the clinical infectious diseases program into the Division of Geographic Medicine and Infectious Diseases, continuing as Division Chief until 1998. He has worked in the laboratory and in the field in Latin America, Africa, and Asia on basic and clinical infectious diseases and HIV/AIDS research. From 1998 to 2003, he was Associate Director for International Research and Director of the Fogarty International Center at NIH. Dr. Keusch is a member of the American Society for Clinical Investigation, the Association of American Physicians, the ASM, and the IDSA. He has received the Squibb (1981), Finland (1997), and Bristol (2002) awards of the IDSA. In 2002 he was elected to the IOM.

Rima F. Khabbaz, M.D., is Deputy Director for Infectious Diseases at CDC. Prior to her current position, she served as Director of CDC's National Center

for Preparedness, Detection, and Control of Infectious Diseases and held other leadership positions across the agency's infectious disease national centers. She is a graduate of the American University of Beirut, Lebanon, where she obtained both her bachelor's degree in science and her medical doctorate degree. She trained in internal medicine and completed a fellowship in infectious diseases at the University of Maryland, Baltimore. She joined CDC in 1980 as an Epidemic Intelligence Service Officer, working in the Hospital Infections Program. During her CDC career, she has made major contributions to advance infectious disease prevention, including leadership in defining the epidemiology of non-HIV retroviruses (HTLV-I and II) in the United States and developing guidance for counseling HTLV-infected persons, establishing national surveillance for hantavirus pulmonary syndrome following the 1993 U.S. outbreak, and developing CDC's blood safety and food safety programs related to viral diseases. She has also played key roles in CDC's responses to outbreaks of new and/or reemerging viral infections, including Nipah, Ebola, West Nile, SARS, and monkeypox, as well as the 2001 anthrax attacks. She is a fellow of the IDSA and member of the American Epidemiologic Society, the ASM, and the Council of State and Territorial Epidemiologists. She served on IDSA's Annual Meeting Scientific Program Committee and currently serves on the society's National and Global Public Health Committee. In addition to her CDC position, she serves as Clinical Associate Professor of medicine (infectious diseases) at Emory University. She is a graduate of the National Preparedness Leadership Initiative at Harvard University and of the Public Health Leadership Institute at the University of North Carolina.

Stanley M. Lemon, M.D., is Professor of Medicine at the University of North Carolina, School of Medicine, Chapel Hill, North Carolina. He received his undergraduate A.B. degree in biochemical sciences from Princeton University summa cum laude and his M.D. with honors from the University of Rochester. He completed postgraduate training in internal medicine and infectious diseases at the University of North Carolina, Chapel Hill, and is board certified in both. From 1977 to 1983 he served with the U.S. Army Medical Research and Development Command, followed by a 14-year period on the faculty of the University of North Carolina, School of Medicine. He moved to the University of Texas Medical Branch in 1997, serving first as Chair of the Department of Microbiology and Immunology, then as Dean of the School of Medicine from 1999 to 2004. Dr. Lemon's research interests relate to the molecular virology and pathogenesis of the positive-stranded RNA viruses responsible for hepatitis. He has had a longstanding interest in antiviral and vaccine development and has served as Chair of FDA's Anti-Infective Drugs Advisory Committee. He is the past Chair of the Steering Committee on Hepatitis and Poliomyelitis of the WHO Programme on Vaccine Development. He is past Chair of the NCID-CDC Board of Scientific Counselors and currently serves as a member of the U.S. Delegation to the U.S.–Japan Cooperative Medical Sciences Program. He was Co-Chair of the NAS

Committee on Advances in Technology and the Prevention of Their Application to Next Generation Biowarfare Threats, and he recently chaired an IOM study committee related to vaccines for the protection of the military against naturally occurring infectious disease threats.

Edward McSweegan, Ph.D., is a Program Officer at NIAID. He graduated from Boston College with a B.S. in biology in 1978. He has an M.S. in microbiology from the University of New Hampshire and a Ph.D. in microbiology from the University of Rhode Island. He was an NRC associate from 1984 to 1986 and did postdoctoral research at the Naval Medical Research Institute in Bethesda, Maryland. Dr. McSweegan served as an AAAS diplomacy fellow in the U.S. State Department from 1986 to 1988, where he helped to negotiate science and technology agreements with Poland, Hungary, and the former Soviet Union. After moving to NIH, he continued to work on international health and infectious disease projects in Egypt, Israel, India, and Russia. Currently, he manages NIAID's bilateral program with India, the Indo–U.S. Vaccine Action Program, and he represents NIAID in the HHS Biotechnology Engagement Program with Russia and related countries. He is a member of AAAS, the ASM, and the National Association of Science Writers. He is the author of numerous journal and freelance articles.

Mark A. Miller, M.D., is currently the Director of the Division of International Epidemiology and Population Studies for the Fogarty International Center at the National Institutes of Health in Bethesda, Maryland. He is also a Physician at the Yukon-Kuskokwim Delta Regional Hospital in Bethel, Alaska, which primarily serves Native Americans. He previously served as a Medical Officer on the Children's Vaccine Initiative for WHO and CDC, and Medical Epidemiologist for the CDC National Immunizations Program and Epidemiology Program Office, Office of the Director. He also conducted research at the Armed Forces Research Institute for Medical Studies in Bangkok, Thailand, the Yale Arbovirus Research Unit, and Cornell University Medical College.

Dr. Miller received his B.A., magna cum laude, in neuroscience, biology and human ecology from Amherst College in 1983, and his M.D. from Yale University School of Medicine in 1990. He completed his internal medicine residency at Yale New Haven Hospital/ Hospital of St. Raphael and became board certified in 1994. He has served as a member of many professional societies and steering committees, including the Secretary's Advisory Council on Public Health Preparedness Smallpox Modeling and several NSF, HHS, and NIH task forces. He has presented and consulted nationally and internationally for organizations including USAID, the Pan American Health Organization, and the World Bank. Dr. Miller is a reviewer for nine journals, including the *Journal of Infectious Diseases*, *The Lancet*, and the *Journal of the American Public Health Association*. He has won many awards, including the Distinguished Service Medal, from

the U.S. Public Health Service and the CDC. He has published more than 50 scientific articles in the peer-reviewed literature, 9 books and/or book chapters, and more than 50 letters and abstracts.

Paul F. Miller, Ph.D., is Chief Scientific Officer for Antibacterials Research at Pfizer, Inc. He received his undergraduate degree in biology from LeMoyne College and subsequently earned a Ph.D. in microbiology and immunology from the Albany Medical College in 1987. Following four years of postdoctoral studies on yeast molecular genetics at NIH in Bethesda, Maryland, Dr. Miller joined the Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company in Ann Arbor, Michigan, in 1990 as a senior scientist in the Infectious Diseases Department, where he developed a number of novel screens and mechanism-of-action tools. He then moved to Pfizer in 1997 as Manager of the Antibacterials Biology Research group within the Antibacterials, Immunology, and Cancer Zone at the Groton, Connecticut, research labs, and has taken on increasing responsibility since that time. In his current role, he is responsible for all antibacterial research activities through early clinical development, as well as collaboratively establishing R&D strategies in this disease area. His specific research interests and expertise include genetic mechanisms of intrinsic antibiotic resistance in bacteria as well as the use of novel genetic technologies for the elucidation of antibiotic mechanisms of action.

Stephen S. Morse, Ph.D.,[3] is Professor of Epidemiology at the Mailman School of Public Health of Columbia University, and Director of the PREDICT project of the USAID Emerging Pandemic Threats program. He was also founding Director of the Columbia University Center for Public Health Preparedness. He returned to Columbia in 2000 after four years in government service as Program Manager at the Defense Advanced Research Projects Agency, where he codirected the Pathogen Countermeasures Program and subsequently directed the Advanced Diagnostics Program. Before going to Columbia, he was Assistant Professor of Virology at the Rockefeller University in New York, where he remains an adjunct faculty member. He is the editor of two books, *Emerging Viruses* (Oxford University Press, 1993; paperback, 1996), which was selected by *American Scientist* for its list of 100 Top Science Books of the 20th Century, and *The Evolutionary Biology of Viruses* (Raven Press, 1994). He was a founding Section Editor of the CDC journal *Emerging Infectious Diseases* and was formerly an Editor-in-Chief of the Pasteur Institute's journal *Research in Virology*. Dr. Morse was Chair and principal organizer of the 1989 NIAID-NIH Conference on Emerging Viruses, for which he originated the term and concept of emerging viruses/infections. He has served as a member of the IOM-NAS Committee on Emerging Microbial Threats to Health, chaired its Task Force on Viruses, and was a contributor to the result-

[3] Forum member until December 31, 2010.

ing report *Emerging Infections* (1992). He has served on a number of NAS and IOM committees, including the IOM Committee on Xenograft Transplantation. Dr. Morse also served as an adviser to WHO and several government agencies. He is a fellow of the AAAS, the New York Academy of Sciences (and a past Chair of its microbiology section), the American Academy of Microbiology, the American College of Epidemiology, and an elected life member of the Council on Foreign Relations. He was the founding Chair of ProMED, the nonprofit international Program to Monitor Emerging Diseases, and was one of the originators of ProMED-mail, an international network inaugurated by ProMED in 1994 for outbreak reporting and disease monitoring using the Internet. Dr. Morse received his Ph.D. from the University of Wisconsin, Madison.

George Poste, Ph.D., D.V.M., is Chief Scientist, Complex Adaptive Systems Initiative, and Del E. Webb Professor of Health Innovation at Arizona State University (ASU). He assumed this post in 2009. From 2003 to 2009 he directed and built the Biodesign Institute at ASU. In addition to his academic post, he serves on the Board of Directors of Monsanto, Exelixis, Caris Life Sciences, LGC, and the Scientific Advisory Board of Synthetic Genomics. From 1992 to 1999 he was Chief Science and Technology Officer and President, R&D, of SmithKline Beecham (SB). During his tenure at SB he was associated with the successful registration of 31 drug, vaccine, and diagnostic products. In 2004 he was named "R&D Scientist of the Year" by *R&D Magazine*, in 2006 he received the Einstein award from the Global Business Leadership Council, and in 2009 he received the Scrip Lifetime Achievement award voted by the leadership of the global pharmaceutical industry.

He has published more than 350 research papers and edited 14 books on pharmaceutical technologies and oncology. He has received honorary degrees in science, law, and medicine for his research contributions and was honored in 1999 by Her Majesty Queen Elizabeth II as a Commander of the British Empire for his contributions to international security. He is a Fellow of the Royal Society, the Royal College of Pathologists, and the U.K. Academy of Medicine; a Distinguished Fellow at the Hoover Institution, Stanford University; and a member of the Council on Foreign Relations. He has served on numerous government panels related to biosecurity and national competitiveness.

John C. Pottage, Jr., M.D., is the Chief Scientific and Medical Officer at ViiV Healthcare, where he oversees R&D, Regulatory, Safety and Medical Affairs. From 2007–2010 he was vice president for Global Clinical Development in the Infectious Disease Medicine Development Center at GlaxoSmithKline. Previously he was senior vice president and chief medical officer at Achillion Pharmaceuticals in New Haven, Connecticut. Achillion is a small biotechnology company devoted to the discovery and development of medicines for HIV, hepatitis C virus, and resistant antibiotics. Dr. Pottage initially joined Achillion in

May 2002. Prior to Achillion, Dr. Pottage was medical director of Antivirals at Vertex Pharmaceuticals. During this time he also served as an associate attending physician at the Tufts New England Medical Center in Boston. From 1984 to 1998, Dr. Pottage was a faculty member at Rush Medical College in Chicago, where he held the position of associate professor, and also served as the medical director of the Outpatient HIV Clinic at Rush-Presbyterian-St. Luke's Medical Center. While at Rush, Dr. Pottage was the recipient of several teaching awards and is a member of the Mark Lepper Society. Dr. Pottage is a graduate of St. Louis University School of Medicine and Colgate University.

Gary A. Roselle, M.D., is Program Director for Infectious Diseases for the VA Central Office in Washington, DC, as well as the Chief of the Medical Service at the Cincinnati VA Medical Center. He is a Professor of Medicine in the Department of Internal Medicine, Division of Infectious Diseases, at the University of Cincinnati College of Medicine. Dr. Roselle serves on several national advisory committees. In addition, he is currently heading the Emerging Pathogens Initiative for the VA. He has received commendations from the Under Secretary for Health for the VA and the Secretary of VA for his work in the Infectious Diseases Program for the VA. He has been an invited speaker at several national and international meetings and has published more than 90 papers and several book chapters. Dr. Roselle received his medical degree from the OSU School of Medicine in 1973. He served his residency at the Northwestern University School of Medicine and his infectious diseases fellowship at the University of Cincinnati School of Medicine.

Alan S. Rudolph, Ph.D., M.B.A., has led an active career in translating interdisciplinary life sciences into useful applications for biotechnology development. His experience spans basic research to advanced development in academia, government laboratories, and most recently in the nonprofit and private sectors. He has published more than 100 technical publications in areas including molecular biophysics, lipid self-assembly, drug delivery, blood substitutes, medical imaging, tissue engineering, neuroscience, and diagnostics. As a National Research Council postdoctoral fellow, his earliest work at the U.S. Naval Research Laboratory (NRL) demonstrated the translational value of strategies used by organisms that survive environmental extremes to preserve defense products such as biosensors and blood products for field deployment. After a decade at NRL he was recruited to join the Defense Advanced Research Projects Agency, to lead new strategic efforts to extract and exploit useful principles and practices in life sciences and technology and establish an agency-wide strategy for investments in biosciences and biotechnology. As Chief of Biological Sciences and Technology, Dr. Rudolph established a framework for investments that continue today. These include new programs in broad areas of bioscience and technology such as sensors, diagnostics, materials, robotics, biomolecular, cell and tissue engineering,

medical devices, and neuroscience and technology, including the current efforts in revolutionizing prosthetics. He received a meritorious civil service citation from the Office of the Secretary of Defense for his contributions to defining and implementing a new generation of life sciences and national security investments.

In 2003, he left civil service for the private sector and starting new corporate biotechnology efforts. As Chief Executive Officer of Adlyfe Inc., a diagnostic platform company, and Board Chairman of Cellphire Inc., focused on development of novel hemostatic biologics for bleeding injury, he took nascent technology demonstrations and secured venture capital funding and pharmaceutical partnerships while managing all aspects of development toward first human use. These efforts included managing early manufacturing and regulatory strategies required for FDA approval of diagnostics and therapeutics. Most recently, he started a new international nonprofit foundation and, as Director of the International Neuroscience Network Foundation, he has secured corporate and private philanthropic donors to fulfill the mission of the organization focused on brain STEM efforts and clinical trial management in underserved populations. He has a doctorate degree in zoology from the University of California at Davis and an M.B.A. from the George Washington University.

Kevin Russell, M.D., M.T.M.&H., F.I.D.S.A. CAPT MC USN, is the Director, Department of Defense Global Emerging Infections Surveillance and Response System, and Deputy Director, Armed Forces Health Surveillance Center, in the U.S. Department of Defense. In this position, his priorities have been standardization, greater affiliations with world militaries, continuing to introduce scientific rigor into the network, and synchronization with other U.S. government global surveillance programs. He graduated from the University of Texas Health Science Center San Antonio Medical School in 1990; after a family practice internship, he was accepted into the Navy Undersea Medicine program. He was stationed in Panama City, Florida, at the Experimental Diving Unit where he worked in diving medicine research from 1991 to 1995. After a preventive medicine residency with a master's in tropical medicine and hygiene, he was transferred to Lima, Peru, where he became head of the Virology Laboratory. His portfolio included febrile illness (largely arboviral in origin) and HIV surveillance studies in eight different countries of South America, as well as prospective dengue transmission studies. In 2001, he moved back to the United States and became the director of the Respiratory Disease Laboratory at the Naval Health Research Center in San Diego, California. Febrile respiratory illness surveillance in recruits of all services was expanded into shipboard populations, Mexican border populations, support for outbreaks, and deployed settings. Validation and integration of new and emerging advanced diagnostic capabilities, utilizing the archives of specimens maintained at the laboratory, became a priority. A BSL-3-Enhanced was constructed. Projects expanded in 2006 to clinical trials support as Dr. Russell became the Principal Investigator for the Navy site in the FDA Phase III adenovirus vaccines trial, and

more recently to support the Phase IV postmarketing trial of the recently FDA-approved ACAM2000 smallpox vaccine.

Janet Shoemaker is Director of the ASM's Public Affairs Office, a position she has held since 1989. She is responsible for managing the legislative and regulatory affairs of this 42,000-member organization, the largest single biological science society in the world. Previously, she held positions as Assistant Director of Public Affairs for the ASM; as ASM coordinator of the U.S.–U.S.S.R. Exchange Program in Microbiology, a program sponsored and coordinated by the NSF and the U.S. Department of State; and as a freelance editor and writer. She received her baccalaureate, cum laude, from the University of Massachusetts and is a graduate of the George Washington University programs in public policy and in editing and publications. She is a member of Women in Government Relations, the American Society of Association Executives, and the AAAS. She has coauthored articles on research funding, biotechnology, biodefense, and public policy issues related to microbiology.

P. Frederick Sparling, M.D., is professor of medicine, microbiology, and immunology at the University of North Carolina (UNC), Chapel Hill. He is Director of the SouthEast Sexually Transmitted Infections Cooperative Research Center and also the Southeast Regional Centers of Excellence in Biodefense and Emerging Infections. Previously he served as Chair of the Department of Medicine and Chair of the Department of Microbiology and Immunology at UNC. He was President of the IDSA from 1996 to 1997. He was also a member of the IOM Committee on Microbial Threats to Health (1990–1992) and the IOM Committee on Emerging Microbial Threats to Health in the 21st Century (2001–2003). Dr. Sparling's laboratory research has been on the genetics and molecular biology of bacterial outer membrane proteins, with a major emphasis on gonococci and meningococci. His work helped to define the genetics of antibiotic resistance in gonococci and the role of iron-scavenging systems in the pathogenesis of human gonorrhea. Current interests include pathogenesis of gonococcal infections and development of a vaccine for gonorrhea and managing a large multi-institution interactive research group focused on emerging infections and biodefense.

Terence Taylor is the founding President of the International Council for the Life Sciences (ICLS). The ICLS is an independent nonprofit organization registered in the United States and in the European Union. The ICLS is designed to promote best practices and codes of conduct for safety and security in relation to biological risks. Terence Taylor also served as the vice president, Global Health and Security, at the Nuclear Threat Initiative. Prior to these appointments Terence Taylor was Assistant Director at the International Institute for Strategic Studies (IISS) in London and was President and Executive Director of IISS-US in Washington, DC. At IISS, in addition to his overall program responsibilities,

he led the Institute's work on life sciences and security. He has substantial experience in international security policy matters as a U.K. government official (both military and diplomatic) and for the United Nations (UN) both in the field and at UN Headquarters. He was a Commissioner and one of the Chief Inspectors with the UN Special Commission on Iraq, with particular responsibilities for biological issues. His government experience is related to both military field operations and to the development and implementation of policies in relation to arms control and nonproliferation treaties and agreements for both conventional weapons and weapons of mass destruction and the law of armed conflict aspects of International Humanitarian Law. He has also conducted consulting work on political risk assessment and studies of the private biotechnology industry. He was a science fellow at Stanford University's Center for International Security and Cooperation. He was an officer in the British Army with experience in many parts of the world including UN peacekeeping, counterinsurgency, and counterterrorism operations.

Murray Trostle, Dr.P.H., is a Foreign Service Officer with USAID, presently serving as the Deputy Director of the Avian and Pandemic Influenza Preparedness and Response Unit. Dr. Trostle attended Yale University, where he received a master's in public health in 1978, focusing on health services administration. In 1990, he received his doctorate in public health from UCLA. His research involved household survival strategies during famine in Kenya. Dr. Trostle has worked in international health and development for approximately 38 years. He first worked overseas in the Malaysian national malaria eradication program in 1968 and has since focused on health development efforts in the former Soviet Union, Africa, and Southeast Asia. He began his career with USAID in 1992 as a postdoctoral fellow with the AAAS. During his career he has worked with a number of development organizations, such as the American Red Cross, Project Concern International, and the Center for Development and Population Activities. With USAID, Dr. Trostle has served as Director of the child immunization cluster, where he was Chairman of the European Immunization Interagency Coordinating Committee and USAID representative to the Global Alliance on Vaccines and Immunization. Currently, Dr. Trostle leads the USAID Infectious Disease Surveillance Initiative as well as the Avian Influenza Unit.

Mary E. Wilson, M.D., is Associate Professor of Global Health and Population at the Harvard School of Public Health. Her academic interests include the ecology of infections and emergence of microbial threats, travel medicine, tuberculosis, and vaccines. Her undergraduate degree in French, English, and philosophy was awarded by Indiana University; she received her M.D. from the University of Wisconsin and completed an internal medicine residency and infectious disease fellowship at the Beth Israel Hospital in Boston (now Beth Israel-Deaconess Medical Center). She was Chief of Infectious Diseases at Mount Auburn Hospital, a Harvard-affiliated community teaching hospital in Cambridge, Massa-

chusetts, for more than 20 years. She is a fellow in the IDSA and the American College of Physicians. She has served on ACIP of CDC, the Academic Advisory Committee for the National Institute of Public Health in Mexico, and on four committees for the IOM of the National Academies, including the Committee on Emerging Microbial Threats to Health in the 21st Century, whose report (*Microbial Threats to Health: Emergence, Detection, and Response*) was released in March 2003. She has worked in Haiti at the Albert Schweitzer Hospital and leads the Harvard-Brazil Collaborative Course on Infectious Diseases, which is taught in Brazil. In 1996 she was a resident scholar at the Bellagio Study Center, Italy, and in 2002 she was a fellow at the Center for Advanced Study in the Behavioral Sciences in Stanford, California. She was a member of the Pew National Commission on Industrial Farm Animal Production, whose report *Putting Meat on the Table: Industrial Farm Animal Production in America* was released in the spring of 2008. A former GeoSentinel Site Director (Cambridge), she now serves as a Special Advisor to the GeoSentinel Surveillance Network, a global network. She has lectured and published widely, serves on several editorial boards, and is an Associate Editor for *Journal Watch Infectious Diseases*. She is the author of *A World Guide to Infections: Diseases, Distribution, Diagnosis* (Oxford University Press, New York, 1991); Senior Editor, with Richard Levins and Andrew Spielman, of *Disease in Evolution: Global Changes and Emergence of Infectious Diseases* (New York Academy of Sciences, 1994); and Editor of the volume *New and Emerging Infectious Diseases* (Medical Clinics of North America) published in 2008. She joined the Board of Trustees for ICDDR,B (International Centre for Diarrheal Disease Research, Bangladesh) in 2009 and is a member of the Board of Scientific Counselors for CDC, the FXB-USA Board, and the APUA Board of Directors.

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Speaker Biographies

Steven Kenyon Ault, M.Sc., REHS, is a public health biologist and Regional Advisor for Parasitic and Neglected Diseases at the Pan-American Health Organization, Regional Office of the World Health Organization (PAHO/WHO) in Washington, DC. His portfolio includes the coordination of neglected tropical diseases control and elimination focusing on lymphatic filariasis, onchocerciasis, schistosomiasis, and soil-transmitted helminthiasis, and collaboration on leishmaniasis, leprosy, trachoma, fascioliasis, and integrated vector control. He has served with PAHO/WHO in Guatemala and Brazil from 1997 to 2005, and prior to then as Technical Director for Public Health in the U.S. Agency for International Development Environmental Health Project (1994–1997), Deputy Director of the California EPA Comparative Risk Project (1991–1993), Chief of Research Services at the California Integrated Waste Management Board, and senior lecturer in environmental studies at the CSU Sacramento.

Mauricio L. Barreto, M.D., M.P.H., Ph.D., is a Full Professor of Epidemiology at the Instituto de Saude Coletiva, Federal University of Bahia, Salvador, Brazil. His research has covered topics such as schistosomiais, diarrhea, dengue, tuberculosis, leprosy, and asthma. His research program has a multidisciplinary perspective and is focused on environmental and social determinants and the impact of population-based interventions. He has coordinated large epidemiological and evaluative studies in Brazil and Ecuador and participates in several international networks. He has published more than 240 papers in peer-reviewed scientific journals and has participated in several health policy and scientific advisory boards at national and international agencies. He is a fellow of the Brazilian

Academy of Sciences and Editor-in-Chief of the *Journal of Epidemiology and Community Health*.

Chris Beyrer, M.D., M.P.H., is Professor of Epidemiology, International Health and Health, Behavior and Society at the Johns Hopkins Bloomberg School of Public Health. He directs the Johns Hopkins Fogarty AIDS International Training and Research Program, which provides research training in HIV/AIDS for providers from Africa, Asia, and the Commonwealth of Independent States. He is the Founder and Director of the Center for Public Health and Human Rights at Hopkins, which is engaged in research, teaching, and policy work on public health and human rights issues. Dr. Beyrer received his M.D. from the State University of New York, Downstate Medical Center in Brooklyn, New York, and did his public health and infectious diseases training at Johns Hopkins. In 2008 Dr. Beyrer was elected to the Governing Council of the International AIDS Society as a representative for North America. He currently has research and/or training activities under way in Thailand, Burma, China, India, Vietnam, Russia, Kazakhstan, Uganda, Ethiopia, Malawi, and South Africa.

Shing Chang, Ph.D., is the Research and Development Director at DNDi (Drugs for Neglected Diseases initiative, a Geneva-based nonprofit organization devoted to the research and development of drugs for neglected tropical diseases). In this position he has the overall responsibility of building DNDi's project portfolio and advancing the discovery and development of new treatments for neglected diseases.

Prior to joining DNDi in October 2007, Dr. Chang was Senior Vice President of Drug Discovery and Chief Scientific Officer at ICOS Corporation in Seattle. From 1991 to 2006, Dr. Chang held various management positions at Abbott Laboratories in diagnostics and pharmaceutical research, including the post of Divisional Vice President, Infectious Disease Research. From 1978 to 1991, Dr. Chang held various positions at Cetus Corporation, including Vice President of Preclinical and Development. He earned his Ph.D. degree in molecular biology and biochemistry from the University of California, Santa Barbara, and received his postdoctoral training at the University of Wisconsin and Stanford University.

Ezekiel J. Emanuel, M.D., Ph.D., Chair of the Clinical Center Department of Bioethics at the National Institutes of Health, is currently serving as a Special Advisor on Health Policy to the Director of the White House Office of Management and Budget (OMB). He is also a breast oncologist and author.

For the past decade, Dr. Emanuel has worked on global health issues, especially related to malaria and HIV/AIDS. He has trained researchers in developing countries on the ethics of clinical research and conducted numerous studies of ethical issues related to research in developing countries. In his role at OMB,

Dr. Emanuel has been involved in developing President Obama's Global Health Initiative.

He has received numerous awards including election to the Institute of Medicine (IOM) of the National Academy of Sciences and the Association of American Physicians. After completing Amherst College, Dr. Emanuel received an M.Sc. in biochemistry from Oxford University and then attended Harvard University, where he earned his M.D. from the medical school and a Ph.D. in political philosophy.

Christopher Eppig has been a Ph.D. student in the Human Evolutionary and Behavioral Sciences Program and the Biology Department at the University of New Mexico since 2005. He has conducted research on humans in diverse areas, including chemical communication, social behavior, endocrinology, male sexual behavior, and intelligence. His research has been widely covered by international media, including *The Economist*, *The Guaridan*, *Newsweek*, and *ScienceNow*.

Mark B. Feinberg, M.D., Ph.D.,[1] is vice president for medical affairs and policy in global vaccine and infectious diseases at Merck & Co., Inc., and is responsible for global efforts to implement vaccines to achieve the greatest health benefits, including efforts to expand access to new vaccines in the developing world. Dr. Feinberg received a bachelor's degree magna cum laude from the University of Pennsylvania in 1978 and his M.D. and Ph.D. degrees from Stanford University School of Medicine in 1987. His Ph.D. research at Stanford was supervised by Dr. Irving Weissman and included time spent studying the molecular biology of the human retroviruses—human T-cell lymphotrophic virus, type I (HTLV-I) and HIV—as a visiting scientist in the laboratory of Dr. Robert Gallo at the National Cancer Institute. From 1985 to 1986, Dr. Feinberg served as a project officer for the IOM Committee on a National Strategy for AIDS. After receiving his M.D. and Ph.D. degrees, Dr. Feinberg pursued postgraduate residency training in internal medicine at the Brigham and Women's Hospital of Harvard Medical School and postdoctoral fellowship research in the laboratory of Dr. David Baltimore at the Whitehead Institute for Biomedical Research. From 1991 to 1995, Dr. Feinberg was an assistant professor of medicine and microbiology and immunology at the University of California, San Francisco (UCSF), where he also served as an attending physician in the AIDS-oncology division and as director of the virology research laboratory at San Francisco General Hospital. From 1995 to 1997, Dr. Feinberg was a medical officer in the Office of AIDS Research in the Office of the Director of the NIH, the chair of the NIH Coordinating Committee on AIDS Etiology and Pathogenesis Research, and an attending physician at the NIH Clinical Center. During this period, he also served as Executive Secretary of the NIH Panel to Define Principles of Therapy of HIV Infection. Prior to joining

[1] Member of the Forum on Microbial Threats.

Merck in 2004, Dr. Feinberg served as Professor of Medicine and Microbiology and immunology at the Emory University School of Medicine, as an investigator at the Emory Vaccine Center, and as an attending physician at Grady Memorial Hospital. At UCSF and Emory, Dr. Feinberg and colleagues were engaged in the preclinical development and evaluation of novel vaccines for HIV and other infectious diseases and in basic research studies focused on revealing fundamental aspects of the pathogenesis of AIDS. Dr. Feinberg also founded and served as the medical director of the Hope Clinic of the Emory Vaccine Center—a clinical research facility devoted to the clinical evaluation of novel vaccines and to translational research studies of human immune system biology. In addition to his other professional roles, Dr. Feinberg has also served as a consultant to, and a member of, several IOM and NAS committees. Dr. Feinberg currently serves as a member of the National Vaccine Advisory Committee and is a member of the Board of Trustees of the National Foundation for Infectious Diseases. Dr. Feinberg has earned board certification in internal medicine; he is a fellow of the American College of Physicians, a member of the Association of American Physicians, and the recipient of an Elizabeth Glaser Scientist Award from the Pediatric AIDS Foundation and an Innovation in Clinical Research Award from the Doris Duke Charitable Foundation.

Alan Fenwick, O.B.E., is Professor of Tropical Parasitology and Director of the Schistosomiasis Control Initiative at Imperial College London. Dr. Fenwick has lived and worked in Tanzania, Sudan, and Egypt, in each country researching and controlling schistosomiasis and intestinal worms. In 2002 he returned from Africa to be based in the United Kingdom after being awarded funding from the Bill & Melinda Gates Foundation to prove the principle that six African countries were capable of mounting control campaigns against helminths if the resources were available to them. He is a campaigner for increased funding for neglected tropical disease (NTD) control. Mr. Fenwick's work has been recognized by the Queen (OBE and Anniversary medal for research) and by his peers (Donald McKay medal from the RSTMH).

Christy Hanson, Ph.D., is the Chief of the U.S. Agency for International Development's (USAID's) infectious disease division. She received her master's in public health from the University of Minnesota and her Ph.D. in international health systems, with a concentration in health economics, from Johns Hopkins University. Dr. Hanson has more than 15 years' experience in international tuberculosis (TB) control with support to countries in Africa, Asia, and Latin America through her previous positions with WHO, the World Bank, and PATH. She has published and presented widely on various aspects of TB control. She is currently chair of the Stop TB Partnership's Retooling Task Force and is a member of the Global Fund's technical review panel. Dr. Hanson has also published on the economic burden of NTDs and is USAID's technical lead for its NTD Initiative.

She manages the Other Public Health Threat element for USAID, which includes containment of antimicrobial resistance, surveillance, and outbreak response for infectious diseases.

Donald R. Hopkins, M.D., M.P.H., is Vice President (Health) of the Carter Center in Atlanta, Georgia. He oversees the Center's international health programs in 10 African and 6 Latin American countries as well as the Carter Center's Mental Health Program, and he chairs the International Task Force for Disease Eradication. He has led the Guinea Worm Eradication Program at the Carter Center since 1986 and at the Centers for Disease Control and Prevention (CDC) since 1980. Dr. Hopkins is presently a member of the WHO Strategic and Technical Advisory Group on Neglected Tropical Diseases. He has served as consultant on several WHO committees and as a member of the U.S. delegation to seven World Health Assemblies. He participated in the Smallpox Eradication Program (Sierra Leone, India, Ethiopia) and is a former Deputy Director of CDC. He is the author of *The Greatest Killer: Smallpox in History*.

Peter J. Hotez, M.D., Ph.D., is the Distinguished Research Professor and Chair of the Department of Microbiology, Immunology, & Tropical Medicine at George Washington University, and President of the Sabin Vaccine Institute, an affiliated nonprofit research, development, and advocacy organization. Dr. Hotez received a bachelor's degree in molecular biophysics and biochemistry magna cum laude (phi beta kappa) from Yale University, a Ph.D. from Rockefeller University, and a doctorate in medicine from Weill Cornell Medical College. He obtained pediatric residency training at the Massachusetts General Hospital, and postdoctoral training at Yale University School of Medicine. Dr. Hotez's research focuses on vaccine development for parasitic diseases, with an emphasis on recombinant vaccines for hookworm and schistosomiasis. He is Director and Principal Investigator of the Human Hookworm Vaccine Initiative, a product development partnership supported by the Gates Foundation and other sources. Dr. Hotez also has a strong policy interest to promote the control of NTDs and in 2006 at the Clinton Global Initiative Dr. Hotez helped to cofound the Global Network for NTDs for providing access to essential NTD drugs. In 2007, Dr. Hotez became the founding Editor-in-Chief of *PLoS Neglected Tropical Diseases,* and he is currently the President-Elect of the American Society of Tropical Medicine & Hygiene. Dr. Hotez has published more than 200 peer-reviewed journal articles as well as several books, including *Forgotten People, Forgotten Diseases* (ASM Press).

Julie Jacobson, M.D., is a Senior Program Officer at the Bill & Melinda Gates Foundation. Dr. Jacobson, currently supports grants working toward the control of NTDs and works with the development and implementation of new vaccines in the infectious disease group of Global Health. As former Scientific Director of Immunization Solutions and Director of PATH's Japanese encephalitis (JE)

project, she managed a US$35 million grant to accelerate the control of JE in endemic countries by improving data on the distribution of JE, accelerating the development of an improved vaccine and diagnostic tests for JE, and helping countries integrate JE vaccine into immunization programs. In her role as Scientific Director she defined the direction and growth of immunization solutions work by increasing the availability of vaccines to the world's most vulnerable populations. This included work on clinical trials for specific vaccines to directly working with ministries of health and partners in decision making on vaccine introduction and planning. Previously, she was responsible for prioritizing and designing field activities for PATH's Children's Vaccine Project in the areas including yellow fever and rotavirus. Prior to joining PATH, Dr. Jacobson worked at CDC as an Epidemic Intelligence Officer. In this capacity, she worked in disaster epidemiology and conducted needs assessments for disaster victims, evaluated national surveillance systems, and evaluated the health impact of earthquakes on displaced persons. Dr. Jacobson is a physician with training in clinical tropical medicine and applied epidemiology.

Jean Jannin, M.D., received his medical degree in Paris, France. He also received diplomas in leprology, parasitology, epidemiology, and biostatistics. He also obtained an M.Sc. in public health and graduated from the French National School of Public Health and from the Political Science Institute of Paris. He is General Public Health Inspector of the French Ministry of Health. After 10 years spent in Africa (Cameroon, Gabon, Chad, Congo) in charge of various programs, he came back to the French Ministry of Health before joining WHO in Geneva in 1995. After having been in charge of the African trypanosomiasis program, in 2005 he became Coordinator of Innovative and Intensified Disease Management in the WHO Neglected Tropical Diseases Department of WHO in Geneva.

Charles H. King, M.D., is an infectious disease specialist, epidemiologist, and senior member of the Center for Global Health and Diseases at Case Western Reserve University in Cleveland, and the Schistosomiasis Consortium for Operational Research and Evaluation at the University of Georgia. After completing his medical degree at SUNY-Downstate, he began research on parasitic infections in 1979 during his residency at University Hospitals of Cleveland. Since 1984, he has been active on parasite control and immunology research in Kenya and has recently focused on modeling and implementation of advanced programs for schistosomiasis control and elimination. His current research focuses on identification of human and environmental ecological drivers of vector-borne parasite transmission, and the design of more effective, integrated programs for parasite control.

Lonnie J. King, D.V.M.[2], is the 10th dean of the College of Veterinary Medicine at The Ohio State University (OSU). In addition to leading this college, Dr. King is also a professor of preventive medicine and holds the Ruth Stanton Endowed Chair in Veterinary Medicine. Before becoming dean at OSU, he was the director of CDC's new National Center for Zoonotic, Vector-Borne, and Enteric Diseases (NCZVED). In this new position, Dr. King leads the Center's activities for surveillance, diagnostics, disease investigations, epidemiology, research, public education, policy development, and diseases prevention and control programs. NCZVED also focuses on water-borne, food-borne, vectorborne, and zoonotic diseases of public health concern, which also include most of CDC's select and bioterrorism agents, neglected tropical diseases, and emerging zoonoses. Before serving as director, he was the first chief of the agency's Office of Strategy and Innovation.

Dr. King served as dean of the College of Veterinary Medicine, Michigan State University, from 1996 to 2006. As at OSU, he served as the CEO for academic programs, research, the teaching hospital, the diagnostic center for population and animal health, basic and clinical science departments, and the outreach and continuing education programs. As dean and professor of large-animal clinical sciences, Dr. King was instrumental in obtaining funds for the construction of a $60 million Diagnostic Center for Population and Animal Health; he initiated the Center for Emerging Infectious Diseases in the college, he served as the campus leader in food safety, and he had oversight for the National Food Safety and Toxicology Center.

In 1992, Dr. King was appointed administrator for the Animal and Plant Health Inspection Service (APHIS), U.S. Department of Agriculture (USDA), in Washington, DC. In this role, he provided executive leadership and direction for ensuring the health and care of animals and plants, to improve agricultural productivity and competitiveness, and to contribute to the national economy and public health. Dr. King also served as the country's chief veterinary officer for five years, worked extensively in global trade agreements within the North American Free Trade Agreement and the World Trade Organization, and worked extensively with the World Animal Health Association. During this time he was the Deputy Administrator for Veterinary Services of APHIS, USDA, where he led national efforts in disease eradication, imports and exports, and diagnostics in both Ames, Iowa, and Plum Island. He spent five years in Hyattsville, Maryland, in staff assignments in Emergency Programs, as well as Animal Health Information. While in Hyattsville, Dr. King directed the development of the agency's National Animal Health Monitoring System. He left APHIS briefly to serve as the director of the Governmental Relations Division of the American Veterinary Medical Association (AVMA) in Washington, DC, and served as the lobbyist for the AVMA on Capitol Hill.

[2] Member and Vice-Chair of the Forum on Microbial Threats.

Dr. King was in private veterinary practice for seven years in Dayton, Ohio, and Atlanta, Georgia. As a native of Wooster, Ohio, Dr. King received his B.S. and D.V.M. from OSU in 1966 and 1970, respectively. He earned his M.S. in epidemiology from the University of Minnesota and received his M.P.A. from American University in Washington, DC, in 1991. Dr. King is a board-certified member of the American College of Veterinary Preventive Medicine and has completed the Senior Executive Fellowship program at Harvard University. He served as president of the Association of American Veterinary Medical Colleges from 1999 to 2000 and was the Vice-Chair for the National Commission on Veterinary Economic Issues from 2000 to 2004. He has served on four NAS committees, including chairing the National Academies' Committee on Assessing the Nation's Framework for Addressing Animal Diseases. He is also Chair of the IOM Committee on Lyme Disease and Other Tick-Borne Diseases and for State of the Science, and he is also chairing the AVMA's Commission for AVMA Vision 2020. Dr. King is currently a member of the IOM Committee on Microbial Threats to Health, is a past member of the Food and Drug Administration's (FDA's) Board of Scientific Advisors, and is past President of the American Veterinary Epidemiology Society. He served as the Chair for the national One Medicine Task Force for the AVMA, which helped start the country's One Health Initiative. Dr. King was elected as a member of the IOM of the National Academies in 2004.

Patrick J. Lammie, Ph.D., M.S., was the Team Leader of the Diseases Elimination and Control Group in the Division of Parasitic Diseases at CDC until he was seconded to the Global Network for Neglected Tropical Diseases in 2009. Dr. Lammie received his Ph.D. from Tulane University in 1983 following doctoral research on lymphatic filariasis. After a postdoctoral fellowship at the University of Pennsylvania, he was a faculty member at Louisiana State University Medical Center in New Orleans before moving to CDC. At CDC, Dr. Lammie was involved in both laboratory and field work focused on understanding the pathogenesis of lymphatic filariasis. From this work, he became involved with public health efforts aimed at eliminating filariasis at the community level through mass drug administration in Haiti, Guyana, American Samoa, and other countries. Beyond his work at CDC, he serves as an Adjunct Professor at both Emory University and the University of Georgia and as a member of the Executive Group of the Global Alliance for the Elimination of Lymphatic Filariasis and of WHO's Working Group on the Monitoring and Evaluation of NTD Programs. At the Global Network, Dr. Lammie is the Technical Director, and his work supports the development and implementation of NTD control and elimination programs.

Harold Margolis, M.D., is the Director of the Dengue Branch of CDC in San Juan, Puerto Rico. He previously served as Director of the Pediatric Dengue Vaccine Initiative, a program of the International Vaccine Institute. Dr. Margolis has had a long prior association with CDC, beginning as an Officer of the Epidemic

Investigation Service, stationed at the Arctic Investigations Program in Anchorage, and ending as Director of the Division of Viral Hepatitis, where he was instrumental in the worldwide introduction of the hepatitis B vaccine. He is a board-certified pediatrician, a fellow of the American Academy of Pediatrics, and a fellow of the Infectious Diseases Society of America. His research and public health interests have focused on evaluation and introduction of new vaccines, molecular epidemiology of hepatitis viruses, and development of evidence-based public health policy. Dr. Margolis is the author or coauthor of 180 peer-reviewed publications, including 35 book chapters or proceedings.

Marian C. McDonald, Dr.P.H., M.P.H., M.A., is Associate Director of Health Disparities for the National Center for Emerging and Zoonotic Infectious Diseases at CDC. She has worked in women's health and minority health as an educator, scientist, writer, and advocate for three decades. She received her Dr.P.H. and M.P.H. from the University of California at Berkeley School of Public Health, and holds a master's in women's studies from Goddard College. Since going to CDC in 2002, she has provided leadership to numerous efforts to advance the health of women, minorities, and vulnerable populations. She envisioned and chaired the first International Conference on Women and Infectious Disease (ICWID) in Atlanta in 2004, and chaired the second ICWID in 2006. She serves on CDC's Health Equity Work Group and works on agency efforts to address social determinants of health. In 2009 she spearheaded CDC's work on Neglected Infections of Poverty and continues to contribute to the leadership of these efforts. She has worked extensively in Latino health since the 1990s, founding and directing a number of Latino health projects. Dr. McDonald was formerly a professor at Tulane University's School of Public Health and Tropical Medicine, where she pioneered coursework on gender, race, and ethnicity in health. She has published on women's health, vulnerable populations in preparedness, using the arts in health promotion, and neglected infections of poverty. Her awards include CDC's highest Health Equity Award and the Award for Distinguished Service to the Greater New Orleans Latino Community. She is a member of Delta Omega, the National Public Health Honor Society.

Mary Moran, M.B.B.S., Grad Dip FAT, has more than 20 years' experience in health policy and practice, including 10 years specializing in neglected disease policy. She has conducted projects for a wide range of public and multilateral health organizations with a focus on policy solutions for emerging issues related to neglected disease research and development. In 2004, Ms. Moran founded the research group that became Policy Cures at the London School of Economics & Political Science, later transferring it to the George Institute for Global Health in Sydney.

Prior to forming the group, she worked for more than a decade in emergency medicine; was a diplomat and policy analyst with the Australian Department

of Foreign Affairs & Trade; was Director of Médecins Sans Frontières (MSF) Access to Essential Medicines Campaign in Australia; and was a Europe-based policy advocate with MSF on issues relating to access to medicines for neglected patients. Ms. Moran is an Honorary Senior Lecturer at the London School of Hygiene and Tropical Medicine, and an expert adviser to WHO, the European Commission, the European and Developing Countries Clinical Trials Partnership, the Global Alliance for Vaccines and Immunization, the Organization for Economic Cooperation and Development, and the Wellcome Trust.

Eric A. Ottesen, M.D., is Director of the Lymphatic Filariasis Support Center at the Task Force for Global Health, Technical Director of the NTD Control Program of RTI International, and Adjunct Professor in the Department of Global Health at the Rollins School of Public Health at Emory University. He received his A.B. from Princeton University in 1965 and his M.D. from Harvard University in 1970, and he is board certified by the American Board of Pediatrics. Formerly head of the Clinical Parasitology Section of the National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH) (1975–1994), and Project Leader of the Filariasis Elimination Programme at WHO (1995–2001), he currently manages a Gates Foundation grant for operational research focused on "Resolving the Critical Challenges Now Facing the Global Programme to Eliminate Lymphatic Filariasis" and provides technical support to USAID-funded efforts in 14 countries to control or eliminate NTDs through programmatically integrated approaches.

Dr. Ottesen's research interests have centered principally on host responsiveness to parasitic helminth infections (primarily filariasis, onchocerciasis, and schistosomiasis) and on the relationship between allergic and parasitic diseases. Professional activities now target the elimination of lymphatic filariasis worldwide (especially program monitoring and evaluation), integrated control of NTDs, and the clinical and immunological aspects of filarial disease.

Lorenzo Savioli, M.D., M.Sc., DTM&H, is the Director of the Department of Control of Neglected Tropical Diseases of WHO. He graduated in Rome with degrees in medicine in 1977, in tropical medicine in 1979, and in infectious diseases in 1985. He has an M.Sc. in parasitology from the London School of Hygiene and Tropical Medicine and the DTM&H from the Royal College of Physicians of London. In the 1970s he developed a fascination for classical clinical semeiology and tropical medicine and in 1979 decided to go to Zanzibar to work in the small district Hospital of Chake Chake on the island of Pemba. In 1986 he started the Pemba Island Schistosomiasis Control Programme, which a few years later was extended to include the control of soil-transmitted helminthiasis. In 1991, he joined WHO in Geneva as the medical officer in charge of the Programme on Intestinal Parasitic Infections and in 1996 was appointed Chief of the Schistoso-

miasis and Intestinal Parasites unit. As Director of the NTD department, Dr. Savioli has overseen a portfolio of a large number of tropical diseases, ranging from schistosomiasis and other helminthiasis including the Guinea Worm eradication programme to the control of human African trypanosomiasis, Buruli ulcer, and leishmaniasis. Under his leadership, WHO has exponentially expanded support for prevention and treatment programs and developed a global strategy on preventive anthelminthic chemotherapy that is the base of large-scale interventions that regularly target millions of children and adults in endemic areas. He is Senior Associate in the Department of International Health of the Bloomberg School of Public Health, Baltimore, Maryland, and a Fellow of the Islamic Academy of Sciences, Amman, Jordan. In 1986 he received the First Prize of the Rorer Foundation for Medical Science for Italian Medicine for Developing Countries.

Jerry M. Spiegel, M.A., M.Sc., Ph.D., is Director, Global Health, Liu Institute for Global Issues, and associate professor, School of Population and Public Health at the University of British Columbia (UBC) in Vancouver, Canada. He was also founding President of the Canadian Coalition for Global Health Research and is a member of the UBC Neglected Global Disease Initiative Working Group. He directs research projects on applying an eco-bio-social approach to dengue in Ecuador and Cuba as part of a broader research program on globalization, social organization, and health that also includes initiatives in strengthening of health worker capacity to respond to extreme drug-resistant TB and HIV/AIDS in South Africa.

Rick L. Tarleton, Ph.D., received his Ph.D. from Wake Forest University in 1983, continuing research on *Trypanosoma cruzi* infection and Chagas disease that he began as an undergraduate. He joined the faculty of the University of Georgia in 1984 as an Assistant Professor in the then Department of Zoology and is currently a Distinguished Research Professor and UGA-AA Distinguished Research Chair in Cellular Biology. He is also founding Director, Center for Tropical and Emerging Global Diseases, University of Georgia (1998–2001); Burroughs Wellcome Fund Scholar in Molecular Parasitology (1995–2000); member, Wake Forest University Board of Visitors (1996–2004); member, NIH Tropical Medicine and Parasitology Study Section (1996–2000); Director, NIH Tropical Disease Research Unit on Vaccine Development for Chagas Disease (1998–2003); Founder and President, the Chagas Disease Foundation (2008 to present); and member, WHO/TDR Disease Reference Group on Chagas Disease, Human African Trypanosomiasis and Leishmaniasis (2009 to present). Dr. Tarleton has published more than 100 peer-reviewed studies, nearly all in the area of Chagas disease. His specific research focus is the mechanisms of immunity and

disease in *T. cruzi* infection (causative agent of human Chagas disease) and the development of diagnostics, therapeutics, and vaccines.

Mary E. Wilson, M.D.,[3] is Associate Professor of Global Health and Population at the Harvard School of Public Health. Her academic interests include the ecology of infections and emergence of microbial threats, travel medicine, tuberculosis, and vaccines. Her undergraduate degree in French, English, and philosophy was awarded by Indiana University; she received her M.D. from the University of Wisconsin and completed an internal medicine residency and infectious disease fellowship at the Beth Israel Hospital in Boston (now Beth Israel-Deaconess Medical Center). She was Chief of Infectious Diseases at Mount Auburn Hospital, a Harvard-affiliated community teaching hospital in Cambridge, Massachusetts, for more than 20 years. She is a fellow in the IDSA and the American College of Physicians. She has served on ACIP of CDC, the Academic Advisory Committee for the National Institute of Public Health in Mexico, and on four committees for the IOM of the National Academies, including the Committee on Emerging Microbial Threats to Health in the 21st Century, whose report (*Microbial Threats to Health: Emergence, Detection, and Response*) was released in March 2003. She has worked in Haiti at the Albert Schweitzer Hospital and leads the Harvard-Brazil Collaborative Course on Infectious Diseases, which is taught in Brazil. In 1996 she was a resident scholar at the Bellagio Study Center, Italy, and in 2002 she was a fellow at the Center for Advanced Study in the Behavioral Sciences in Stanford, California. She was a member of the Pew National Commission on Industrial Farm Animal Production, whose report *Putting Meat on the Table: Industrial Farm Animal Production in America* was released in the spring of 2008. A former GeoSentinel Site Director (Cambridge), she now serves as a Special Advisor to the GeoSentinel Surveillance Network, a global network. She has lectured and published widely, serves on several editorial boards, and is an Associate Editor for *Journal Watch Infectious Diseases*. She is the author of *A World Guide to Infections: Diseases, Distribution, Diagnosis* (Oxford University Press, New York, 1991); Senior Editor, with Richard Levins and Andrew Spielman, of *Disease in Evolution: Global Changes and Emergence of Infectious Diseases* (New York Academy of Sciences, 1994); and Editor of the volume *New and Emerging Infectious Diseases* (Medical Clinics of North America) published in 2008. She joined the Board of Trustees for ICDDR,B (International Centre for Diarrheal Disease Research, Bangladesh) in 2009 and is a member of the Board of Scientific Counselors for CDC, the FXB-USA Board, and the APUA Board of Directors.

[3] Member of the Forum on Microbial Threats.