UNDERSTANDING THE ECONOMICS OF MICROBIAL THREATS

PROCEEDINGS OF A WORKSHOP

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Forum on Microbial Threats

Board on Global Health

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Acronyms and Abbreviations

AMR	antimicrobial resistance
ART	antiretroviral therapy
ARV	antiretroviral
BARDA	Biomedical Advanced Research and Development Authority
BRICS	Brazil, Russia, India, China, and South Africa
CARB-X	Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator
CDC	U.S. Centers for Disease Control and Prevention
DRG	diagnosis related group
EID	emerging infectious disease
EPR	emergency preparedness and response
FDA	U.S. Food and Drug Administration
G20	Group of Twenty
GCBR	global catastrophic biological risk
GDP	gross domestic product
GPEI	Global Polio Eradication Initiative

IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
IHR	International Health Regulations
IMI	Innovative Medicines Initiative
IPV	inactivated polio vaccine
JEE	Joint External Evaluation
LPAD	Limited Population Pathway for Antibacterial and Antifungal Drugs
MDG	Millennium Development Goal
OECD	Organisation for Economic Co-operation and Development
OIE	World Organisation for Animal Health
OPV	oral poliovirus vaccine
PEF	Pandemic Emergency Financing Facility
PPR	*peste des petits ruminants*
PVS	Performance of Veterinary Services
R&D	research and development
SARS	severe acute respiratory syndrome
SDG	Sustainable Development Goal
SIR	susceptible-infected-recovered
TB	tuberculosis
TME	transferable market exclusivity
VAPP	vaccine-associated paralytic polio
VDPV	vaccine-derived poliovirus
WHO	World Health Organization
WPV	wild poliovirus

1

Introduction

Microbial threats, including endemic and emerging infectious diseases and antimicrobial resistance (AMR), can cause not only substantial health consequences but also enormous disruption to economic activity worldwide. While scientific advances have undoubtedly strengthened our ability to respond to and mitigate the mortality of infectious disease threats, events over the past two decades have illustrated our continued vulnerability to economic consequences from these threats. For example, during the 2014–2016 Ebola virus disease outbreak in West Africa, the countries of Guinea, Liberia, and Sierra Leone suffered a cumulative economic loss of at least 10 percent of gross domestic product (UNDG Western and Central Africa, 2015). The severe acute respiratory syndrome (SARS) outbreak in 2002–2004 led to an estimated economic impact of $18 billion in East Asia (Fan, 2003) and cost the world economy $40 billion (Lee and McKibbin, 2004). To get a better understanding of the potential direct economic costs of future major infectious disease events, the National Academy of Medicine's Commission on a Global Health Risk Framework calculated the average expected economic losses from infectious disease crises to cost $60 billion per year in the 21st century (GHRF Commission, 2016). Furthermore, an influential report on AMR in 2016 estimated that the economic cost of lost global production from resistant bacteria could amount to $100 trillion by 2050 if not adequately addressed (Review on Antimicrobial Resistance, 2016). As the world becomes more integrated, the global costs of infectious diseases are expected to rise.

Infectious disease outbreaks can disrupt the economy through various channels. The most obvious may be the direct and indirect effects of mor-

tality and morbidity, which drive the cost of health care and influence the availability of labor and income forgone (Fonkwo, 2008). Another channel that can disrupt the economy is from behavioral effects including social responses of individuals, organizations, and governments influenced by the fear of contagion (Bali et al., 2016). With information, news, and rumors instantly traversing the globe in an increasingly hyperconnected world, fear can become explosively contagious—and it is fear of the pathogen, not the pathogen itself, that often drives behavioral change which then affects the economy (Burns et al., 2006). Specifically, fear of infection may lead government officials to close borders and schools, investors to lose confidence, and individuals to change consumption and social patterns such as avoiding public transportation, movie theaters, restaurants, and other public gatherings. Such was the case in Hong Kong during the SARS epidemic, when mortality from the disease was relatively low at around 900 deaths, yet air traffic fell by nearly 80 percent and retail sales by 50 percent (Lee and McKibbin, 2004; Siu and Wong, 2004).

While there is increasing awareness of these consequences, a deep understanding of the economic dimensions of microbial threats remains incomplete, leaving the world vulnerable to significant economic impacts (Drake et al., 2012; GHRF Commission, 2016). It is still unclear how the aforementioned channels interact with one another to produce cascading effects, disrupt livelihoods, and drive up costs for the afflicted country, neighboring countries, and the world. Furthermore, the practice of modeling the costs as well as risks of microbial threats in the short, medium, and long terms is in its infancy. Other modeling challenges include consensus on the information and assumptions to incorporate, where to find the data, how to deal with uncertainty, and how to analyze, use, and communicate the results to the relevant stakeholders for action (Knight et al., 2016). These issues are further complicated by the fact that the economic impact of various types of microbial threats—endemic infectious diseases, emerging infectious diseases, and AMR—have often been calculated using different methodologies and presented and communicated differently, such as through cumulative cost versus average expected annual loss.

Additionally, the estimates of microbial threat risks are rarely factored into country-level macroeconomic assessments (Sands et al., 2016). As a result, governments underestimate the risk of infectious disease outbreaks, implementing economic policies that largely underinvest in preparedness (World Bank, 2017). On the public health side, strategies and interventions to tackle these risks are often naïve to economic issues. As many sectors have the potential to be affected by these threats, international and country-level coordination and multisectoral partnerships are imperative to preserve global economic stability (GHRF Commission, 2016).

WORKSHOP OBJECTIVES

To assess the current understanding of the interaction of infectious disease threats with economic activity and suggest potential new areas of research, an ad hoc planning committee under the auspices of the Forum on Microbial Threats at the National Academies of Sciences, Engineering, and Medicine planned a 1.5-day public workshop on understanding the economics of microbial threats.[1] This workshop built on prior work of the Forum on Microbial Threats (IOM, 2004, 2010a,b; NASEM, 2016, 2017) and aimed to help transform current knowledge into immediate action. The following topics were explored during the workshop[2]:

- Economic costs from infectious diseases that may place a disproportionate burden on low- and middle-income countries but affect regional and global stability
- Gaps in assessing economic costs of microbial threats through multiple channels of disruption, including dynamics of fear-based behavioral change
- Critical opportunities and challenges to model and develop metrics of risk, including identifying and using appropriate data, dealing with uncertainty, and building analytical tools to understand the potential economic consequences of infectious diseases
- Strategies to incorporate estimates of infectious disease risk to macroeconomic assessments of economic growth to ensure these risks are reflected in financial markets, business investment decisions, and flows of development assistance, and to link these assessments to incentives for action to minimize the threats
- Implications for upstream and downstream strategies, policies, and interventions that various sectors of government, multilateral institutions, and others may carry out in preventing and mitigating the economic costs
- Collaboration and coordination mechanisms among various stakeholders and across the sectors of public health, animal health, economics, travel, trade, commerce, and agriculture, among others

[1] The planning committee's role was limited to planning the workshop, and this Proceedings of a Workshop was prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants, and are not necessarily endorsed or verified by the National Academies of Sciences, Engineering, and Medicine, and they should not be construed as reflecting any group consensus.

[2] The full Statement of Task is available in Appendix A.

The 1.5-day workshop was held on June 12 and 13, 2018, in Washington, DC, and was chaired by Peter Sands, executive director of The Global Fund to Fight AIDS, Tuberculosis and Malaria. Workshop speakers and participants contributed by sharing perspectives from government, academia, and private and nonprofit sectors. With multisectoral participation, the workshop aimed to build more mutual understanding and to bridge those in the economic world with those with public health and clinical experience. The workshop comprised 1 keynote address and 29 speaker presentations over 3 sessions. During the final session, speakers and discussants broke into three groups to identify potential knowledge gaps, research priorities, and strategies to advance the field in understanding the economics of microbial threats.

ORGANIZATION OF THE PROCEEDINGS OF THE WORKSHOP

In accordance with the policies of the National Academies, the workshop did not attempt to establish any conclusions or recommendations about addressing the economics of microbial threats, and instead focused on the information presented, questions raised, and improvements recommended by individual workshop participants. Chapter 2 includes highlights from the keynote presentation on how economic analysis can contribute to global health decision making. Chapters 3 through 5 examine the economics of different types of microbial threats, including endemic infectious diseases, emerging infectious disease outbreaks, and AMR. Specifically, Chapter 3 focuses on the economic cost of endemic infectious diseases. It presents specific examples from global efforts to combat polio, HIV/AIDS, and tuberculosis. Chapter 4 discusses the economics and modeling of emerging infectious diseases and biological risks. It presents the economic costs of past epidemics such as pandemic influenza, Ebola, and Zika, and models for potential future economic consequences. Chapter 5 focuses on cost issues pertaining to AMR. It discusses direct and indirect costs related to AMR, the cost-effectiveness of interventions to mitigate AMR, and the effect of AMR beyond the health sector.

Chapters 6 through 8 focus on the economic perspectives of investing in preparedness to counter microbial threats. Chapter 6 highlights the costs and benefits related to national preparedness initiatives and features perspectives on public health and veterinary services and the One Health approach to building national capacities. Chapter 7 reviews the challenges of accelerated research and development of medical products to address AMR. It reviews opportunities and barriers to incentivizing product discovery and development. Chapter 8 features opportunities to invest in sustainable solutions to microbial threats. It presents issues pertaining to

international collective action and economic bottlenecks in the supply chain of medical products across Africa.

The final two chapters provide potential strategies and final observations made by some participants of the workshop to move the field forward. Chapter 9 provides an overview of next steps suggested during the breakout groups' discussions that took place during the final session of the workshop, as well as the subsequent discussion and general synthesis. Chapter 10 presents reflections on lessons learned and concluding remarks from the workshop.

2

The Economics of Global Health and Microbial Threats

To open the workshop and provide context for the subsequent presentations and discussions, Lawrence H. Summers, president emeritus and Charles W. Eliot University Professor of Harvard University, offered his perspective on the value of understanding the economics of global health and microbial threats. After Summers's address, Peter Sands, executive director of The Global Fund to Fight AIDS, Tuberculosis and Malaria, reflected on the keynote presentation and spoke about the desired outcomes of the workshop.

PERSPECTIVES ON PRIORITIES FOR USING ECONOMICS FOR GLOBAL HEALTH

In his keynote address, Lawrence H. Summers, president emeritus and Charles W. Eliot University Professor of Harvard University, began by asserting that economic analysis has the potential to make significant contributions to the field of global health. He said,

> It is hard to imagine an area of research, an area of knowledge, an area of human service where the stakes are larger than in global health, where the issues affect literally the difference between life and death for millions, if not tens of millions of people each year.

With an issue of such great magnitude, Summers stated that there are two major perspectives surrounding the role of economics in global health.

One perspective affirms that to apply economic analysis to health

trivializes a profound moral issue, he said. This viewpoint, he explained, states that it is wrong to think in terms of money, prices, and trade-offs, such as trading off one disease against another or trading off availability of one kind of treatment against another kind of treatment. Rather, it asserts that the issue is better framed in absolute moral commitments. According to Summers, there is a role for this perspective, and its advocates have been successful in raising the issue of health on the global agenda over recent decades. The Alma Ata Declaration is an example of such progress, which defined health as a human right and called for "health for all" to be achieved through a primary health care approach (WHO, 1978). The Millennium Development Goals (MDGs),[1] which guided the global development agenda from 2000 to 2015, as well as the more recent Sustainable Development Goals (SDGs),[2] which succeeded the MDGs in 2016, have similarly elevated health to the status of a global priority.

The second perspective, Summers described, considers the use of economic analysis to be a moral imperative given the scale and importance of global health challenges. Actions and policies are constrained by limited resources, he said, and this means that difficult choices must be made related to investment priorities. Summers added that proponents of economic analysis believe that the choices related to resource allocation and strategic planning are best made on the basis of rational analysis and data as opposed to reflex or emotional instinct. Summers supported this second viewpoint, believing that economic analysis can make important contributions to global health decision making.

From this point of view, Summers outlined four priority areas of economic analysis for global health that he believed would benefit for further discussion during the workshop (see Box 2-1). Firstly, he said that economic analysis should demonstrate the effect of global diseases on economic performance, as well as the high rate of return on well-designed interventions devised to counter them. The *Global Health 2035 Lancet Commission Report* established the case that the economic value of improvements in health was substantial relative to the overall economic growth of countries. For instance, reductions in mortality from improved health services were estimated to account for 11 percent of economic growth in low- and middle-income countries over recent years, and certain health investments demonstrated attractive economic benefits exceeding costs by a factor of

[1] The MDGs included five goals specifically focused on health: goal 1 on poverty and hunger; goal 4 on child mortality; goal 5 on maternal health; goal 6 on HIV/AIDS, malaria, and other diseases; and goal 7 on environmental sustainability, including safe water and sanitation (WHO, 2015).

[2] SDG 3, on good health and well-being, lists 13 targets pertaining to maternal and child health, infectious diseases, noncommunicable diseases, and universal health coverage (UNDP, 2016).

BOX 2-1
Four Potential Priority Areas for Using Economic Analysis to Improve Decision Making in Global Health Investments

1. *Investment case*: Economics can assess the value of investing in health interventions, comparing the rates of return of health investments across a range of interventions as well as comparing these investments with competing interests from other sectors of the economy.
2. *Resource allocation*: Economics can guide the allocation of resources within the health sector to maximize reductions in pain and suffering.
3. *International assistance*: Economics can evaluate the best approach to develop and present international assistance programs and address issues of fungibility.
4. *Incentive design*: Economic analysis can contribute to the design of better incentives around both health care provision and medical product development.

SOURCE: Summers presentation, June 12, 2018.

about 9 to 20 between 2015 and 2035 (Jamison et al., 2013). Summers noted that there is more work needed on this priority area, such as further economic analyses performed on a country-by-country basis and for other health-sector interventions.

Regarding the second priority area, Summers said economic analysis can guide decisions on resource allocation within the health sector. Summers highlighted three questions that could be answered with economic decision making:

1. Which diseases are associated with the most cost-effective treatments?
2. Where are research funds best spent to reduce pain and suffering or extend life?
3. What are the benefits of different types of investments?

Over recent years, the global health community has developed common metrics to evaluate the global burden of disease and the resulting suffering and loss of life. Despite these common metrics, he said every disease seems to have its own advocacy strategy to determine payoff for investment. He added there is currently no method to make strategic choices across resource allocation options. As an example, Summers described the challenge health systems face when deciding between increased funding directed toward care provision versus clinical research.

Regarding the third priority area, Summers stated that economic analysis can be used to evaluate and strengthen the effect of international development assistance for health. In particular, he said it could raise the issue of the fungibility of international aid. *Fungibility* is a term that refers to a product or resource's interchangeability. As an illustrative example, Summers explained that donor funds for health provided to a country do not necessarily translate into an equivalent amount spent in the health sector. The country's government can decide to reduce its funding to the health sector by the same amount and reallocate funds for a different use, he said. According to Summers, there is growing evidence from the evaluation of donor funds for social sectors like health and education that assistance can lead to government budget reallocation rather than incremental spending. Fungibility can occur both between sectors, as in health care versus other broad areas, and also within the health sector. When donor resources are provided to primary health care, Summers said it can often lead to increased government spending in other health sectors (e.g., tertiary care), rather than increasing the pool of resources for primary health care. Summers outlined potential ways to counter this effect, including matching grants tied to government expenditure and careful monitoring of donor efforts. Given the need for greater economic reasoning around the incentives of international assistance, Summers noted that this priority area is an opportunity for collaboration between economics and health researchers.

Regarding the fourth priority area, he said economic analysis can provide insight into designing incentives around health care provision and medical product development. Summers shared the example of physicians in the United States being reimbursed for gastroenterological procedures but not for diet and weight loss counseling, often leading to more procedures being performed and less counseling being provided. These incentives work against the provision of preventive care. Similarly, he noted that many global health institutions have called for the development of new antibiotics to be held in reserve in case of future outbreaks of antibiotic-resistant pathogens. There is no incentive structure in place, however, to encourage pharmaceutical companies to undertake this mission, according to Summers. If they were to develop such a product, he noted they would likely not be able to charge its true value.

Summers concluded by reflecting on the recent trends in global health. While the international community has been able to celebrate the control of infectious diseases in certain parts of the world, they persist in many other parts. As some countries benefit from falling rates of communicable diseases and rising incomes, they are now confronted with rising rates of noncommunicable diseases. Summers said that facing these challenges will require a multifaceted approach with collaboration among experts from the fields of health science, pharmaceutical science, and economics.

REFLECTIONS FROM THE KEYNOTE PRESENTATION

Peter Sands, executive director of The Global Fund to Fight AIDS, Tuberculosis and Malaria, provided a few remarks in response to Summers's presentation and then outlined the desired outcomes of the workshop. Sands noted that while the huge economic and human costs posed by microbial threats may be obvious to those attending this meeting, policy makers rarely consider these threats when making economic decisions. This consideration would only happen in exceptional circumstances such as during a major infectious disease outbreak, he said. Despite the availability and value of economic tools, such as the ones described by Summers, Sands argued that based on his experiences, the world of global health is sometimes reluctant to use these tools. However, resources are limited and using available data and tools to make explicit decisions on trade-offs and investments seems the most reasonable path to follow, in his view.

Sands further reflected on the challenges of using economics to understand microbial threats. He noted that while a number of academic institutions and organizations have done a large amount of work to assess the economic burden and costs of microbial threats, the evidence base for this field is quite fragmented with varying methodologies being used. For example, the methodologies being used to understand the economics of antimicrobial resistance are different from those being used for endemic infectious diseases. Additionally, much of the economic cost of emerging infectious disease outbreaks stems from people getting scared of contracting the disease and subsequently changing their behaviors to avoid being infected—this factor may also call for a different type of modeling. While different methodologies may be needed at times to understand the complexities of the economics of microbial threats, Sands suggested that research silos could be reduced in this field. These silos may be the result of failures of communication between those working in public health and clinical medicine, and those working in economics, he said.

Finally, Sands highlighted the need to use economics to ensure there are appropriate medical products to counter microbial threats. He emphasized the importance of addressing the economic misalignment of incentives and market failure issues as described by Summers, which explain the lack of investment in preparedness efforts such as the development of new antibiotics. According to Sands, changing the incentives is necessary to make a sustainable improvement to the current situation for medical products research and development (R&D).

Reflecting on the breadth of topics to be covered in the workshop, Sands highlighted a few desired outcomes of the workshop. First, he hoped that the workshop would help create a shared vision on the best ways of illuminating the economic impact of microbial threats as well as to identify

the role of economic tools in facilitating the financing of pandemic preparedness. Additionally, he anticipated that the workshop would shed light on better approaches using economic tools to unblock some of the impediments to preparedness, mitigation strategies, and accelerating R&D of medical products. Finally, Sands hoped that the workshop would uncover where and how economic tools could be leveraged to inform choices on investing in critical health interventions.

3

The Economic Cost of Endemic Infectious Diseases

Session I, part A, of the workshop explored the economic cost of endemic infectious diseases, focusing on diseases that disproportionately affect low- and middle-income countries but also affect regional and global financial stability. The diseases presented in this session each highlight different aspects of the economic considerations for endemic infectious diseases: polio is on the brink of eradication; HIV has transitioned from an emerging infection to an endemic disease; and tuberculosis (TB) has a high mortality rate and often affects individuals during their working age. The session was moderated by Thomas Inglesby, director of the Center for Health Security at the Johns Hopkins Bloomberg School of Public Health. Kimberly Thompson, president of Kid Risk, Inc., opened the session with an overview of the economic case for eradicating polio, evaluating the costs and benefits of both eradication and control strategies. Katharina Hauck, senior lecturer in health economics from the Imperial College London, followed with a discussion on the economic impact of HIV/AIDS on labor productivity and quality of life. Finally, Anna Vassall, professor of health economics at the London School of Hygiene & Tropical Medicine, described the costs and value of TB control programs and interventions.

ECONOMIC CASE FOR ERADICATING POLIO

Kimberly Thompson, president of Kid Risk, Inc., began by outlining four questions she hoped to address regarding the economics of polio eradication:

- What are the economic implications of polio control versus eradication? What are the economic costs if polio is not eradicated?
- What have been the economic benefits of the Global Polio Eradication Initiative (GPEI)?
- How can the global community build an economic case to keep the world free of polio after the two remaining regions achieve eradication?
- How can the global community ensure that the necessary investments in activities and functions will be made to sustain a polio-free world?

Pathophysiology of Polio

Thompson described the pathophysiology of polio to illustrate the complexities of modeling the disease. Polio is a positive-stranded RNA virus that exists in three stable forms: serotypes 1, 2, and 3. Live forms of the virus include the oral poliovirus vaccine (OPV), wild poliovirus (WPV), and vaccine-derived poliovirus (VDPV). Thompson noted that OPV—which contains a live attenuated virus—is low cost and easy to administer. It causes an infection in vaccine recipients who can then pass the vaccine-derived infection on to other members of their community. This infection induces an immunologic response that provides protection to both vaccinated individuals and infected community members against future infection and paralysis upon reinfection.

Unlike WPV, the OPV strain of the virus is extremely unlikely to cause central nervous system symptoms. However, OPV can occasionally mutate and begin to act like WPV. In these cases the virus strain is known as VDPV. In approximately 1 out of 2.7 million OPV-induced infections, VDPV can produce a case of vaccine-associated paralytic polio (VAPP) (GPEI, 2015). In populations with low OPV uptake, there may be enough susceptible, unvaccinated individuals nearby to sustain a paralytic polio outbreak if this were to occur. In rare cases, some individuals with B-cell related immunodeficiencies may take a long time to clear the infection and represent a potential source for reintroduction of the virus known as immunodeficiency-related VDPV or iVDPV. Because of this potential for paralytic polio cases in regions that use the oral vaccine, Thompson cautioned that OPV can only aim to achieve polio "control"—that is, a reduction of polio cases as opposed to complete eradication.

An inactivated form of the virus is used in the injectable form of the vaccine, known as inactivated polio vaccine (IPV). IPV is significantly more expensive and more difficult to administer than OPV as it is administered using sterile syringes. In contrast, IPV does not cause an active infection in vaccine recipients, only an immunologic response, and thus there is no risk

for VAPP cases or secondary spread to others—this allows for complete polio "eradication." According to Thompson, the different patterns associated with WPV transmission, OPV infection, OPV immune response, and IPV immune response make the economic implications of polio infection and intervention complicated to model.

Economic Implications of Polio Control Versus Eradication

Thompson summarized several key findings related to the economics of polio control versus eradication. She reviewed an economic analysis study indicating that "high control" is not an optimal outcome for diseases—like polio—where eradication is possible (Barrett, 2013). According to a cost-benefit analysis, the potential future cost savings of full eradication are high enough that deficit-financed spending is justified in the case of eradication programs as demonstrated by an analysis on polio eradication efforts in the Americas (Musgrove, 1988). Additionally, Thompson highlighted research that quantified the health and economic benefits of U.S. investments in polio control and eradication since 1955 (Thompson and Tebbens, 2006). The retrospective study, using a dynamic poliovirus transmission model, demonstrated that these efforts prevented more than 1 million cases of paralytic polio. Because of treatment cost savings, the investment resulted in net economic benefits exceeding $180 billion, which does not include the intangible costs of suffering, death, and averted fear.

A subsequent study revealed that transitioning from OPV-based control strategies to IPV-based eradication strategies, even in low-income settings, resulted in lower cumulative costs and cases of paralytic disease over a 20-year period (Thompson and Tebbens, 2007). This literature suggests that the benefits of intensively pursuing polio eradication outweigh its challenges, in light of the higher cumulative costs of a wavering commitment to eradication. Thompson cited the case of India, which achieved polio eradication in 2011 following an intensive national campaign and is now refocusing vaccination resources on other targets, such as measles and rubella (Cochi, 2017).

Economic Benefits of the Global Polio Eradication Initiative

Thompson also spoke on the economic benefits of GPEI, a global initiative launched in 1988 and coordinated by the World Health Organization (WHO), Rotary International, the U.S. Centers for Disease Control and Prevention, the United Nations Children's Fund, and the Bill & Melinda Gates Foundation. She reviewed a retrospective and prospective analysis of the expected costs and cases related to polio with and without the initiative (Tebbens et al., 2010). At the time, the study assumed that eradication

would occur by 2012. Expected net benefits were estimated to be $40–$50 billion between 1988 and 2035, plus an additional $17–19 billion accounting for the benefits of vitamin A supplements, which are commonly coadministered alongside polio vaccination campaigns.

When GPEI succeeds in eradicating the poliovirus, she said significant investments will still need to be made to keep the world polio free. Thompson described a subsequent study analyzing long-term poliovirus risk management policy options assuming eradication by 2016. The study also assumed that following eradication, OPV use would be discontinued and replaced with routine immunization of IPV through the year 2024, thus eliminating the potential for VAPP and WPV reemergence. In this scenario, the transition to IPV would yield an expected $16–17 billion in net benefits between 2013 and 2052, in comparison with the continued use of OPV (Tebbens et al., 2015). These estimates depend on GPEI adopting optimal risk management strategies, including continued high-quality surveillance, access to vaccine stockpiles, and maintaining community immunity prior to OPV cessation. Thompson noted that the magnitude of the benefits supports an economic case for sustained efforts after eradication is achieved. She also noted that the study needs to be updated to take into account that GPEI partners extended the current strategic plan to 2019.

Thompson concluded her remarks by noting the role economists can play in ensuring future investments in polio control and eradication. She described how economists are able to provide policy makers with data and analysis to evaluate potential options, but they are not the decision makers. However, she said, the work of economists can be used to hold policy makers accountable for decisions regarding these investments.

ECONOMIC IMPACT OF HIV/AIDS

Katharina Hauck, senior lecturer in health economics from the Imperial College London, described the links between HIV and gross domestic product (GDP), a principal indicator of a country's economy (see Figure 3-1). She explained that HIV affects GDP through multiple pathways. For example, health expenditure and lost income from the disease's morbidity and mortality negatively affect household income, reducing consumption as well as savings and investments in income-generating activities. This in turn lowers investment in capital and lowers labor productivity and GDP. Moreover, Hauck pointed out that HIV-infected individuals may value present benefits more than future benefits based on fear of illness and shorter life expectancy; this might reduce their incentives to invest in education, which further reduces labor productivity and GDP. Another pathway to consider is that children of HIV-infected individuals may become orphans when their parents pass away, which may reduce investments in education. As a

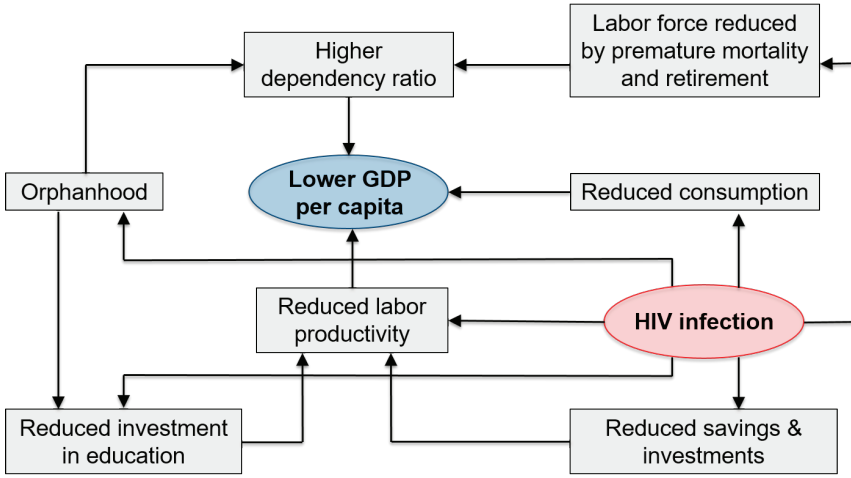

FIGURE 3-1 Multiple pathways link HIV infection and gross domestic product (GDP).
SOURCES: Hauck presentation, June 12, 2018; adapted from WHO, 1999. Reprinted from *The World Health Report, 1999: Making a Difference*, Health and Development in the 20th Century, Page 11, Copyright (1999).

larger proportion of individuals contribute less to the economy from caring for individuals affected by HIV, this may lead to higher dependency ratios. This higher dependency ratio is also influenced by an overall labor force that is reduced by premature mortality and retirement from HIV infection.

Hauck explained that the relationship between HIV and GDP can be modeled with a general equilibrium economic model. General equilibrium approaches in economics attempt to explain the functioning of a system made up of interacting parts using a single mathematical framework. These frameworks, however, are limited by the validity of the assumptions that underlie them. Current research efforts on the economics of HIV focus on improving the data and understanding the interactions that feed into the model. Hauck argued that an improved model will allow for a better prediction of return on investment related to national-level health policies surrounding HIV/AIDS.

Focus on Labor Productivity and Health-Related Quality of Life

With better individual and household data, economists have begun to focus on the key factor identified in the general equilibrium model: labor productivity. Hauck presented a cross-sectional study of more than 17,000 individuals from nine communities with high prevalence of HIV in

Zambia (Thomas et al., in review). The study compared productive days lost attributable to health-seeking behavior and illness over the past 3 months, between HIV positive and HIV negative individuals. The difference in productive days lost per month between the two groups was less than 1 day, which could be a result of the day that HIV positive individuals needed to collect their monthly supply of antiretroviral (ARV) drugs. According to Hauck, these estimates of lost productivity are much lower than those described in previous literature. As it is challenging to compare HIV positive and HIV negative patients using cross-sectional study designs, researchers carry out studies that track patients over time to assess any changes in productivity and income over their productive life. For instance, a study followed 54 HIV positive individuals working in Kenyan tea plantations until the end of their work lives. The researchers found that as many as 3 years before an AIDS-related termination, workers with HIV/AIDS were absent from the job more often and could not continue with their usual output when on the job (Fox et al., 2004).

Furthermore, Hauck noted that other studies indicate a second fall in productivity seen earlier in the lifetime of an HIV-infected individual, right before the initiation of antiretroviral therapy (ART) and lasting approximately 1 year (Larson et al., 2013). She described a scenario of an individual becoming sick and starting treatment, after which their productivity levels recover almost to the levels of an HIV negative individual. This pattern was demonstrated in a study measuring the working days of individuals in two Kenyan tea plantations. Additional dips in productivity can occur over an individual's lifetime because of treatment failure or resistance to first-line treatment. Hauck pointed out that these declines in health status, especially in the middle of a productive work life, should be prevented given the effect of falling labor productivity on GDP.

Hauck stated that ART has been successful not only in restoring labor productivity but also improving health-related quality of life. She presented a study that evaluated the health-related quality of life of both HIV-infected and uninfected individuals at various stages of life in South Africa and Zambia (Thomas et al., 2017). The study detected no difference in perceived quality of life between HIV-infected individuals on ART for more than 5 years compared with uninfected individuals. The same study revealed that in Zambia, 43 percent of HIV-infected individuals were unaware of their status before participating in the survey, and 12 percent were aware but were not in care (Thomas et al., 2017). Hauck argued that this finding suggests the continued challenge of late linkage to care and delayed treatment initiation.

Implications for Policy Design

Hauck stated that the studies on the effect of HIV on productivity and quality of life have implications for effective policy design. She reiterated that the studies suggest the success of ART not only in restoring labor productivity but also health-related quality of life, removing differences between HIV negative and HIV positive individuals. They also highlight persistent challenges, including late linkage to care and initiation of treatment. People who are unaware of their HIV status may drive the epidemic by infecting their sexual partners. According to Hauck, there is therefore a strong economic rationale for frequent testing and early intervention to reduce the number of new infections.

Another important aspect to consider when designing policy is the need for individual incentives, she added. HIV positive individuals bear the cost of preventing the further spread of HIV to their sexual partners, yet do not reap any individual benefits for this effort (because they are already infected). Policies often assume that HIV-infected people are altruistic, Hauck said, hoping that once they know their status they will take steps to prevent passing on the disease. She continued, however, that the evidence is inconclusive related to changes in risky sexual behavior after a person tests positive for HIV. The idea of altruism contradicts traditional economic theories of rational behavior. According to these economic theories, people only consider their own individual costs and benefits when making decisions.

Economic models, according to Hauck, support a universal "test and treat" strategy. This strategy involves initiating ART for HIV positive individuals as soon as they are diagnosed. She added that early ART is beneficial not only for the patients, who reap health benefits, but also for their sexual partners, who will have a lower risk of contracting the disease. However, as HIV positive individuals do not typically face immediate symptom decline in the early stages of their disease, they may have little motivation to initiate or adhere to treatment because of the low level of potential benefits during this phase (Thomas et al., 2017). Given this challenge, Hauck concluded that health policies should focus on testing and prevention measures targeting both HIV negative and HIV positive individuals, with an additional focus on adherence counseling.

COSTS AND VALUE OF TUBERCULOSIS CONTROL

Anna Vassall, professor of health economics at the London School of Hygiene & Tropical Medicine, described the strong investment case that can be made for TB control programs. TB has a high mortality rate, and it is the leading cause of death among infectious diseases, with 1.7 million

deaths per year (WHO, 2017; The Global Fund, 2018). It often affects people during their working age, which in turn leads to a detrimental effect on the economy in countries with a high burden of TB. Vassall argued that the effect of TB on mortality and productivity makes TB control a worthwhile investment.

Economics of Tuberculosis Control

The cost of the TB treatment regimen is relatively low. In low- and middle-income countries, a 6-month course of TB treatment can cost as little as $20 per patient, and, when effective, it prevents onward transmission of the disease (Laurence et al., 2015). Vassall explained that this figure rises when accounting for the costs of the health systems needed to deliver the treatment, and may fluctuate based on the high variability of treatment costs across different countries. In many low- and middle-income settings, the costs rise to between $100 and $200, while in high-income settings and countries faced with complex, drug-resistant cases (e.g., Russia), the figure can exceed $10,000 per case (WHO, 2017). Nevertheless, both TB treatment and control continue to be listed as leading health interventions in terms of cost-effectiveness in most low- and middle- income countries (Maher et al., 2007; Horton et al., 2017).

Economic analysis supports TB interventions because of the effect of the disease on poverty, said Vassall. TB infection is indolent, and infected individuals may go 6 months or more before seeking care. During this time, they suffer from adverse health effects and lost income, which can lead to behaviors such as selling assets, taking out loans, and withdrawing children from school (see Figure 3-2). Vassall described a study estimating that up to 40 percent of households in South Africa with a TB infection faced catastrophic expenditures (Foster et al., 2015). She presented additional research that models the positive impact of effective treatment of drug-sensitive and multidrug-resistant TB and expanded access to TB care on catastrophic financial costs faced by families in South Africa and India (Verguet et al., 2017). The study further highlights the need for not only effective service delivery but also social protection strategies for TB patients, in order to have a positive effect on poverty.

This evidence accompanied rising investments in TB control in high-burden countries, predominantly led by increased funding from country-level resources (WHO, 2017). Though the total resources allocated to TB control are increasing, they continue to be insufficient, Vassall said. If new resources are to be designated to TB control, it is not clear where the funding would be most effective. To explain this, she described an economic analysis performed in South Africa that evaluated the costs versus the health benefits in disability-adjusted life years from prevention, expanded access

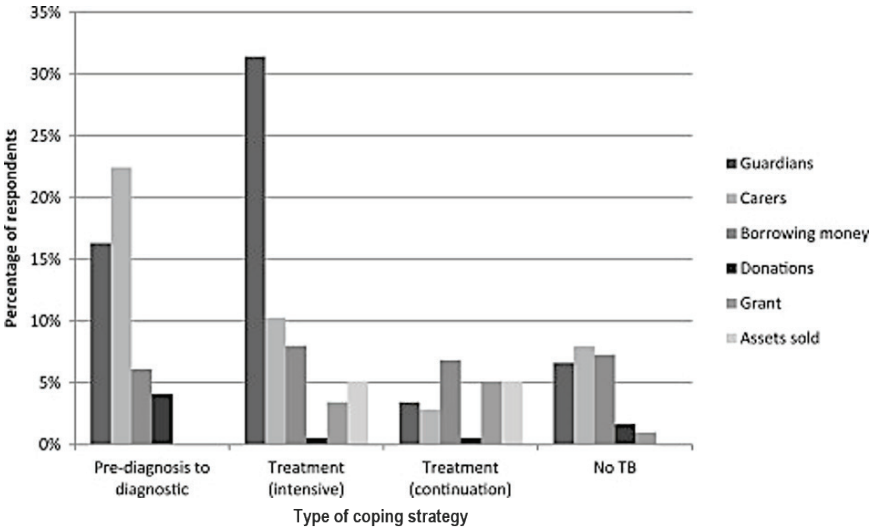

FIGURE 3-2 Percentage of respondents using financial coping strategies related to tuberculosis (TB) infection in South Africa.
SOURCES: Vassall presentation, June 12, 2018; adapted from Foster et al., 2015.

to care, and improved treatment quality for TB (Menzies et al., 2016) (see Figure 3-3). The results suggested that there are no obvious low-cost, high-return options for TB control. Policy makers can invest small amounts and achieve a low level of impact, or make a larger investment for a higher return. The analysis concluded by highlighting the need for a comprehensive "combination" package of interventions to control the disease, though this would require the country to increase baseline TB funding by a factor of two to three. While this strategy would strain the public-sector budget, it would also be associated with substantial reductions in health and economic costs borne by patients, she said.

New Technology Development and Uptake for Tuberculosis Control

Vassall discussed the challenge of new technology development and uptake for TB care, noting that even when these technologies become available, they might not prove to be cost-effective. The rapid TB diagnosis tool Xpert, for example, was predicted to be highly cost-effective though expensive particularly in low- and middle-income settings (Vassall et al., 2011). In reality, when the technology was employed in South Africa, it proved to have no effect on mortality while requiring additional services for implementation (Vassall et al., 2017). Vassall noted that this experience

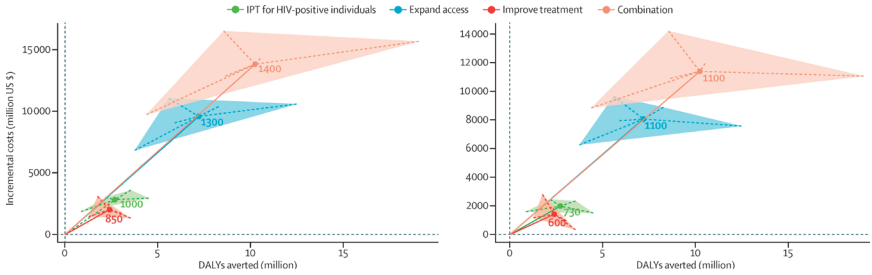

FIGURE 3-3 Cost-effectiveness ratios of potential tuberculosis (TB) intervention strategies in South Africa.
NOTES: Left graph: Health service perspective. Right graph: Societal perspective (combines patient and health service cost). DALY = disability-adjusted life year; IPT = isoniazid preventive therapy. Dashed lines connect model results to average outcomes. Shaded areas represent the heterogeneous model results for each scenario.
SOURCES: Vassall presentation, June 12, 2018; Menzies et al., 2016.

highlighted the need for broader health system investments and a further analysis of the supply-and-demand interactions that dictate how patients proceed through the health care pathway (see Figure 3-4).

Vassall argued that the demand for and supply of quality interventions such as new technologies are affected by a variety of proximal and distal constraints. Some constraints may become apparent through scale up or may indirectly affect the care pathway (Vassall et al., 2016). For example, on the demand side, there may be proximal constraints such as those that directly block knowledge, access, uptake, or adherence to treatment options. These proximal constraints are in turn influenced by distal constraints such as underlying values and preferences, cultural norms, and household resources. On the supply side, the knowledge and behavior of health care providers as well as the availability of staff and supplies may be potential proximal constraints; distal factors such as human resource availability, health financing, and the functioning of health systems may influence those proximal constraints. Vassall concluded that investment packages need to not only focus on the technologies but also address the various proximal and distal constraints to ensure that patients get the care they need.

DISCUSSION

Inglesby summarized the following points he captured from the presentations:

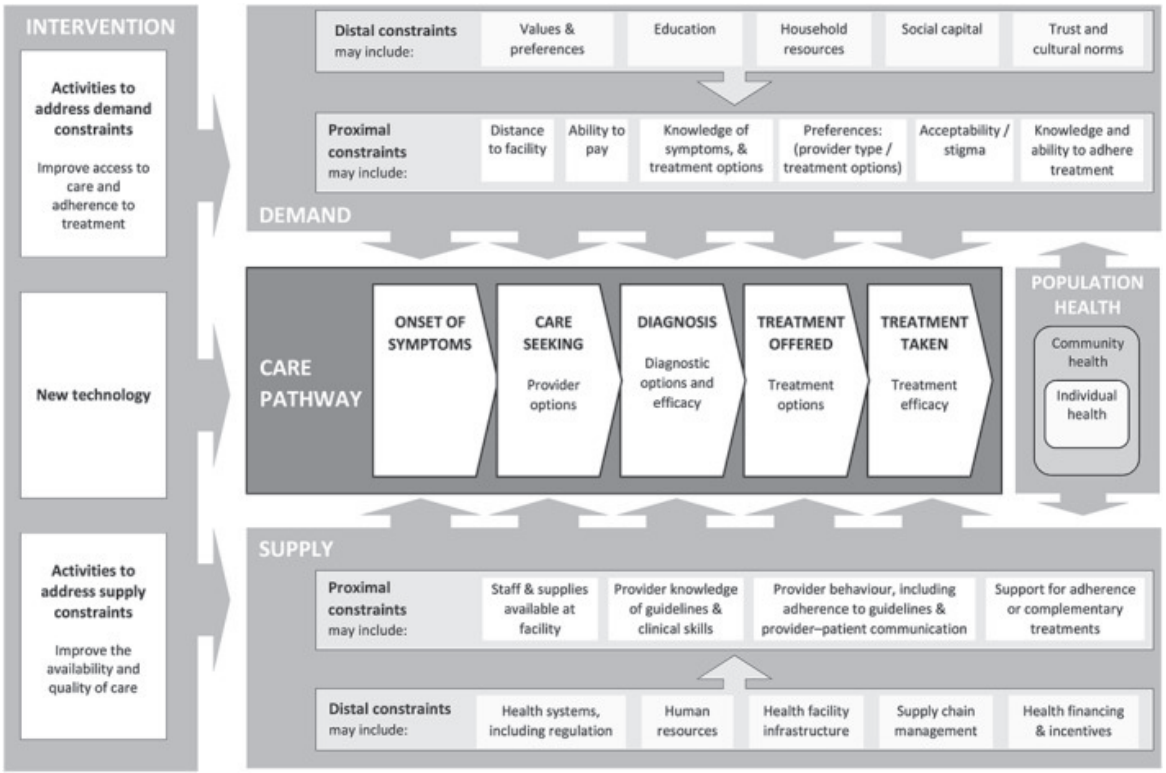

FIGURE 3-4 Conceptual framework for identifying demand and supply constraints in the context of introducing interventions in the care pathway.
SOURCES: Vassall presentation, June 12, 2018; Vassall et al., 2016.

- Control strategies and interventions for polio, HIV, and TB are complex and distinct for each disease.
- Global goals and campaigns play an important role in driving such efforts.
- To reflect real-world situations, economic models depend on effective implementation and human behavioral responses.
- Testing and case detection for these diseases are critical but are associated with significant costs.
- Different technologies, drugs, and vaccines affect calculations in economic analyses.
- Future investment on these strategies should be a concern as a decrease in funding may jeopardize the progress already made.

The discussion began with the topic of using economics to understand the social and behavioral aspects of endemic diseases. Jennifer Gardy, associate professor at the University of British Columbia's School of Population and Public Health, raised the issue of the ethical principles of reciprocity and altruism related to TB and HIV. She explained that patients take on a burden when they seek and subsequently receive treatment, and are therefore owed support by the public health system. She asked how individual economic incentives and social support are being used to address this challenge. Vassall responded that economic incentives are in fact being used, and cited a recent study that suggested that conditional cash transfers and social support had a positive effect on TB treatment (Wingfield et al., 2017). She said that advocates for TB control are bringing attention to economic incentives by focusing on the catastrophic costs related to the disease. Hauck said that there are a few studies on the efficacy and cost-effectiveness of conditional cash transfers to keep adolescent girls in schools, because of the link between school attendance and early infection with HIV (Baird et al., 2012; Pettifor et al., 2016). The evidence, however, is inconclusive and dependent on the subgroups analyzed, the people who receive the cash, and the method by which they receive it.

Ramanan Laxminarayan, director of the Center for Disease Dynamics, Economics & Policy, commented on the "fear factor" of infectious diseases—that is, how they affect behavior change in individuals who are not infected. In addition, when the incidence of a certain disease declines, countries stop paying attention, often leading to a resurgence of the disease, which has been the case in Sri Lanka with malaria and in Venezuela with polio. He also noted that the problem that ministers of finance face is the sheer magnitude of health care costs. These costs can be as much as billions of dollars, leading to what he described as "billion-itis," making it difficult for any meaningful economic analysis to prove useful for resource allocation. Laxminarayan concluded by asking whether there is a need

to expand focus beyond direct health care costs to include the behavioral choices of those not infected, including individuals in the agricultural and industrial sectors. To clarify this point, he explained that in Paraguay the major economic effect of malaria fell on those not infected, as they had to change crop choices to anticipate the increase of malaria cases during harvest seasons.

Thompson responded by highlighting the need to calculate the economic value of cases prevented, not just the number of actual cases. This presents a challenge, she said, as it is far more difficult to count cases prevented, which further demonstrates the need for modeling. She added that past modeling efforts focused only on case numbers and failed to note the potential for disease resurgence. Thompson emphasized the importance of clearly emphasizing the risk of disease resurgence to policy makers, particularly when the strategies needed to address these threats are no longer in place such as in the case of Venezuela. She argued that models should assign value to cases prevented to ensure sustained efforts even when case numbers are low.

Hauck responded to Laxminarayan's question by sharing her insights on HIV. She suggested that with the arrival of an effective treatment for HIV, individuals might perceive the costs of infection to be lower. She noted that HIV has evolved from a life-threatening illness to a chronic condition—a fact that changes the underlying incentive structure. This demonstrates the need to educate the public further on the side effects of treatment and the continued danger of infection, she said. She argued that policies should account for how individuals make decisions based on time and risk preferences in the context of competing infectious disease threats like malaria. Vassall emphasized the need for a greater understanding of the impact of borrowing not only on families facing financial catastrophes because of TB infection, but also in the communities to which they belong. The current studies only look at the economic effect at the individual/household level, but it is clear that the economic decisions at this level ripple into the community as it affects the lenders' household savings and investment horizons, she said.

Patrick Hickey, chair of the Department of Pediatrics at the Uniformed Services University of the Health Sciences, noted that as some countries approach adequate control for a specific disease, allocating resources efficiently to identify and treat the last few cases becomes a primary challenge. He asked how useful economic models can be in regard to "last mile" concerns. Thompson responded by explaining that countries and their partners need to determine where the last mile is, and to understand the associated barriers to care (e.g., undervaccination and undertreatment). Related to economic models, she added that sometimes strategies are overly optimistic and do not reflect the uncertainty of what happens in the field. She noted

that models must account for increasing costs over time as progress is made toward goals. She described a study characterizing the cost function of vaccination campaigns as coverage increases (Ozawa et al., 2018). Thompson argued that when eradication is the goal, associated costs will be higher, but the long-term benefits will be substantial enough to outweigh them.

In response to Hickey's question, Hauck added that there is a trade-off between equity and efficiency related to this question about the costs of reaching the last mile. Costs for the last case of a disease can be high, but if society wants to deliver benefits to remote or marginalized communities, they must weigh the challenge of efficiency against the goal of equity, she said. She also noted that there are significant benefits to the elimination of the last cases of a disease. This eradication dividend is gained not only by the country itself, but also by other countries in the region and the global community. As an example, she said that all countries were able to eliminate smallpox surveillance and vaccination following the eradication of the disease. She added that studies are currently under way to assess if the success with smallpox case can be translated to other diseases.

In contrast, Vassall said that TB is not at the last mile stage yet, particularly because of challenges with latent TB, but there is nevertheless a need to expand focus beyond health services. Currently, she said health systems rely on infected individuals to present themselves to facilities, but in the future health workers will need to actively search for cases, which will have higher cost implications. She noted there are little data on the cost of finding new cases, and that treatment costs are only estimates and often do not reflect actual costs in peripheral facilities.

The discussion shifted to the topic of using economics in the policy world. Jeffrey Duchin, health officer and chief of the Communicable Disease Epidemiology and Immunization Section for Public Health—Seattle and King County, Washington, asked about the effect of economic modeling on policy makers, and how to use models for infectious diseases as powerful tools to create change in policy. Thompson responded by referencing her experience with GPEI. She explained that close collaboration, open communication, clarifying questions, and shared understanding with policy makers throughout the process have been critically important.

Thompson also noted that policy-making partners have been helpful in highlighting trends and future challenges. She remarked that while models must capture the complexity of the disease's biology and epidemiology, they must also be accessible to ministers of health and finance. Hauck added that researchers must devise methods to provide answers more quickly than the 6-year waiting period associated with randomized control trials. She said economic modeling and other economic research tools (e.g., quasi-experimental methods including difference in differences and regression discontinuity analysis) are cheaper, faster, and are increasingly being used

in the context of public health. Vassall noted that the underlying policy environment of a country is important as it in turn affects the utilization of economic modeling. She argued that even when economic analysis does not drive action, it can still move policy debate forward by disproving fallacious arguments (e.g., "TB care is not cost-effective"). She emphasized the need for researchers to spend time in the countries under study to understand the local context and build local ownership. This type of long-term engagement, she said, facilitates the institutionalization of economic advice and strengthens the countries' capacities.

Continuing the discussion on policy, Jesse Goodman, professor of medicine at Georgetown University, noted that benefits and costs related to microbial control efforts change over time, and communicating this to policy makers with short-term decision horizons is a challenge. He further argued that there are externalities associated with policy decisions, as present-day decision makers may not own the downstream costs and benefits of their actions. Goodman asked panelists to share their experiences accounting for these concerns in political or practical situations.

Thompson explained that everything is dynamic, and that economic analyses must tackle these dynamics according to the uncertainty and variability in different country contexts regarding their interventions, policies, and preferences. She added that technical work must be done to get the modeling right first, and then results can be translated and put into context for policy makers and their staff. With regard to externalities, she noted that the polio program has been conservative about characterizing the costs and benefits over time, as it is important to make sure they are not double counted. According to Thompson, polio eradication efforts' largest benefit to other diseases stems from having established a large surveillance network of laboratories and field activities to control and eradicate the disease. These resources proved critical during the 2002–2004 severe acute respiratory syndrome outbreak and more recently for the Ebola response in Nigeria.

Hauck responded to Goodman's question of changing costs and benefits related to control efforts by stating that for HIV these changes are mainly relevant to the cost of the drug treatment. These uncertainties include unknown future prices of ART, particularly with respect to second-line drugs, and the speed at which drug resistance will develop. In addition, she noted that several health system costs (such as service delivery platforms) are shared across multiple interventions taking advantage of economies of scope, but calculating these costs is challenging.

Vassall agreed with Goodman's comments and observed that TB research has historically used cohort models that estimate the number of deaths prevented. She noted that there is now an opportunity to use new methods to capture cases averted and account for potential long-term gains

and savings to health systems, even though assessing longer-term effects introduces more uncertainties. On the topic of policy makers, Vassall shared the example of top-level stakeholders making decisions to increase funding or launching new control initiatives, but with no follow-up action and disbursements of funds. She stated that there is a need to focus on how policy makers operate and the mechanism necessary for them to implement relevant policies.

4

The Economics and Modeling of Emerging Infectious Diseases and Biological Risks

During session I, part B, of the workshop, speakers explored the economics and modeling of emerging infectious diseases and biological risks. The session, moderated by Rebecca Katz, associate professor of global health at Georgetown University, opened with an overview of the cost of pandemic influenza by Martin Meltzer, senior economist and distinguished consultant for the U.S. Centers for Disease Control and Prevention (CDC). Anas El Turabi, Frank Knox fellow in health policy at Harvard University, followed with a discussion on assessing economic vulnerability to emerging infectious disease outbreaks. Carlos Castillo-Chavez, professor of mathematical biology at Arizona State University, then presented on an epidemiological-economic model that explicitly incorporates human behavioral responses influenced by infectious disease outbreaks. Thomas Inglesby, director of the Center for Health Security of the Johns Hopkins Bloomberg School of Public Health, concluded the session with a presentation on infections that have the potential to cause significant harm to the global economy and international security.

COST OF PANDEMIC INFLUENZA

Martin Meltzer, senior economist and distinguished consultant for CDC, discussed the economics of planning and preparing for influenza pandemics. Influenza pandemics are inevitable, but they vary greatly in terms of timing, severity, and populations affected. Influenza pandemics can occur anywhere from every 10 to 50 years (Potter, 2001). The timeline for influenza pandemics complicates communication with policy makers,

who are significantly more motivated by immediate problems than a potential problem in the next decades, he said. Influenza pandemics also vary in terms of mortality risk. The 1918 pandemic resulted in an estimated 675,000 deaths in the United States and 50 million deaths worldwide, while the 2009 H1N1 pandemic resulted in an estimated 12,500 deaths in the United States and 285,000 deaths worldwide (Taubenberger, 2006; Shrestha et al., 2011; Dawood et al., 2012). Estimates of macroeconomic impact are also important to consider as influenza pandemics, even if short in duration, can cause billions of dollars in economic loss and affect gross domestic product (GDP) (Meltzer et al., 1999; McKibbin and Sidorenko, 2007; Fan et al., 2016).

Economic Modeling for Influenza Pandemic

Meltzer highlighted the potential for economic modeling to guide preparedness efforts against pandemic influenza, as it can provide information that can be useful when planning for rationing, shortages, and prioritization of interventions during an epidemic. He added that unless things change drastically in terms of technologies, come the next pandemic, there are likely to be shortages in medical countermeasures (at least initially). so the question is who gets to receive the care first. He reiterated that plans must be flexible and nimble, and respond to the unique characteristics of the outbreak as it happens. As an example, he noted that in 2009 many people over the age of 65 had a degree of unexpected immunity to H1N1. He argued:

> Of course, everybody remembers 1918, but if you plan solely for 1918, you will miss what happened in 2009, and you will be underprepared and woefully not ready to address the problem correctly. You have to allow for a great deal of variability.

Meltzer described models that provide information about mortality from pandemics and the effect of vaccines. It is difficult to make precise mortality estimates about future pandemics, even with good economic and epidemiologic models, he said. Death rate estimates are in the form of a range of potential outcomes depending on gross clinical attack rates, which are not a precise prediction.

Meltzer said that economic models can help evaluate the cost-effectiveness of vaccination programs by age group and risk, including comorbid conditions and pregnancy. Economic analysis of vaccination has produced positive rates of return for every age and risk group but at varying magnitudes (Meltzer et al., 1999). Categorizing people into age and risk groups can help determine who to vaccinate first in the case of a supply shortage

during a pandemic. For example, population groups can be evaluated either by their risk of death or by their potential future returns to society, the latter of which would favor vaccinating working-age people before the elderly. Meltzer noted that determining the best approach to this type of valuation is beyond an economic problem and is up for debate for society. He added that the best way to carry out an economic analysis, from his experience, is by using simple models that are transparent, take account of uncertainty about the severity and size of impact of the pandemic, and are readily accessible to the public.

Stockpiling and Nonpharmaceutical Interventions

Many economic models have suggested the benefit of stockpiling vaccines, antiviral drugs, and mechanical ventilators to prepare for an influenza pandemic, but the effect of this strategy is limited and attacks only part of the crisis, according to Meltzer. The problem is not merely a shortage of material supplies, but also of human resources, he said. As an example, he described the limitations of stockpiling mechanical ventilators, which require trained critical care nurses and respiratory therapists to effectively operate (Ajao et al., 2015) (see Figure 4-1). This illustrates the need for flexible planning and consideration of a system's maximum capacity to use a commodity when deciding on the amount to stockpile, he concluded.

Additionally, nonpharmaceutical interventions, such as school closures to limit the spread of the virus, can be considered as a response strategy to an outbreak. Meltzer noted that these strategies work in some situations, albeit with limitations. He described a natural experiment in Texas during

	Number of Total Additional Patients Who Can be Ventilated Nationwide by Capacity Level		
Component and subcomponents	**Conventional Capacity Level**	**Contingency Capacity Level**	**Crisis Capacity Level**
Space: Beds	8200–16,400	**26,200–52,400**	88,600–177,300
Staff:			
Physicians	**6300–18,900**	47,800–143,400	114,700–220,500
Respiratory therapists	22,500–67,500	39,400–101,300	**56,300–135,000**
Critical care nurses	25,200–50,300	50,300–100,600	75,500–301,900

FIGURE 4-1 Constraints in the U.S. health care system for ventilation therapy by capacity level.
SOURCES: Meltzer presentation, June 12, 2018; adapted from Ajao et al., 2015. Ajao, A., S. V. Nystrom, L. M. Koonin, A. Patel, D. R. Howel, R. Baccam, T. Lant, E. Malatino, M. Chamberlin, and M. I. Meltzer, "Assessing the capacity of the U.S. health care system to use additional mechanical ventilators during a large-scale public health emergency," *Disaster Medicine and Public Health Preparedness*, volume 9, issue 6, pages 634–641, reproduced with permission.

the 2009 H1N1 influenza pandemic where a school district that closed public schools during the outbreak was compared to neighboring school districts that mostly remained open. The population near the school district that closed reported a significant reduction in visits to emergency rooms from influenza-like illness during the closure period (Copeland et al., 2013). After those schools reopened, however, rates of illness rose once again. According to Meltzer, the lesson here is that during a pandemic, schools must close early and close for a long time until vaccines are available. Both of these approaches can be difficult political decisions to make, he said—a fact that underscores the need for the support of businesses and communities when implementing pandemic response strategies.

ASSESSING ECONOMIC VULNERABILITY TO EMERGING INFECTIOUS DISEASE OUTBREAKS

Anas El Turabi, Frank Knox fellow in health policy at Harvard University, stated that economic analysis can take two forms: the "snow-globe" approach and the "empiricist" approach. The snow-globe method attempts to build mathematical models of the world in its current state, which are then "shaken" to hypothesize the consequence of a given scenario. Simulations can be repeated to create a dataset of potential outcomes, but the results depend on model inputs and assumptions. The empiricist approach, on the other hand, attempts to measure effects after a real-world event has happened. According to El Turabi, not enough of the latter is happening for infectious disease outbreaks. He stated that there is a "need to move from a modeled world to a measured world."

Role of Economic Analysis for Outbreaks

El Turabi presented a framework of the economic impacts of an infectious disease that includes three components: transmission dynamics, economic impact, and disease dynamics (see Figure 4-2). According to the framework, the pathogen in a reservoir infects humans (often through vectors), which can lead to an outbreak. This infection causes a biological response, including illness and death, which subsequently affects consumption and productivity in both the short and long term. In addition, there is a social response to the outbreak from individuals (e.g., change travel patterns to avoid disease prone area), organizations including private companies and nongovernmental actors (e.g., rescind investment commitments), and governments (e.g., impose regulations and a *cordon sanitaire*).[1] Taken together, these responses lead to significant economic damages associated

[1] A blockade enacted to prevent the spread of individuals afflicted by an infectious disease.

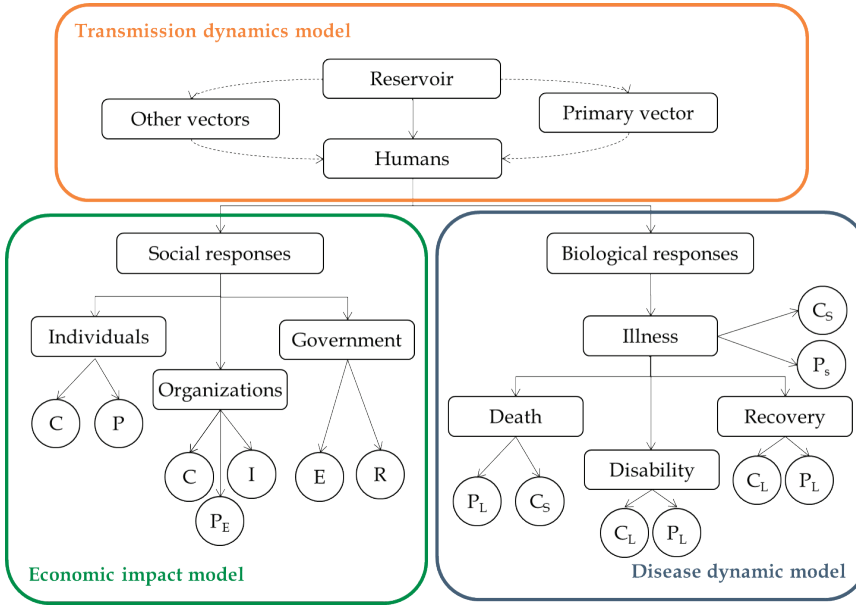

FIGURE 4-2 A simplified framework of the economic impacts of an infectious disease.
NOTE: C = consumption; C_L = long-term consumption; C_S = short-term consumption; E = expenditure; I = investment; P = productivity; P_E = export; P_L = long-term productivity; P_S = short-term productivity; R = regulation.
SOURCE: El Turabi presentation, June 12, 2018.

with their effect on consumption and productivity. According to El Turabi, this economic impact, particularly from social responses, is often the forgotten dimension of analysis related to emerging outbreaks.

El Turabi noted that different factors might affect a country's economic vulnerability to an infectious disease event. Intrinsic vulnerability is defined as the likelihood an infectious outbreak will occur in a given country or context (Sands et al., 2016). Strengthening pandemic preparedness through strong health systems is a way to bolster intrinsic vulnerability. Intrinsic vulnerability and preparedness are evaluated through Joint External Evaluations, a voluntary and multisectoral process to assess country capacity to prevent, detect, and rapidly respond to public health risks. He added that while assessing the economic vulnerability is an intersectoral issue, the vulnerability of the industry sector has been not examined rigorously or consistently yet to understand fully the potential effect of major outbreaks on private enterprises.

Economic Effects of the Ebola and Zika Epidemics

For the last portion of his presentation, El Turabi presented case studies of the economic effects of the Ebola epidemic in West Africa and the Zika epidemic in Latin America, highlighting their differing disease dynamics. He described the disease dynamics of Ebola as a "raging forest fire" and Zika as a "slow burn," though both significantly affected human health (see Table 4-1). Zika has infected more people than Ebola, but the clinical syndrome is much less severe in the acute stage. The difference in fear induced by the visible hemorrhagic condition of Ebola versus apathy from the flulike symptoms or neurological complications experienced with Zika is a key qualitative factor in comparing the two diseases, he said.

El Turabi noted that the different characteristics of Ebola and Zika explain the different behavioral responses and economic impacts generated by these diseases. Recent estimates on Ebola and Zika from 2016 and 2017 demonstrate these distinctions in both the short and long terms following the outbreaks. Short-term costs of the West African Ebola epidemic are estimated to be approximately $3 billion, while a long-term assessment of Ebola's effect on population distributions, migration, and investment confidence remains incomplete (World Bank, 2016). Estimates of the short-

TABLE 4-1 Epidemiology of Public Health Emergencies of International Concern, Ebola Versus Zika

	Ebola	Zika
PHEIC dates	August 2014–March 2016	February 2016–November 2016
Months PHEIC active	20	10
WHO regions affected during PHEIC period	1	4
Countries reporting during PHEIC period	3	60 (+18 with active transmission pre-2015)
Estimated cases during PHEIC period	28,639	518,000
Deaths attributed	11,316	15
Indirect deaths from health care diversion	~10,000 additional malaria deaths	None estimated
Status at end of PHEIC	Quiescent	Active

NOTE: PHEIC = public health emergency of international concern; WHO = World Health Organization.
SOURCE: El Turabi presentation, June 12, 2018.

term economic impact of Zika across the Latin American region range from $7–18 billion; long-term costs related to lifetime care of microcephaly patients may be as high as $11 billion (UNDP-IFRC, 2017).

According to El Turabi, there is a trend of large economic losses occurring even after a relatively modest event. He reiterated that this scenario is typically driven by human behavioral response—a phenomenon that El Turabi believes needs far more research. Economic effects can also long outlast the epidemiologic events themselves. Finally, El Turabi concluded that better postevent analysis and data collection are needed to calibrate and refine predictive models.

EPIDEMIC RISK MODELING: MEASURING THE EFFECT OF AVERSION BEHAVIOR AND CASCADING SOCIAL RESPONSES

Carlos Castillo-Chavez, professor of mathematical biology at Arizona State University, presented on epidemic risk models that incorporate human behavioral responses. He began by describing the "susceptible-infected-recovered" (SIR) model, a mathematical model that can be used to evaluate disease outbreaks and predict epidemiologic outcomes (Huppert and Katriel, 2013). The SIR model is able to make accurate short-term predictions when provided with the appropriate information inputs and has been successful in modeling the rapid spread of several recent epidemics such as the severe acute respiratory syndrome outbreak in Canada (Choi and Pak, 2003); however, it does not explicitly include behavioral responses to disease risk.

Dynamics of Human Behavior and Infectious Diseases

Castillo-Chavez proceeded in describing models that incorporate human behavior. He first pointed out an agent-based simulation of an influenza outbreak in Portland, Oregon, that examined disease transmission based on the physical contact patterns that result from movements of individuals between locations.[2] He showed a simulation of a scenario of an influenza epidemic where nobody changes their behavior (carrying out their normal activities), versus a scenario where 75 percent of the population avoids social contact. This model suggests that different types of human behavior and decisions affect the spread of infectious diseases, which have implications for public health interventions and policies (Eubank et al.,

[2] An agent-based model is a type of computational model that is used to study complex systems by examining the way individual agents of a system behave, as a function of individual characteristics and interactions with each other and the environment, according to predefined rules (IOM, 2015).

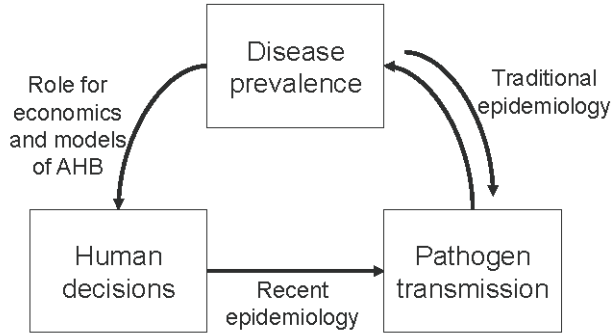

FIGURE 4-3 Epidemiologic models accounting for adaptive human behavior.
NOTE: AHB = adaptive human behavior.
SOURCE: Castillo-Chavez presentation, June 12, 2018.

2004). However, while this kind of model explicitly assigns behavioral rules for all individuals, it often requires the modeler to specify ex ante how changing incentives modify behavior and therefore is limited in its ability to aid in designing incentives (Fenichel et al., 2011).

According to Castillo-Chavez, accounting for human behavior is challenging when modeling a complex adaptive system of human disease dynamics,[3] as the model must consider human decision making, disease transmission, and disease prevalence (see Figure 4-3). Disease risks both affect and are affected by human decisions, which creates a feedback loop whereby infection levels drive behaviors and human decisions shape disease spread (Fenichel et al., 2011). These human decisions are determined by trade-offs when humans consider the scarcity of time, money, and other resources, he said. While people might value their own health status, they can also value family, relationships, work, and social activities that affect their decision making and exposure to infectious diseases. With these various sources of trade-offs, people can change their behaviors in response to changing circumstances and incentives. They make these decisions based on the best available information, but they may be missing key information, he added.

[3] A complex adaptive system is a collection of individual agents with freedom to act in ways that are not always predictable and whose actions are interconnected (Plsek and Greenhalgh, 2001).

An Epidemiological-Economic Model to Account for Human Behavior

Taking these factors into account, Castillo-Chavez introduced a model that combines the SIR model and an economic behavioral model, also known as an epidemiological-economic model (Fenichel et al., 2011).[4] It explicitly models the trade-offs that drive human-to-human contact decisions in response to disease risk. The model assumes that people make decisions to maximize utility (an index of well-being) based on their health status, their understanding of disease risk, and their evaluation of future potential scenarios. That is, the model recognizes that individuals, particularly those who are susceptible to the disease, may respond to disease risks by limiting contacts but may also derive utility from contacting others, which may lead to an increase in disease prevalence. The model further assumes that people have instantaneous access to information when they make decisions. He noted that unlike traditional nonlinear contact models, this model focuses on trade-offs not based explicitly on the basic reproductive number of the disease, R_0.[5] To Castillo-Chavez, R_0 implicitly includes disease-free behavior and confounds biological aspects of the pathogen with social aspects of adaptive human response to disease risk; thus, it may not reliably guide postoutbreak disease management.

Castillo-Chavez highlighted how the results of this model reveal that adaptive human behavior can have a significant effect on disease dynamics (see Figure 4-4), and thus have critical implications for developing public health policies, such as social distancing policies that alter the incentive structure of humans contacting each other. Analyzing both behavior and disease dynamics, he argued, may shed light on how to develop incentives for individuals to change their behavior for an optimal, cost-effective disease response strategy. He concluded that this kind of work requires a better understanding of human behavior and collaboration of different disciplines.

IMPACT AND FUTURE OF GLOBAL CATASTROPHIC BIOLOGICAL RISKS

Thomas Inglesby, director of the Center for Health Security of the Johns Hopkins Bloomberg School of Public Health, highlighted the importance of understanding global biological risks that are acute, fast-moving, and consequential in terms of health and economic impact. He argued for the need to better communicate these type of risks among scientists, researchers, and policy makers. Recognizing this need, he and his team at

[4] "Epi[demiological]-economic models merge economics and epidemiology by explicitly analyzing individual behavioral choices in response to disease risk" (Fenichel et al., 2011).

[5] R_0 is defined as the number of secondary infections in an uninfected population that is generated from the initial introduction of a pathogen.

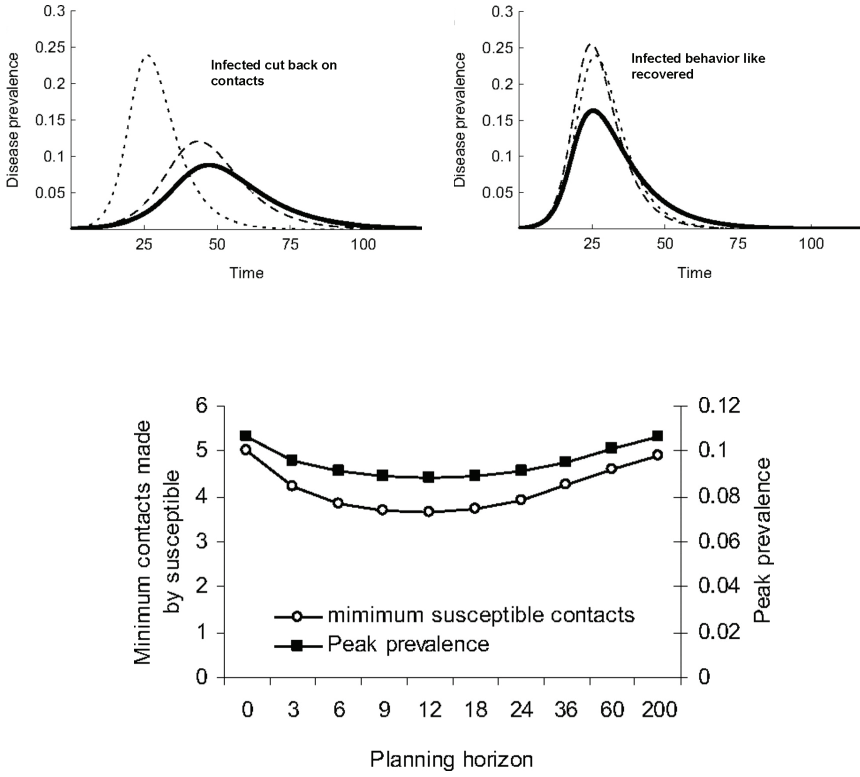

FIGURE 4-4 Human behavior affects peak influenza prevalence.
NOTES: Time and planning horizon on the x-axes are measured in days. The dotted curve represents the standard susceptible-infected-recovered (SIR) ex ante analysis where individuals do not respond to the risk of contracting the disease. The solid curve represents the results of the simulation where human behavior responds to disease states. The dashed line represents an ex post analysis of an outbreak's R_0 based on the SIR model. The upper left graph depicts a scenario where infected individuals benefit from changing their behavior in response to their illness, leading to lower modeled peak prevalence. The upper right graph depicts a scenario where infected individuals find benefit from not responding to the disease, thus increasing the risk for susceptible individuals and increasing their behavioral response. The bottom graph demonstrates that susceptible individuals initially lower their social contacts when they have longer planning horizons, leading to lower peak disease prevalence. As the planning horizon increases further, however, they increase contacts and prevalence rises.
SOURCES: Castillo-Chavez presentation, June 12, 2018; adapted from Fenichel et al., 2011.

the Johns Hopkins Center for Health Security created a term that encapsulates these risks called global catastrophic biological risks (GCBRs) along with a working definition:

> Events in which biological agents—whether naturally emerging or re-emerging, deliberately created and released, or laboratory engineered and escaped—could lead to sudden, extraordinary, widespread disaster beyond the collective capability of national and international governments and the private sector to control. If unchecked, global catastrophic biological events would lead to great suffering, loss of life, and sustained damage to national governments, international relationships, economies, societal stability, or global security. (Schoch-Spana et al., 2017)

Inglesby argued that GCBRs warrant heightened attention because of their extraordinary consequences, including damages to governments, economy, and society. He also argued that they are potentially tractable problems and that categorizing these set of risks under a term like GCBRs could help the global community work in a concerted way to prevent colossal consequences. He added that scientists have helped drive global concern or action on other widely accepted global catastrophic risks, such as nuclear weapons, climate change, and artificial intelligence, and could see the same happening for GCBRs.

A Retrospective Look at Global Catastrophic Biological Risks

Inglesby provided three examples of GCBRs. He noted that the 1918 influenza pandemic is an archetypal example of a GCBR because of its extreme economic and social impact in addition to its large mortality toll—an estimated 50 million people. The case fatality rate was 1–2 percent (Taubenberger, 2006). Most notably, he said the disease's short-term effect on governments and economies was undetectable over the years that followed; however, the effect of a similar pandemic today would likely be far more severe with the increased convenience of travel and globalization. Global consequences from this type of pandemic might include high absenteeism caused by fear, conflicts among countries over access to therapeutics, and disruptions to critical infrastructure, government, commerce, air traffic, and the military.

Inglesby presented smallpox as another example of a GCBR for its potential to reemerge and cause devastating global effects as seen prior to its eradication in 1977. The case fatality rate was 30 percent, killing more than 2 million people annually before the eradication campaign began (CGDEV, 2007; CDC, 2016b). Given the recent de novo synthesis of horsepox, a virus closely related to smallpox, there is increasing concern of an accidental or purposeful reintroduction of smallpox, which was extremely

transmissible among humans and had a high case fatality rate as noted earlier (Noyce et al., 2018). Inglesby emphasized that today's population would be immunologically naïve to smallpox globally, and that the societal impact would depend on the efficacy of global governance, public health measures, medical countermeasures, and other responses.

Finally, he described a more recent example, between 2005 and 2007 related to the pandemic potential of H5N1 influenza, which was spreading fast among bird populations in Africa, Asia, and Europe. It had a high case fatality rate of more than 50 percent among humans, though no sustained human-to-human transmission developed (Neumann et al., 2010). If the virus evolves naturally to have a high case fatality rate and becomes readily human transmissible or if it is deliberately manipulated to become so and purposefully reintroduced, this in fact would constitute a GCBR according to Inglesby. A virus with these types of properties would be efficient and lead to sustained and perhaps permanent damage to society. Governments and the global community would have to take extraordinary action to swiftly develop and deploy medical countermeasures, he said.

Future Global Catastrophic Biological Risks

Looking into the future, Inglesby described the characteristics of potential pandemic pathogens. Based on a poll of experts in the field, the highest risk for a future pandemic will likely be from a respiratory RNA virus, with characteristics such as segmented genome, cytoplasmic replication, small genome host size, high host viremia, and zoonotic relationships (Adalja et al., 2018). Inglesby noted that these are the most probable attributes for the next major outbreak, but they are by no means definite: smallpox, for example, is a DNA virus that replicates in the nucleus. He also added that CDC considers H7N9 influenza as the greatest pandemic risk, which has a 40 percent case fatality rate (Xiang et al., 2016).

Inglesby noted that factors such as the presence of effective vaccines and therapeutics and the range of disease vectors determine the pandemic potential of the disease, but these limitations are malleable, as pathogens can evolve through deliberate or natural modifications. Some experts also raise the risk of fungi, whose thermal range limitations could be overcome by natural selection or biological engineering in the near future. Inglesby pointed out that biotechnology facilitates pathogen targeting against specific populations with shared genetic history. This kind of technology could also be applied to designing novel or artificial organisms harmful to existing life, as well as pathogens targeting livestock or plant food sources, which could have devastating consequences for the global food supply.

Economic Analysis of Biologic Threats

Inglesby stated that several economic analyses of these biologic threats have demonstrated the magnitude of their impact, although the estimates vary. One study concluded that pandemic mitigation programs could save as much as $360 billion over the next century (Pike et al., 2014), while another estimated that future pandemics could cost the global economy as much as $500 billion per year (Fan et al., 2018). Additionally, a World Bank study estimated that a 1918-style pandemic would result in a $1.5 trillion loss in global GDP (Burns et al., 2006).

Inglesby proposed further studies on the economic consequences of GCBRs. He argued that more studies need to examine the effect of pandemics with case fatality rates that are greater than that of the 1918 influenza pandemic. He also urged for more studies that take into consideration effects that are beyond lives lost and income lost to prolonged societal instability, prolonged interruption of international trade, and collapses of industries and governments. Finally, he pointed to the need for studies that consider the economic effects of pandemics with different dynamics than influenza such as smallpox and deliberately initiated events.

DISCUSSION

Katz summarized some of the key points raised during the presentations. In her view, she noted that there was a need for the following:

- Accounting for significant variability and uncertainty in pandemic preparedness planning;
- Undertaking post-hoc analyses of outbreaks and investing in understanding social responses to gain a more comprehensive view on the economic consequences of outbreaks;
- Explicitly incorporating adaptive human behavioral responses in economic and disease modeling as they can change the course of epidemics; and
- Performing more economic analyses on GCBRs because of their potential effect on governance, international relations, and society.

The discussion with the audience began with a focus on human behavioral responses to infectious disease outbreaks. Peter Daszak, president of EcoHealth Alliance, asked Castillo-Chavez to expand on the relationship between incorporating human behaviors into modeling and the estimates of R_0 of an infectious disease outbreak. Castillo-Chavez said that R_0 is calculated based on underlying assumptions of a problem where biological aspects of the pathogen with social aspects of adaptive human responses

are confounded. However, it is important to parse this out, he noted, as problems like infectious diseases are dealt with in a heterogeneous manner, which can lead to multiple disease states. For example, a disease like HIV has multiple modes of transmission and does not have a single endemic state. Heterogeneity across individuals with varying social dynamics and behavior often leads to different decisions and different endemic states, particularly if long-term dynamics are considered. He noted that heterogeneity makes modeling complicated so it gets ignored as it can pose a challenge in finding policies that can be implemented easily. However, he argued that policies that ignore uncertainty and behavior miss opportunities to have a significant effect.

Katharina Hauck, senior lecturer in health economics from the Imperial College London, asked Castillo-Chavez about the extent to which adaptive human behavior can reduce the threat of pandemics during the eradication and elimination stages. She noted that individuals might demand less prevention as prevalence declines, making eradication difficult. Castillo-Chavez reiterated that modeling behavioral responses is critical but a great challenge. He mentioned a study that examined the HIV epidemic among a homosexually active population in San Francisco. The study assumed that even though homosexual people would want to move into a welcoming environment that accepts homosexual people such as the Castro neighborhood in San Francisco, they would also be dissuaded to go if they were aware of the high levels of HIV infection. In other words, "recruitment" to the homosexual population depended on levels of infection. However, Castillo-Chavez noted that while this population in San Francisco was well informed of the risks, when the bathhouses opened back up, the infections increased again. This led to oscillations in incidence of the disease, he said. As mortality from HIV/AIDS has dropped over the years, behaviors have changed in response to the trend. These modeling efforts are not always precise, he said, but they shed light on the importance of understanding how adaptive behaviors shape epidemics.

Jeffrey Duchin, health officer and chief of the Communicable Disease Epidemiology and Immunization Section for Public Health—Seattle and King County, Washington, asked panelists if they had seen modeling of pseudo-outbreaks, meaning an increase in the number of cases reported that is not associated with an actual increase in disease incidence but found to be an artifact. He noted that these often arise through social media-generated scares, but they can have real consequences in health and economics. He noted that the autism scare could be considered such a pseudo-outbreak as it affects conducting effective immunization programs. Inglesby responded that the focus on syndromic surveillance in public health can lead to tradeoffs and shortfalls in routine public health priorities. He explained that cities often chase false signals in the electronic surveillance systems, resulting

in huge costs, though there is a lack of economic analyses that calculate them.

Meltzer added that public health officials and policy makers often make decisions on outbreak response and resource allocation up front with incomplete information, including uncertainty about how people will respond to interventions. Modeling decision making during an outbreak requires making assumptions about a population's compliance with interventions, such as self-isolation, and how their behaviors change over time. Meltzer emphasized there is no way to guarantee the results of these models to policy makers, but data from previous outbreaks can be helpful. He also cautioned that human behaviors change quickly and modeling human behavior produces great variability, so models may not be able to provide public health officials with an estimate of an outbreak's magnitude without a great deal of variability.

Castillo-Chavez also commented on Duchin's question, illustrating two examples of behavioral responses related to the contagion effect. He described a study evaluating Internet activity following the case of Ebola in the United States. The study suggested that television news segments on imported Ebola cases led to significant increases in Ebola-related Internet searches and Twitter activity (Towers et al., 2015). A similar behavioral correlation was observed related to the incidence of copycat events following school mass shootings, although the mechanisms in that scenario remain unclear (Towers et al., 2018). He reiterated that the media indeed influences behavior and any contagion effect.

El Turabi commended the empirical evidence from such studies and urged for more social science research for infectious disease outbreaks. He cited the large amounts of research and development funds directed toward developing new vaccines in contrast to relatively low amounts spent to understand vaccine uptake behavior. El Turabi argued for a dramatic shift to quadruple the funding to build capacity in this area, and noted that current efforts from Wellcome Trust and the U.K. Department for International Development, who are building a platform for rapid social science research in the context of infectious disease outbreaks, is a starting point (DFID-Wellcome Trust, 2018).

The discussion then focused on technical aspects of modeling, particularly on incorporating data. Jennifer Gardy, associate professor at the University of British Columbia's School of Population and Public Health, asked how to inform advanced parameters of utility functions that modify the models described in the session, considering there are already challenges with setting basic transmission and recovery rate parameters. She was interested in the types of data necessary for retrospective analysis, future model development, and real-time efforts when dealing with the next pandemic. Castillo-Chavez said that models can easily be fit to available data. What

is more important about models, however, is incorporating the influence of human decision making into these models, he said. As an example, he described the uncertainty around estimating social contacts during an influenza outbreak. He argued for a new approach that evaluates how people make decisions in relation to the evolving epidemiology of an outbreak and pointed out that people often change their behaviors in such a way as to mitigate the epidemic. He concluded that behavior is being ignored by current models, and that moving forward it should be incorporated into analysis related to a variety of relevant situations.

Also in response to Gardy's question, Meltzer referred back to the example he highlighted in his presentation about naturally occurring experiments related to school closures in Texas during the 2009 H1N1 influenza pandemic (Copeland et al., 2013). He argued that this historical experience can be used to model and plan for future disease outbreaks. If quick answers are needed in the face of a new outbreak, he said assumptions must be made. The key is for these assumptions and their implications to be clear and straightforward when presenting the model to policy makers. He reiterated that models are not meant to provide accurate predictions of the future, but rather to describe the relationships and "levers," or potential response actions, that influence the disease and human behaviors.

El Turabi highlighted methodological practice from CDC and the United Nations Children's Fund that provides near real-time opinion polling in emergency outbreak scenarios for making decisions in the field. He noted that these preagreed frameworks and rapid assessment tools could feed back into emerging disease models. He also noted the need to build capacity to do these rapid polls in an ethically robust and reactive manner.

Anna Vassall, professor of health economics from the London School of Hygiene & Tropical Medicine, asked El Turabi about the potential for preepidemic data collection and experimental evidence, rather than relying on real-time measurements for post hoc models. El Turabi said that the tools for modeling are not restricted and should include preemptive evidence on behavior gathered prior to outbreaks, with the understanding that behaviors may change in the face of threats and uncertainty. He stated that he is skeptical regarding preferences being consistent during an outbreak. He shared the example of decision making for cancer treatments, stating that people who do not have cancer, when asked, want to be very involved in the treatment choice. This preference changes with the greater threat and uncertainty of an actual cancer diagnosis. He maintained that live analysis, during disease outbreaks, is also important.

Meltzer cautioned that there are limited resources available for real-time measurements particularly during large-scale outbreaks. In 2009, CDC measured the uptake of influenza vaccine during the pandemic through a cumbersome telephone interview as there was no data available on the char-

acteristics of those receiving vaccination. School closure analysis is similarly limited by the lack of a central registry of such events at the national or even state levels, so researchers rely on social media for data. He added that it is also difficult to collect data on when the schools reopen. At a certain point, he said, it takes immense person power to track and measure such data. Therefore, Meltzer said that selection of data to be measured should be judicious and prioritized, since there are insufficient resources to measure every possible variable, and not every parameter is equally valuable.

5

The Cost Dimensions of Antimicrobial Resistance

Session I, part C, of the workshop explored the different dimensions of cost of antimicrobial resistance (AMR). The session was moderated by Keiji Fukuda, director and clinical professor at The University of Hong Kong School of Public Health. In his opening remarks, he stated that while the global community has recognized the severity of AMR, there has been inadequate action against the problem. To bolster effective action, he said, the costs of AMR as well as the costs of the interventions to counter it are critical to understand, as they are among the major factors that policy makers consider in their decision-making process.

The session began with a discussion on the direct and indirect costs of AMR by Mukesh Chawla, advisor for health, nutrition, and population at the World Bank. Mark Pearson, deputy director of employment, labor, and social affairs for the Organisation for Economic Co-operation and Development (OECD), followed with an evaluation of the cost-effectiveness of interventions to counter AMR. Ramanan Laxminarayan, director and senior fellow of the Center for Disease Dynamics, Economics & Policy, concluded the session with a presentation on reconceptualizing the issue of AMR to build the investment case.

CONSIDERATIONS FOR ESTIMATING THE COST OF ANTIMICROBIAL RESISTANCE: DIRECT VERSUS INDIRECT COSTS

Mukesh Chawla, advisor for health, nutrition, and population at the World Bank, discussed the methodologies and modeling results of the

World Bank's efforts to assess the economic cost of AMR. He noted that his presentation draws on various studies, including two recent ones from the World Bank (Adeyi et al., 2017; Ahmed et al., 2017). Before delving into his presentation, Chawla cautioned that costing analyses are based on various assumptions, but they can be made robust by narrowing the variability of these inputs.

Direct and Indirect Costs of Antimicrobial Resistance

According to Chawla, AMR affects the economy through four channels that lead to either direct or indirect costs: increase in human mortality and morbidity, increase in livestock mortality and morbidity, and the "fear factor." Direct costs of AMR include health care expenditures and resources used to treat the disease, such as hospitalization expenses and medications. Indirect costs of AMR are derived from present and future costs to society from the loss of outputs caused by a reduced labor supply and lower productivity attributable to increased morbidity and mortality. In addition, Chawla noted that the fear factor of infectious disease outbreaks could lead to border restrictions, which may increase trade and transport margins that cause a fall in exports. In sum, he highlighted that these types of channels of disruption need to be considered when calculating the economic impacts of AMR.

Chawla reviewed the methodology that the modeling team at the World Bank used to calculate the economic impacts of AMR (Ahmed et al., 2017). While the modeling team at the World Bank drew inspiration from a KPMG study that looked at the global economic impact of AMR (KPMG, 2014), the team employed different methods—namely using the GLOBE_DYN, which is a multisectoral, multicountry, and multiagent recursive dynamic computational general equilibrium model that uses the Global Trade Analysis Project.[1] Through this modeling technique, a range of AMR incidence scenarios were compared to the base case scenario of a world without AMR, with marginal effects of AMR measured as the difference in the progression of economic variables (including gross domestic product [GDP], exports, and health care expenditures) between the scenarios. The analyses compared AMR severity across four income regions based on the current World Bank country classifications—low-income, lower middle-income, higher middle-income, and high-income (Adeyi et al., 2017; Ahmed et al., 2017). These AMR scenarios included possibilities of low case (5 percent resistance rate), middle case (current resistance rate until year 15 and then

[1] Recursive dynamic computational general equilibrium models are solved sequentially and assume that behavior depends only on current and past states of the economy. For more information about GLOBAL_DYN, see McDonald et al., 2013.

40 percent onward), and high case (current resistance rate until year 15 and then 100 percent onward), drawing from a study conducted by the RAND Corporation (Taylor et al., 2014).

Economic Cost of Antimicrobial Resistance

Chawla highlighted some of the findings from the model simulations. In terms of direct costs of AMR, health care expenditures would increase in tandem with rising cases of AMR (see Figure 5-1). Results also show that additional health care expenses in 2050 would be $0.33 trillion in the low AMR scenario, while in the high AMR scenario they would amount to $1.2 trillion annually (Ahmed et al., 2017).

For indirect costs, Chawla stated that AMR makes a significant negative impact on GDP (see Figure 5-2). Compared to the base case, GDP

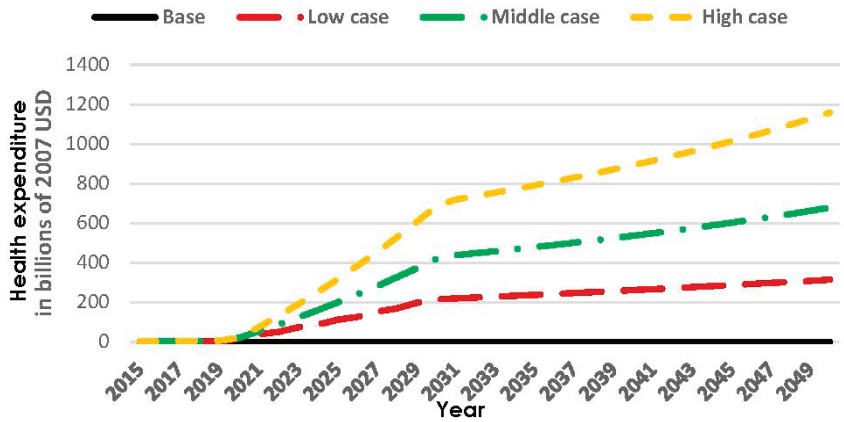

FIGURE 5-1 Impact of antimicrobial resistance (AMR) on additional health expenditures.
NOTES: USD = U.S. dollars. Health expenditure (in terms of an additional direct household tax) is represented on the y-axis and time is represented on the x-axis. Projected costs are for three scenarios of AMR: Low case assumes 5 percent resistance rate, middle case assumes current resistance rate until year 15 and then 40 percent onward, high case assumes current resistance rate until year 15 and then 100 percent onward.
SOURCES: Chawla presentation, June 12, 2018; Ahmed et al., 2017. Ahmed, Syud Amer; Baris, Enis; Go, Delfin S.; Lofgren, Hans; Osorio-Rodarte, Israel; and Thierfelder, Karen. 2017. Assessing the Global Economic and Poverty Effects of Antimicrobial Resistance. © World Bank. https://elibrary.worldbank.org/doi/abs/10.1596/1813-9450-8133 Creative Commons Attribution CC BY 3.0 IGO.

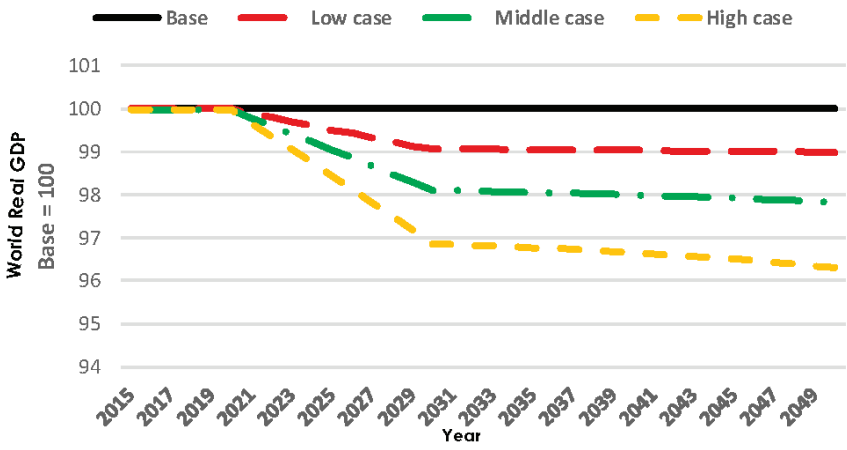

FIGURE 5-2 Impact of antimicrobial resistance (AMR) on world gross domestic product (GDP).
NOTES: GDP = gross domestic product. The global economic output is represented on the y-axis and time is represented on the x-axis. Projected declines are for three scenarios of AMR: Low case assumes 5 percent resistance rate, middle case assumes current resistance rate until year 15 and then 40 percent onward, high case assumes current resistance rate until year 15 and then 100 percent onward.
SOURCES: Chawla presentation, June 12, 2018; Ahmed et al., 2017. Ahmed, Syud Amer; Baris, Enis; Go, Delfin S.; Lofgren, Hans; Osorio-Rodarte, Israel; and Thierfelder, Karen. 2017. Assessing the Global Economic and Poverty Effects of Antimicrobial Resistance. © World Bank. https://elibrary.worldbank.org/doi/abs/10.1596/1813-9450-8133 Creative Commons Attribution CC BY 3.0 IGO.

would be 1.1 percent lower in 2050 under the low AMR scenario and 3.8 percent lower in 2050 under the high AMR scenario (Ahmed at al., 2017). He pointed out that the GDP decline stabilizes after people and economies adjust to the new circumstances as resources are reallocated with different patterns of new investments. Similar effects of decline are seen with regard to global exports and livestock exports.

After highlighting the individual direct and indirect costs, Chawla presented the cumulative economic cost of AMR. To calculate this, the modeling team derived the present values for the differences for GDP, exports, and extra health expenditures between the AMR scenarios and the base case at four social discount rates (see Table 5-1).[2] At the intermediate dis-

[2] A social discount rate is "typically used to derive a net present value as a summary measure of the effect of projects with streams of economic benefits and costs that are uneven over time" (Ahmed et al., 2017).

TABLE 5-1 Cumulative Costs of Antimicrobial Resistance (AMR) in Trillions (in 2007 U.S. dollars)

	Social Discount Rate			
Scenario	0%	1.4%	3.5%	5.5%
GDP				
Low case	–40.4	–29.3	–18.7	–12.7
Middle case	–74.5	–53.7	34.0	–22.7
High case	–118.6	85.4	–53.7	–35.7
Exports				
Low case	–10.8	–7.8	–5.0	–3.4
Middle case	–19.9	–14.3	–9.0	–6.0
High case	–31.7	–22.8	–14.3	–9.5
Household tax to finance extra health expenditure				
Low case	8.0	5.8	3.8	2.6
Middle case	14.8	10.7	6.8	4.6
High case	23.6	17.14	10.8	7.2

NOTE: GDP = gross domestic product.
SOURCES: Chawla presentation, June 12, 2018; adapted from Ahmed et al., 2017. Ahmed, Syud Amer; Baris, Enis; Go, Delfin S.; Lofgren, Hans; Osorio-Rodarte, Israel; and Thierfelder, Karen. 2017. Assessing the Global Economic and Poverty Effects of Antimicrobial Resistance.

count rate of 3.5 percent, the costs associated with the high AMR scenario amount to $53.7 trillion in lost GDP, $14.3 trillion in lost exports, and $10.8 trillion in additional health expenditures, amounting to a total loss of $80 to $90 trillion (Ahmed et al., 2017). Chawla pointed out that this figure is larger than previous costing studies by a factor of 20 and should motivate deliberate global action to minimize future global impact.

COST-EFFECTIVENESS OF INTERVENTIONS TO LIMIT THE SPREAD OF ANTIMICROBIAL RESISTANCE: A PERSPECTIVE FROM OECD

Mark Pearson, deputy director of employment, labor, and social affairs for OECD, discussed the cost-effectiveness of interventions aimed at countering AMR. He noted that his presentation focuses on human health and draws on data from the European Centre for Disease Prevention and Control and the World Bank. He first presented on the country-specific AMR

rates in OECD and Group of Twenty (G20) countries. He then described simulations estimating the cost-effectiveness of efforts to address AMR.

Antimicrobial Resistance in OECD and the G20

Pearson described projections of AMR by predicting country-level drug resistance rates in OECD and G20 countries through the year 2030 based on eight bacteria-antibacterial drug combinations. OECD used a machine learning approach to predict AMR by not applying the same rates of increase across all countries but rather forecasting partial correlates of drug resistance in human health, such as health spending and out-of-pocket expenses.[3] These datasets were used to develop an ensemble model that includes linear mixed-effects regression, exponential smoothing, and random forest techniques. He noted that a drawback of the machine learning approach is that it enters numbers into a "black box," making it impossible to determine why some countries are doing better than others. Despite this drawback, the model is capable of providing more reliable estimates compared to using a single technique, he said. While the patterns vary across countries, the model estimates that generally AMR will increase to approximately 25 percent between 2015 and 2030. Some countries, including Iceland, the Netherlands, and Norway, will see a more modest rise in AMR, and other countries, including Indonesia, the Russian Federation, and Turkey, will experience more severe outcomes. The relationship between antibiotic use and resistance is not one to one, he added.

Pearson also described the difference in resistance trends for first-, second-, and third-line treatments. Resistance to first-line antibiotic therapies in OECD countries is projected to decline, though resistance to second- and third-line therapies will rise. In G20 countries, including China, India, and Russia, resistance will likely rise for all first-, second-, and third-line therapies, he said. He cautioned that as third-line therapies are used more frequently, the resistance also increases more quickly for them than with any other lines of therapy for both OECD and G20 countries.

Cost-Effectiveness of Efforts to Address Antimicrobial Resistance in OECD and European Union Countries

Pearson described a cost-effectiveness analysis that used a dynamic microsimulation model to calculate the impact of AMR in OECD and

[3] Machine learning approach is a method of data analysis that automates analytical model building, allowing computer systems the ability to learn from data, identify patterns, and make decisions, without explicit programming. Partial correlation measures the degree of association between two variables, while controlling or adjusting the effect of one or more additional variables.

European Union countries by 2050 depending on a series of transition probabilities of relevant diseases in a population that might become resistant to antibiotics.[4] Then from a literature review, the researchers examined the factors that might affect those transition probabilities, and identified six policy approaches that could tackle inappropriate use of antimicrobials: (1) delayed prescriptions, (2) mass media campaigns, (3) enhanced environmental hygiene, (4) improved hand hygiene, (5) rapid diagnostic tests, and (6) antibiotic stewardship programs (OECD, 2017).

Pearson revealed that the selected AMR interventions were associated with significant reductions in deaths, particularly improved hand hygiene. He then compared the cost of implementing these interventions with their projected cost savings, focusing only on direct costs borne by hospitals. The hospital sector was specifically chosen, as it is motivated to take action to reduce resistance in order to reduce associated patient care costs. By highlighting the probabilistic estimates of the interventions' likelihood of cost-effectiveness and savings, Pearson stated that mass media campaigns and delayed prescription programs are associated with low costs but also have low levels of associated savings; meanwhile hand hygiene was associated with low costs and high savings. Improved hand hygiene demonstrated a 95 percent likelihood of being cost saving. He added that nearly all the interventions described had a high probability of being not only cost-effective, but also cost saving within the hospital sector. Pearson concluded that the implementation of a combination of hospital-based AMR interventions could lead to savings of more than 2 million disability-adjusted life years by 2050.

RECONCEPTUALIZING ANTIMICROBIAL RESISTANCE TO BUILD THE INVESTMENT CASE

Ramanan Laxminarayan, director and senior fellow of the Center for Disease Dynamics, Economics & Policy, discussed building the investment case for controlling AMR. He addressed the distinctive aspects of AMR and how its understanding must be reshaped and enhanced in not only health, but also other sectors including livestock and the environment.

[4] Dynamic microsimulation models are frequently used in health policy to predict or study the effects of intervention strategies over time, using microlevel data such as an individual's development of a disease. Costs (e.g., health care expenditures) and outcomes (e.g., avoided deaths) are attached to each health status (e.g., healthy, sick, or dead) to estimate the cost and effectiveness expected for each intervention studied. Transition probabilities are calculations of health changes over time between health statuses.

Reconceptualizing the Impact of Antimicrobial Resistance on Human Health

Laxminarayan began by highlighting the unique nature of AMR. He said that the issue of AMR is often framed similarly to common diseases when, in fact, it is fundamentally different because it underlies both infectious and chronic diseases. Antibiotics are crucial to address both, as many infectious diseases are not vaccine preventable and antibiotics represent the only treatment option, and for many chronic diseases antibiotics are part of the treatment approaches needed to control these diseases. The medical community's experience with antibiotics is relatively short—antibiotic treatment was only discovered in the early 20th century—and its experience with resistance to these drugs is even shorter. While concern for AMR has existed for decades, the recent increase in resistance from 1 percent to more than 40 percent occurred after the year 2000 (Review on Antimicrobial Resistance, 2014).

Another unique aspect he noted was that although antibiotic use patterns have contributed to present-day rates of AMR, antibiotics have also saved many lives and advanced the field of medical care. Laxminarayan stated that while the global community is focused on the costs of AMR today, the innumerable benefits of antibiotics to humans all over the world need to be recognized, as is the case with fossil fuel. He explained that oil has become increasingly depleted but not before allowing societies to build entire economies and roads on the back of oil—and that should be the approach to thinking about AMR. Moving forward, he added, the global community needs to think about how to get the best value out of antibiotics in the best possible way. Laxminarayan said this involves investing in the replenishment of the stock of effective antibiotics and conservation of existing ones through infection preventive measures (e.g., improved hand hygiene and vaccination) or prioritizing antibiotic use in certain conditions (e.g., restricting the use of antibiotics for acne treatment).

Laxminarayan also pointed out that the way to think about AMR's consequences on human health needs to go beyond only focusing on the death tolls from drug-resistant pathogens. He highlighted that AMR deeply affects care-seeking behaviors. He described a scenario in which an elderly patient might forgo a hip replacement surgery because of the higher associated risk of a postoperative infection and has to live with a bad hip for several more years. He reiterated that behavioral adaptations in response to not having access to effective antibiotics or any antibiotics at all are likely to be significant, and he urged the audience to think about these often overlooked ramifications.

Antimicrobial Resistance Beyond the Health Sector

Laxminarayan argued for the need to focus on the effects of AMR beyond the health sector, especially as the majority of antibiotics are used on animals. China consumes more than half of the world's antibiotics, and the majority of these medications are used for livestock (Zhang et al., 2015). While the use of these antibiotics has boosted the productivity of livestock and helped reduce the price of meat, Laxminarayan noted that protein production has negative environmental impacts related to air emissions, water, and climate.

He specifically argued that antibiotics have a direct impact on the environment when they affect the microbiome of public spaces. A study of the Ganges river, for example, suggested a twentyfold increase in circulating NDM-1 proteins—a marker of antibiotic-resistant organisms—during the annual pilgrimage season when there is mass bathing of 10 million people (Ahammad et al., 2014). He also noted the lack of appreciation for the consequences of dumping tons of antibiotics into concentrated ecosystems such as rivers in China, where there might be tens of thousand times more concentration of resistance genes than found in typical groundwater. He stated that the overall consequences of circulating antibiotics in the environment is poorly understood.

Laxminarayan concluded with his perspectives on investing in AMR mitigation efforts. He emphasized that current thinking around the benefits of new antibiotics is mainly focused on the health sector, but more analysis is needed to understand the effect of AMR on other sectors. He also noted that though funding for AMR response from the global community has risen over recent years, the majority of this funding goes toward antibiotic discovery. He urged that a higher proportion of these funds should be directed toward strategies related to diagnostics, vaccines, and conservation of existing effective antimicrobials.

DISCUSSION

Because a key theme of the workshop is how to influence policy and decision makers to invest in countering microbial threats, Fukuda asked the three speakers to share how they would like to see future funding targeted to reduce the threat of AMR.

- Pearson highlighted the need to focus on two issues: the livestock sector and discovery of new antimicrobials. He specifically argued the importance of identifying credible alternatives that will help reduce the massive use of antibiotics while not heavily disrupting the livestock sector. He shared experiences from Europe where

the production model has moved away from antibiotic use while maintaining competitiveness in the livestock sector, and believed that these experiences can be used to convince other countries like China and Brazil to follow a similar path. On his second point, he expressed his concerns regarding the inadequate pipeline of new antimicrobials. He called for more efforts directed toward developing new antibiotics as well as vaccines, rapid diagnostics, and conservation strategies.

- Chawla reiterated Pearson's point that more attention is needed on the livestock sector. Chawla highlighted the challenge of higher production costs for farmers, and the resistance from some governments that are not readily committing to reduce the use of antibiotics in livestock. He suggested that a fund to counter AMR could be set up to pay for costs associated with new policies to incentivize low- and middle-income countries.
- Laxminarayan urged for fundamental changes in the way the global community manages antibiotics and infectious diseases in both humans and animals. He argued that while he is not opposed to funds going to research and development, there is a strong need to invest in conservation and prevention measures.

Fukuda opened the discussion to the audience, starting with questions on the viability of specific interventions to reduce the threat of AMR. Mary Wilson, clinical professor of epidemiology and biostatistics in the School of Medicine at the University of California, San Francisco, asked about the potential benefit of vaccines as a prevention measure for both humans and livestock to reduce antibiotic use. Laxminarayan responded that there is huge potential for both existing and potentially new vaccines to prevent infections as well as to reduce antibiotic use. He stated that current research is evaluating how vaccines can reduce antibiotic consumption.

Martin Meltzer, senior economist and distinguished consultant at the U.S. Centers for Disease Control and Prevention, asked about the sustainability of interventions that aim to reduce AMR but have short life spans and need continuous monitoring for effectiveness—such as hand washing. He asked the panelists to reflect on actions that will change antibiotic use not only in the short term but also in the long term, before a new set of tools such as novel antibiotics are introduced. Laxminarayan noted that current tools, such as the pneumococcal conjugate vaccine prevent the need for antibiotics and reduces both antibiotic-susceptible and antibiotic-resistant diseases. He argued that a tuberculosis (TB) vaccine would prevent both TB-resistant and TB-susceptible infections. On the sustainability of behavioral interventions, he agreed that the effect can wane with time unless a new social norm is created. Pearson responded that the declining success of

behavioral interventions, like hand washing, was integrated in the models he presented, but the interventions were nonetheless demonstrated to be cost-effective. He pointed out that some interventions are more structural, like delayed prescription policies, where the patients have to wait for 3 days before being prescribed the antibiotics and at which point the patients may not need the drugs because they have recovered in that time frame.

Carlos Castillo-Chavez, professor of mathematical biology at Arizona State University, asked how to reduce resistance of antimicrobials by effectively managing hospital-acquired infections and methods to appropriately treat and deliver the drugs to patients in ways that are not cost-prohibitive. He noted the practice of cycling or mixing antibiotics to prevent resistant nosocomial infections, which can have limitations, versus isolation of these cases, which can be more effective but expensive.[5] Laxminarayan responded by noting that a large body of research has recently been published, establishing heterogeneity of antibiotics as a superior strategy to cycling. Castillo-Chavez acknowledged this literature, particularly stemming from the agriculture sector, but emphasized that there are still issues of resistance even with heterogeneity and that the crux of the question is the need to redesign how and where to deliver antibiotics to reduce resistance within hospital settings. Laxminarayan agreed that this is a question to consider and that part of the answer depends on the various costs of isolation.

The discussion turned to AMR in the context of low- and middle-income countries. Anas El Turabi, Frank Knox fellow in health policy at Harvard University, reflected on the equity dimension of AMR. He noted that economic loss from health in low- and middle-income countries typically point to mortality and morbidity from diseases like HIV, TB, and malaria, yet much of the discussions on AMR often focus on hospital-acquired infections, which are not always the biggest driver of mortality and morbidity in these countries. He asked the panelists to comment on this divergence, and on whether the interventions that are likely to work in high-income settings will also work for the AMR challenges of low-income countries. Laxminarayan noted that AMR has become an engine for many types of health interventions and is now tied to the universal health care agenda. Chawla stated that interventions taken from high-income countries to reduce AMR will be particularly difficult in countries with fragmented health systems, since the issue can be political, and it is difficult to manage prescriptions and antibiotic use by individual health care providers.

[5] Similar to crop rotation, cycling prioritizes a set of antibiotics to use against specific diseases during a determined time period before rotating to a period of restriction. The aim is that one particular drug would not be encountered by the pathogen during restriction cycles to prevent a mechanism of resistance from developing. Alternatively, a mixing strategy randomly allocates an appropriate antibiotic to patients within the same patient cohort, and is also referred to as a heterogeneity strategy (Beardmore et al., 2017).

Peter Daszak, president of EcoHealth Alliance, also asked about the status of AMR in low- and middle-income countries, specifically about the scalability and feasibility of antibiotic-free livestock in these locations. Laxminarayan noted that removing antimicrobial growth promoters and replacing them with more labor effort would cost about $1.50 per pig, and paying this amount is a choice that producers and consumers are able to make (Laxminarayan et al., 2015). He stated that livestock facilities in China and India are becoming state of the art, so it would be possible for them to transition to antibiotic-free livestock production. Pearson agreed that livestock production in China and India is characterized by high technology factories that can be regulated, making it feasible to change their production model. Chawla offered a different view, not fully agreeing that production facilities in these countries have become totally modern and concentrated for a feasible introduction of measures to reduce antibiotics.

Highlighting another issue from the livestock sector, Dennis Carroll, director of the Global Health Security and Development Unit at the U.S. Agency for International Development, noted that the biggest policy makers of livestock production are in the private sector as they make decisions about how investments are made. He added that many multinational livestock producers are making their own conclusions to move toward greater antibiotic stewardship in the interest of future profit concerns and their economic bottom line. He asked the panelists to share ideas on how to expand this type of thinking to incentivize the private sector as catalysts for change in the general fight against AMR but relying on the perceived economic benefits. Pearson responded by describing the motivations for the private sector as seeking first-mover advantage. After the first-mover advantage has been used, Pearson explained that it is difficult to rely on the private sector because they might fear incurred costs from taking further action while not reaping any benefits. Therefore, he stated that public–private partnerships are needed to catalyze industry-wide changes.

Kimberly Thompson, president of Kid Risk, Inc., commented that antibiotics should be considered as a global public good and suggested that there is a need for a public management strategy and a shared realization that all stakeholders are implicated in AMR. She asked how incentives can be created to unite interest groups to take society-level interventions to address AMR. Pearson responded that it is necessary to involve civil society to create social movements, and pointed out that some infectious diseases like HIV have strongly associated civil society embedded in the population. In contrast, civil society seems virtually nonexistent for AMR beyond the usual stakeholders who interact with the United Nations agencies. He argued that the lack of connection with the wider population and civil society has made it difficult to develop a movement around AMR to push for investments and policies that restrict antibiotic use.

Finally, the discussion ended on the participants reflecting on the enormous costs of AMR. Dean Jamison, professor emeritus of global health at the University of California, San Francisco, highlighted the complexities of defining the billion or trillion dollar cost associated with past and forthcoming use of antibiotics. Ed Whiting, chief of staff and director of policy of the Wellcome Trust, noted that the large estimates of impact have been helpful to create a political narrative for raising the issue on the global agenda. Laxminarayan responded by arguing that overstating the problem does not help, and large estimates require further unpacking. He added that calculations relying on past AMR trends and costs of antibiotics do not necessarily translate to future costing estimates, as the role of antibiotics will likely evolve. Pearson argued that the numbers associated with the future cost of AMR (estimated to be as large as the global financial crisis) helped raise the issue to the level of national policy makers, but big numbers do not always help to find solutions. He stated that breaking down the costs faced by different actors, and comparing these costs with interventions to evaluate their cost-effectiveness, will help to identify potential investments. Chawla reiterated that all costing exercises are limited by their underlying assumptions, but that these costing studies are nevertheless helpful as a starting point for an evaluation of market incentives. The field of economics has the potential to generate insights into the incentives around antibiotic use and research and reveal future solutions, he said.

6

Investing in National Preparedness Initiatives Against Microbial Threats

During session II, part A, of the workshop, speakers explored the challenges and opportunities of investing in national preparedness initiatives to counter future microbial threats. The session was moderated by Beth Cameron, vice president for global biological policy and programs at the Nuclear Threat Initiative. She provided opening remarks, highlighting the importance of investing in preparedness to counter infectious disease threats to avoid the high costs of outbreak response. There has been some progress in preparedness efforts, as several countries have strived to implement capacities to boost preparedness by complying to international preparedness instruments including the International Health Regulations (IHR) and the Performance of Veterinary Services (PVS) Pathway; furthermore, the global community has begun to understand the cost of preparedness through the Joint External Evaluation (JEE).[1] However, she said there are several gaps that need to be filled to achieve robust preparedness at the country level and around the globe and hoped that the presenters would illuminate opportunities to overcome these challenges.

The session began with a review by Tolbert Nyenswah, director general of the National Public Health Institute of Liberia, of Liberia's experience

[1] The IHR is an international agreement that is legally binding on 196 of the World Health Organization's member states. The aim of the IHR is to help the global community to prevent and respond to public health events that may have international consequences. The PVS Pathway, developed by the World Organisation for Animal Health (OIE), aims to sustainably improve the compliance of a country's veterinary services with OIE international standards. The JEE is a voluntary, collaborative process to assess a country's capacity under the IHR to prevent, detect, and rapidly respond to public health threats.

building microbial threat preparedness capacities through the development of a national action plan. Andreas Gilsdorf, consultant on public health security, then described the challenges and opportunities of implementing the IHR and investing in outbreak preparedness and response. Franck Berthe, senior livestock specialist at the World Bank, followed with a discussion on the PVS Pathway to help facilitate investments for preparedness that affect health systems. Finally, Katherine Lee, assistant professor, Department of Agricultural Economics and Rural Sociology, University of Idaho, reviewed the economics of implementing a One Health approach to address microbial threats.

EPIDEMIC PREPAREDNESS: LESSONS FROM LIBERIA

Tolbert Nyenswah, director general of the National Public Health Institute of Liberia, shared his experiences with strengthening epidemic preparedness capacities in Liberia. He discussed the country's response to recent infectious disease epidemics and their economic impact, and he highlighted the importance of investing in national action plans to prepare for microbial threats.

Economic Impact of Ebola and Other Infectious Diseases

The Ebola outbreak significantly affected trade, travel, and health service delivery in Liberia (CDC, 2016a). Nyenswah reflected on the outbreak's consequences, including school closures, hospital closures, airline disruption, reduced economic activity, and social isolation. The World Bank has estimated the economic impact of Ebola for Guinea, Liberia, and Sierra Leone amounts to $2.8 billion (World Bank, 2016). He noted that prior to 2014, Liberia experienced nearly double-digit growth in its gross domestic product (GDP). The outbreak, combined with falling global commodity prices, led to a reduction in annual GDP growth to less than 1 percent (World Bank, 2015b) (see Figure 6-1). He added that the economic impact is outlasting the epidemiological effects in the region and that Liberia is still having difficulty recovering from the crisis, particularly with stagnation in the mining and service sectors.

Since the Ebola epidemic, Liberia has experienced additional outbreaks of several other infectious diseases, including measles, Lassa fever, meningococcal disease, and monkey pox, a disease that had not occurred in more than 20 years. Specifically in 2017, Liberia experienced 39 different outbreaks, three of which required a humanitarian response (NPHIL, 2017). In April 2017, there was a bacterial meningitis outbreak, which many people feared was a reintroduction of Ebola, but with the help of the U.S. Centers for Disease Control and Prevention (CDC), the Liberian govern-

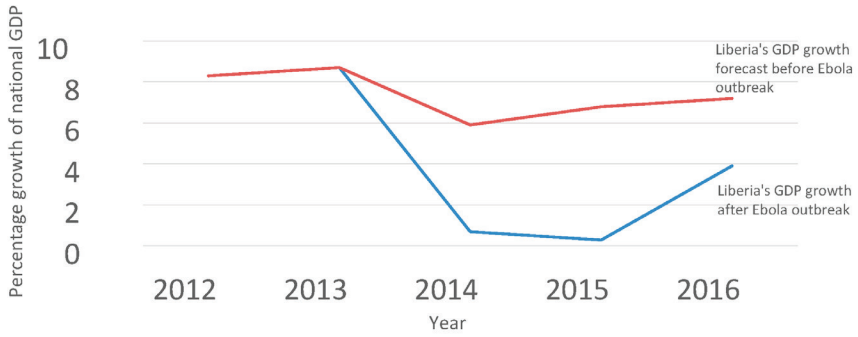

FIGURE 6-1 Impact of Ebola on gross domestic product (GDP) growth in Liberia, 2012–2016.
SOURCES: Nyenswah presentation, June 12, 2018; data from World Bank, 2015b.

ment responded to it swiftly (Patel et al., 2017). He argued that despite having controlled these outbreaks, the economy of the country was affected.

Strategic Planning for Epidemic Preparedness

Nyenswah described Liberia's progress on epidemic preparedness and the importance of national action plans to enhance health security. He explained that national action plans based on global or regional initiatives are subject to routine internal and external assessments based on established metrics such as those outlined in the Global Health Security Agenda Action Packages and JEE tool. National action plans, he added, should engage players across multiple sectors to ensure alignment of individual sector activities and crosscutting activities with national priorities. These plans should also include simulation and training activities to avoid loss of historical memory or complacency among rapid response teams caused by staff turnover and infrequency of outbreaks, he said.

Nyenswah explained that in Liberia the training package for the standardized rapid response teams incorporates strategies from the national epidemic preparedness and response (EPR) plan, the National Technical Integrated Disease Surveillance and Response guidelines, as well as lessons learned from the Ebola crisis. This package was used to train hundreds of rapid response team members at the national and district levels in 2016. While this type of training is an important step toward a standardized approach for the management of major outbreaks, he repeated that the national EPR plan requires regular refresher training and simulation exercises to sustain efficacy.

An additional benefit of national action plans, Nyenswah noted, is to help identify how to balance preparedness needs with resource constraints. When new activities to address national priorities for preparedness are added to the action plans, they can be mapped to existing opportunities, and where appropriate, leverage resources from across different projects and sectors. The Field Epidemiology Training Program,[2] through the African Field Epidemiology Network and CDC, has been successful in preparedness planning in some of the districts in Liberia, he added.

Nyenswah described the importance of integrating the One Health approach in the national action plan.[3] He noted that Liberia has made progress with implementing this approach with the development of a national One Health Coordination Platform in 2017. This platform sets out to coordinate and ensure multisector participation, resource mobilization, accountability, and transparency at all levels. This platform, he added, has facilitated the development of strategic operational and costing plans for rabies prevention and control and antimicrobial resistance (AMR). Nyenswah stated that as part of its One Health approach, Liberia has also prioritized adherence to the PVS Pathway, focusing on animal vaccines and medicines, veterinary laboratory services, and livestock officer training. The pathway has led to the creation of Ministry of Agriculture offices at the district level, better coordination between country-level agriculture officers and district level staff, and formal partnerships with private veterinary providers.

POTENTIAL CHALLENGES AND OPPORTUNITIES FOR INVESTING IN NATIONAL-LEVEL PREPAREDNESS

Andreas Gilsdorf, consultant on public health security, described the challenges and opportunities for investing in preparedness initiatives to counter infectious diseases through the lens of monitoring and evaluation of the IHR. He noted that despite the growing body of knowledge on the economic impact of microbial threats, policy makers are not doing enough to address the issue.

Challenges for Investing in Preparedness Initiatives

Gilsdorf presented several challenges that inhibit adequate action to strengthen outbreak preparedness and response. He noted that while the

[2] The program trains field epidemiologists around the world, giving them critical skills to collect, analyze, and track data to prevent infectious disease outbreaks.

[3] One Health is "a collaborative, multisectoral, and transdisciplinary approach—working at the local, regional, national, and global levels—with the goal of achieving optimal health outcomes recognizing the interconnection between people, animals, plants, and their shared environment" (CDC, 2018).

IHR is the most important legal framework on global health security, the specific details presented in the IHR are open to interpretation and lack precision on priorities, making it difficult to use the document as a tool to catalyze national preparedness and response. Many of the IHR targets have a long timeline, which is not attractive to policy makers, also making its implementation challenging. Additionally, Gilsdorf pointed to the issues of making the investment case for prevention, such as the difficulty to measure what was avoided, and the high startup cost to pay for staff and equipment. Moreover, funding for these initiatives is typically not coordinated, nor is it necessarily embedded in the national planning cycle, he said.

Gilsdorf highlighted the multitude of organizations and tools involved in national preparedness efforts. There are many donors involved, each that tend to have their own particular perspectives and interests. He argued that although different tools such as the JEE and PVS are useful, they often overlap and have separate implementation approaches that can lead to different recommendations. This further creates a challenge for policy makers trying to choose a way forward.

Multisectoral Coordination for Preparedness

Because of the multiple players in preparedness efforts, Gilsdorf emphasized the need for multisectoral coordination within government agencies, across international organizations, and with the private sector, as well as high-level political commitment and supporting legal structures. He highlighted that the involvement of the private sector is particularly needed for better exchange of information and better use of limited resources. While this coordination can be difficult, it can lead to better and more sustainable results.

Gilsdorf noted that existing mechanisms could be leveraged or new ones could be created to facilitate coordination among different groups. He highlighted the importance of having the relevant players meet with one another on a regular basis to better understand each other's aims and needs. On the operational level, setting up joint emergency operation centers could allow stakeholders across and within agencies to be better coordinated as well as run everyday operations in between outbreaks, and does not require investing in any specialized equipment.

He also noted the importance of joint outbreak investigation teams and simulation exercises conducted by multidisciplinary teams, where roles and responsibilities are distributed across teams, which builds trust and understanding. He shared his experience participating in a tabletop simulation for Group of Twenty health ministers in 2017. The exercise helped to create awareness among leaders of the consequences of implementing an adequate and effective response during major outbreaks. He concluded that while

preparedness initiatives and multisectoral collaboration can be expensive, they are worth the investment. He reiterated the need for moving toward a multisectoral collaboration approach with better understanding of the perspectives of the different stakeholders involved.

USING THE PERFORMANCE OF VETERINARY SERVICES PATHWAY TO BOLSTER PREPAREDNESS

Franck Berthe, senior livestock specialist at the World Bank, discussed the PVS Pathway and its implications for strengthening health systems. He began by describing a recent outbreak in Burundi of *peste des petits ruminants* (PPR), a viral infection affecting small ruminants such as goats and sheep (OIE, 2018a). He noted that the World Bank, working with its partners at the Food and Agriculture Organization of the United Nations and OIE, were able to quickly assess the needs and launch a successful vaccination program because of the country's strong health and veterinary service networks.

Performance of Veterinary Services Pathway

The PVS Pathway is a cyclical process made up of four phases that aim to sustainably improve a country's veterinary services by addressing food safety, veterinary medicine, antimicrobial resistance, zoonotic diseases, laboratory infrastructure, and human resources (OIE, 2018b). Berthe described the four phases of the process. First, the orientation phase provides information and lessons on veterinary services generally as part of regional or subregional workshops, which are valuable as they bring together countries with common interests and shared challenges. Next, the evaluation phase uses the PVS evaluation tool to assess country-level resources and capacities, as well as additional follow-up and more narrowed focus tools such as the PPR tool. The planning phase includes the PVS gap analysis, which determines and confirms the country's veterinary service priorities and helps to develop an indicative costing of the resources required for the implementation of the activities identified (see more details in the next section). Finally, the targeted support phase consists of supporting the implementation of the actions identified in the planning phase and linking interventions with JEE and PVS recommendations. Berthe shared examples of targeted support activities including assisting countries on drafting legislation, integrating services through a One Health approach, providing laboratory support, and veterinary professional education.

Berthe presented examples from Thailand and Ethiopia that illustrate country responses to the PVS evaluation and the PVS gap analysis findings. In Thailand, PVS results from 2012–2013 were used to successfully advo-

cate for a 13 percent increase in the budget of the Department of Livestock Development, recruit additional veterinarians, create a new government agency division focused on livestock feed safety, and develop new regulations on animal welfare and food product manufacturing (OIE, 2018b). In Ethiopia, the findings from the PVS gap analysis in 2012 led to the creation of a mobile phone-based animal health information system, improved reporting on animal processing facilities, and a road map to improve veterinary services (OIE, 2018b).

Performance of Veterinary Services Gap Analysis

Berthe described the four steps for implementing the PVS gap analysis (see Figure 6-2). Step 1 is the determination of the country's high-level priorities across five pillars: livestock development and trade, animal health, veterinary public health, laboratories, and management. During this step, countries have the opportunity to decide on their priorities for policy development by identifying two to four priority areas within each of the five pillars. Step 2 involves defining the expected results by setting critical competency target levels for the next 5 years. The PVS tool scores countries on a scale of 1 to 5, so Berthe noted that countries decide the score they want to achieve within the 5-year timeline. Steps 3 and 4 include developing a plan of activities under each critical competency and determining their costs using a spreadsheet tool that links the activities to a costing database. The most important outcome of this analysis is the development of a 5-year

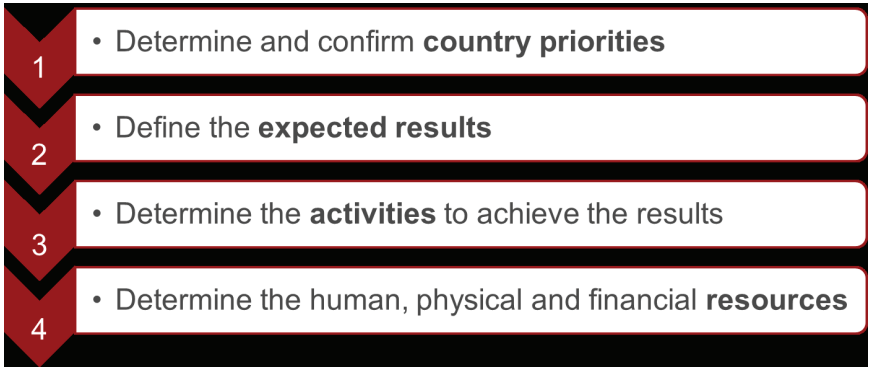

FIGURE 6-2 The Performance of Veterinary Services (PVS) gap analysis tool in four steps.
SOURCE: Berthe presentation, June 12, 2018.

budget for veterinary services with operational and investment components, he concluded.

According to Berthe, 115 out of 181 OIE members have requested PVS gap analysis, and 95 countries have actually gone through this process. However, only 22 of these reports are publicly available on the OIE website, and an additional 37 reports have been shared with the donor community and development partners. He noted that making these reports public is critical as these results are not only relevant to the country itself but can also be used by other countries or agencies when designing national or regional projects.

Berthe shared an example of the World Bank Regional Sahel Pastoralism Support Project that invested $50 million in Burkina Faso, Chad, Mali, and Senegal toward animal health initiatives (World Bank, 2015a). The project includes activities to upgrade the infrastructure and capacities of national veterinary services and support surveillance and control of priority animal diseases. These investments were selected based on the PVS analyses previously conducted in these countries. Beyond a domestic exercise, Berthe concluded that the PVS Pathway and gap analysis tool guide the design and implementation of investments to strengthen veterinary health systems toward compliance with international standards. The PVS findings have revealed how chronically underresourced veterinary services are in many countries. He added that the PVS Pathway is a shift away from the short-term, vertical, single disease programs approach.

COSTS AND BENEFITS OF IMPLEMENTING A ONE HEALTH APPROACH AGAINST MICROBIAL THREATS

Katherine Lee, assistant professor, Department of Agricultural Economics and Rural Sociology, University of Idaho, described the costs and benefits of the One Health approach to microbial threat preparedness. She began her presentation by laying out three questions that need to be addressed to understand the economics of microbial threats and One Health: What is the value of managing infectious disease threats? When should we invest in management? How should we build the management framework to cost-effectively address these risks? Within this framework, she said the question is then if there is a place for One Health to cost-effectively approach some of these emerging infectious diseases.

Understanding the Value, Timing, and Strategy to Counter Emerging Infectious Diseases

Over the past 50 years, zoonotic infectious disease outbreaks have increased in frequency and severity (Jones et al., 2008). These outbreaks

are increasing in relation to rising agricultural intensification, globalization, and changing patterns of interactions between humans and food sources. Lee explained that these outbreaks are associated with significant economic impact and thus there is value in investing in the management of them, especially through early detection and rapid response, to change the trend of increasing emerging infectious diseases. She highlighted the opportunity for the One Health approach to reduce and mitigate zoonotic outbreaks by targeting interventions on both wildlife and livestock.

Because these risks are dynamic, the timing of investments is also important, and economic analysis can determine the value of investments made at different points in time (see Figure 6-3). She noted that early investments in outbreak prevention are more cost-effective than later investments in outbreak response (Pike et al., 2014). However, she cautioned that there is a threshold where the expected damages for the projections of future events exceed whatever the returns are from investing in a preventive framework or an early response framework for managing these risks. While it is important to take time to evaluate options and strategies, according to Lee, "Investing early is investing better. But we better not wait too long to sort this out."

Once there is understanding about how timing fits into the problem, Lee stated the final question is how to design policies to effectively address the risks. Lee presented research that examined how the $5.4 billion the United States appropriated to the 2014–2016 West Africa Ebola epidemic

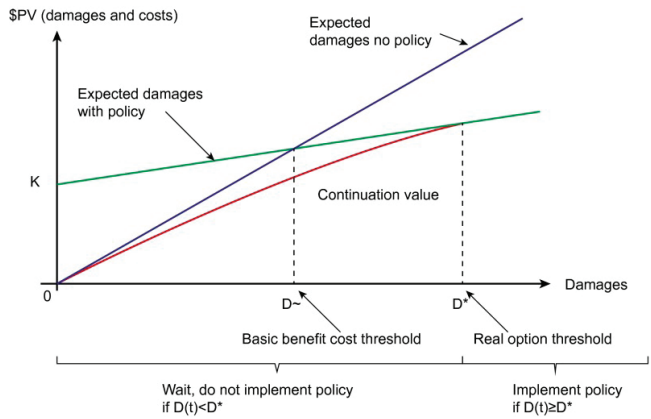

FIGURE 6-3 Real options economic modeling to analyze timing and cost of policy implementation to address pandemic threats.
NOTE: D = damages; K = cost; PV = present value.
SOURCES: Lee presentation, June 12, 2018; Pike et al., 2014.

response could have been spent—either to prevent the outbreak from happening or to rapidly respond to the outbreak by mobilizing capital and labor to the source of that outbreak and mitigate the damages (Berry et al., 2018). The study found that an upfront investment of about $1 billion in mobile capital, a global network of laboratories, and highly trained surveillance teams placed in high-risk areas around the globe would serve as insurance against continuous threat of emerging infectious diseases. This network would employ best management practices and respond quickly to outbreaks as they occur, resulting in savings of more than $10 billion in reduced costs from avoiding expected future emerging disease impacts. Therefore, she argued that this option would be better than waiting for an outbreak to occur and spend millions in response.

One Health and Land Use

Lee moved on to describing how to better address emerging infectious disease threats through a One Health approach. She said one way to think about this is through examining other overlapping global issues such as land use changes, specifically surrounding land conversion for industrial purposes versus conservation efforts. According to Lee, greater land conversion is associated with more frequent interactions with wildlife, and therefore an increase in emerging infectious disease outbreaks. While the benefits of land conversion are clear—namely economic growth and job creation—further research is needed to evaluate the costs, which include loss of carbon storage, loss of wildlife habitats, and higher disease incidence, she said. Lee argued that the topic of land use requires quantifying and assessing trade-offs as well as regulation, since industry and policy makers often ignore the externalities of their decisions on how much land they want to convert in a given year.

In conclusion, Lee said there is a huge opportunity for both research and policy developments using a One Health approach to managing multiple global issues simultaneously. She called for better understanding of the total economic costs, both direct and indirect, of emerging infectious disease events to inform policy options. The health costs associated with lost ecosystems, she added, can be used to build discussion and change incentives for the implementation of a One Health approach.

DISCUSSION

As moderator, Cameron posed the first question to the panelists, asking them to identify an area that they would like policy makers to prioritize for strengthening national preparedness for microbial threats.

- Nyenswah stated that he would push for a One Health approach to preparedness, linking animal health and human health surveillance and response efforts. He noted that he has witnessed the benefits of this strategy in the context of rabies, Lassa fever, yellow fever, malaria, and Ebola control in Liberia.
- Gilsdorf called for increased multisectoral collaboration with a clear understanding of each sector's needs and agreement on a way to work together. In addition, he emphasized the importance of investing in training the public health workforce responsible for outbreak preparedness and response.
- Berthe agreed that investing in implementing a One Health approach is critical, focusing on educating the new generation of public health workers to prevent them from working in siloes.
- Lee noted that investment in prevention is a difficult sell to policy makers. Therefore, she proposed highlighting the direct and indirect costs of existing health threats, including livestock diseases and vector-borne illnesses. She shared the example of malaria, which has numerous indirect costs including its effect on tourism and lost productivity. She argued that showing the actual costs of such threats to policy makers would make a stronger investment case for prevention as well as introducing the cobenefits of the One Health approach to manage them.

Cameron opened up the discussion to the audience, which first focused on specific issues related to the development and implementation of preparedness efforts. Jay Siegel, former chief biotechnology officer of Johnson & Johnson, asked about the current research efforts in the field of behavioral economics and communications to support the design and implementation of interventions for outbreak preparedness and response. Lee stated that there is much to learn from studies that evaluate public thinking and the adoption of new practices around topics such as climate change. She highlighted the need to understand how people discount future values to consider present benefits or costs. Berthe agreed that when it comes to behavior, providing facts is not enough. He cited AMR as an example where knowledge has not been sufficient to address this threat. Therefore, he highlighted the need for investing in health systems that can respond when an unexpected outbreak occurs. Gilsdorf noted that it is critical to invest in communication research to achieve behavioral change and consider the way information is transmitted and has evolved through new media and new styles of journalism and political activity.

Thomas Inglesby, director of the Center for Health Security of the Johns Hopkins Bloomberg School of Public Health, asked the panelists for examples of a strong national One Health intervention and its key

features. Berthe responded by listing champions of One Health including Bangladesh, Botswana, Liberia, Senegal, and Vietnam. He added that the global response to H5N1 influenza has raised the profile of the One Health approach, but that there is a need for better indicators to consistently measure the success in implementing this approach.

Kimberly Thompson, president of Kid Risk, Inc., noted the challenge of accounting for the full effect of preparedness efforts that are put in place and wondered about the possibility of leveraging existing health networks and initiatives to help support these efforts that can lead to systemwide impact. Thompson asked how these challenges are taken into account when modeling the cost of preparedness efforts. Berthe responded by stating that there is a need to invest in systems. He noted that veterinary services and food safety are examples of systems that should be in place for routine services and can be ready in case they are needed to respond to an outbreak. Gilsdorf argued that preparedness should not focus on one or two diseases, but instead be generic enough to be able to counter a variety of threats. Measuring the success of this approach, however, is more difficult compared to disease-specific programs, he said. Nyenswah stated that preparedness programs should be holistic, and involve emergency operation centers, training, capacity building, and simulation exercises. While Cameron recognized the importance of investing in strengthening health systems, she highlighted the challenges of raising funds for this purpose and noted that these efforts may need to be linked to specific diseases to be successful. This allows policy makers to understand and demonstrate the linkages between investments and outcomes, she said.

Patrick Hickey, chair of the Department of Pediatrics at the Uniformed Services University of the Health Sciences, asked how the economics community can help policy makers to design interventions with enough specificity to ensure impact, but also enough flexibility to respond to evolving needs. To illustrate his question, Hickey shared his experience in the West Africa Ebola response, where funding was available for building treatments units that were no longer needed but could not be used to address other critical needs. Nyenswah agreed that funding should be flexible enough to respond to changing circumstances. He argued that policy makers should build flexibility into funding programs so the institutions implementing them can respond to evolving situations. He reiterated that in Liberia, it was difficult to move the funding assigned to building temporary Ebola treatment units to focus on health systems strengthening. Gilsdorf agreed that flexible funding is a challenge, and shared his experience interacting with health ministers who said that the issue stems from the realities of zero budgeting for national programs. On interaction with policy makers, Gilsdorf noted that effective communication is essential, which sometimes means simplifying information rather than providing more details.

Martin Meltzer, senior economist and distinguished consultant at CDC, asked the panelists how to measure and best demonstrate the effect of improved surveillance and response when the public health community mainly relies on measuring the effect of an intervention with the number of deaths and cases averted. Nyenswah responded that the number of deaths averted can be a good indicator of the effect of a robust surveillance system. He cited as an example that the improvements made in the health system in Liberia (including a stronger surveillance system) prevented many deaths during several Ebola flare-ups, a meningitis outbreak, and a measles outbreak.

The discussion ended on the topic of building the investment case and persuading policy makers about preparedness. Peter Sands, executive director of The Global Fund to Fight AIDS, Tuberculosis and Malaria, commented that it is difficult to convince governments to make investments toward threats in the future when they face high burdens of diseases in the present. He highlighted the need for a broader definition of health security that starts with the diseases that currently pose the highest risk and build capacities and infrastructure to address those, which would also prepare the world to better respond to future threats. Lee responded by emphasizing the potential for the One Health approach to address preparedness from the perspective of both current endemic and emerging infectious diseases. She shared the example of malaria, where the One Health approach raises issues related to environmental interactions and the breeding grounds for mosquitoes. Nyenswah stated that the resources in low- and middle-income countries are directed according to local burdens of disease. However, he noted, there is an opportunity for a greater impact if the investments coming from development partners are used to implement a more holistic approach after agreeing on shared priorities. He recommended that initiatives focusing on countering infectious diseases prioritize making systemwide impacts instead of creating vertical programs.

Finally, Keiji Fukuda, clinical professor and director of The University of Hong Kong School of Public Health, observed that the health sector has failed to convince policy makers of the need to consider health and preparedness as good investments, rather than see them as expenditures needed to respond to emergencies. He noted that the uncertainty around the inclusion of health as a Sustainable Development Goal demonstrated this challenge and asked panelists to comment on how to shift this paradigm on health investments. Gilsdorf responded by calling for more efforts focused on recognizing infectious diseases as economic and security threats, which in the past couple of years the public health community has been somewhat successful. He noted that building strong health systems should be an issue of high societal concern, but noted that this is difficult given the short-term vision of decision makers.

Cameron concluded the discussion by agreeing with the need to make better arguments on the importance of investments in the health sector. She noted that health broadly, and not only pandemic preparedness, should be considered a security-related investment, and funders and governments should come together to discuss and agree on the right messaging to advocate for this investment.

7

Accelerating Research and Development of Antimicrobial Medical Products

Session II, part B, of the workshop presented commercial perspectives on the opportunities and barriers to accelerating discovery and development of medical products to counter microbial threats, with a focus on antimicrobial resistance (AMR). Panelists examined the role of private-sector incentives and public–private partnerships to address the unique challenges of accelerating pharmaceutical research and development (R&D) for antimicrobials. The session was moderated by Jami Taylor, board advisor at Stanton Park Advisors and included brief remarks from four panelists: Paul Schaper, executive director of global public policy at Merck & Co., Inc.; Joanna Wolkowski, vice president of portfolio and decision analysis at Pfizer Inc.; Thomas Cueni, director general of the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA); and Jonathan Kfoury, managing director of L.E.K. Consulting. A discussion with workshop participants followed.

COMMERCIAL PERSPECTIVES ON OPPORTUNITIES AND BARRIERS TO DISCOVERY AND DEVELOPMENT OF ANTIMICROBIALS

Panelists shared their experiences within the biopharmaceutical industry and discussed key issues pertaining to antimicrobial product discovery and delivery to the market, including incentives, challenges, and strategies. They reflected on the scientific, regulatory, and economic challenges with R&D that are more acute for antimicrobial products and focused on the issue of return on investment for companies engaged in this arena.

The panel members covered a range of existing push and pull incentives designed to address return on investment, and they provided their perspectives on creating a suite of incentives with the potential to stimulate R&D.

Advancing a Suite of Incentives to Support the Research and Development Life Cycle

Paul Schaper, executive director of global public policy at Merck & Co., Inc., noted that Merck has been involved in the antimicrobial arena for more than 80 years. As a result, the company has witnessed many of the challenges that occur prior to the successful launch of new antimicrobials, such as Merck's novel antitoxin targeting *Clostridium difficile* and two antibiotics targeting gram-negative bacteria. Schaper argued that the R&D environment continues to be fragile in light of the scientific, regulatory, and economic challenges that hinder sustained investment in antimicrobials, vaccines, and alternative technologies. He highlighted the need to advance a suite of incentives that balances push and pull incentives, and address reimbursement reform in order to support products through their 10- to 15-year development life cycle.

There has been global high-level political recognition on the importance of new incentives for medical products to combat AMR, but actions thus far have focused on push incentives, which lower the cost of entry toward R&D of a desired product, including grant funding, tax credits, and public–private partnerships (G7 Leaders, 2015; UN, 2016; G20 Leaders, 2017).[1] Push incentives can help during the clinical development stage, but later stages of the product life cycle require pull incentives, Schaper said. Pull incentives are provided during the approval process and after successful drug entry into the market. They supplement income in future sales or guarantee revenues for a product that is delinked from sales volume to encourage sustainable, appropriate use. Schaper called for a broader suite of incentives, from early in the R&D life cycle through bringing a product to market, keeping it there, and making it accessible. Because of the lack of pull incentives, fewer drugs are coming to market, he noted, and several companies have left the antimicrobial development arena despite receiving push incentives such as grants from BARDA.

In addition to misaligned incentives, Schaper highlighted regulatory challenges related to product reimbursement that discourage manufactur-

[1] Several governments and global initiatives have offered push incentives, such as the Biomedical Advanced Research and Development Authority (BARDA) of the U.S. Department of Health and Human Services, the Global Health Innovative Technology Fund headquartered in Japan, and the Innovative Medicines Initiative (IMI) of the European Union.

ers. Most antimicrobials enter the market with noninferiority trials,[2] which compare them to therapies already available on the market. He noted that in Europe, if a product is deemed noninferior, it can only charge the price of the comparable generic medication. Schaper also raised the issue of hospital reimbursement by diagnosis related groups (DRGs), which are fixed compensation rates depending on a patient's diagnosis. This approach encourages facilities to use the least expensive products available even when more expensive, newer products would be more appropriate, he said.

Schaper went on to reflect on another aspect of note with antimicrobial development: the fact that new drugs are usually not used early in their life cycle. When antimicrobials are first available on the market, it may not be clear how to use them. He noted that at this stage, little is known about the resistance profile of circulating pathogens to the new medication. As these data are obtained over time, novel antimicrobials can be used to treat patients in cases where they will be efficacious. Related to this challenge, he said that new payment system models and innovative incentives are needed to ensure that antimicrobial manufacturers are compensated for their investments regardless of actual use.

Ensuring Commercial Viability of Antimicrobial Research and Development

Joanna Wolkowski, vice president of portfolio and decision analysis at Pfizer Inc., provided an overview of Pfizer's programs addressing multiple aspects of AMR, including antimicrobial stewardship, resistance surveillance, regulation, and manufacturing of products to treat and prevent bacterial infections. She reiterated the enormity of the AMR issue—high associated economic costs and millions of affected lives—as well as the obstacles in the R&D process. As it takes 10 to 15 years of investment to bring one drug to market and about 50 compounds involved in the discovery pipeline before reaching one potentially viable product, Wolkowski argued that companies should be adequately rewarded for their investments and risks in finding R&D opportunities within the current marketplace. As a result, Pfizer takes into account the incentives in place and uses financial modeling to identify where and how they can best allocate their investments in AMR for greatest return on investment and impact on patient lives.

Wolkowski also mentioned that return on investment in R&D of medical products is key to maximize the effect on AMR while being fiscally responsible. Yet, for antimicrobials, the financial effect of a drug being

[2] Noninferiority trials compare new products with a control therapy already being used. If a product is successful in a noninferiority trial, it can only be said to be equivalent to the standard of the control. These trials cannot demonstrate therapeutic superiority.

successfully delivered to market can be more uncertain than for other products, she said. For example, standby antimicrobials are expressly developed to be new powerful drugs kept in reserve until a critical need, but Wolkowski noted that companies would be unable to command a commercial value equivalent to its generated societal value. These factors, as well as antimicrobial stewardship initiatives, can discourage investments in new antimicrobials. Wolkowski approached the challenge of ensuring return on investment on antimicrobials by focusing on the reliable returns through the end of a 15-year R&D process and delinking revenues from antimicrobial use.

In the meantime, companies like Pfizer can continue working to counter AMR by improving stewardship as a strategy to preserve the effect of current antimicrobials before new drugs can be brought to the market. In addition, surveillance to track resistance patterns in the environment can help companies identify key antimicrobial targets with potential for new drug development. Wolkowski also suggested exerting influence at key points in the existing regulatory framework that may affect how drugs reach the market, improving the understanding of manufacturing mechanisms, and identifying new ways to combat bacterial infections like the use of vaccines to prevent infections in the first place. She concluded by stating the opportunities in the marketplace need to be examined to help patients in a way that catalyzes and rewards the investments and efforts in R&D. If these strategic trade-offs and implications considering the budget and time constraints are assessed, she said, the R&D model for antimicrobials can be shifted to make it sustainable.

Building Global Allies for Industry-Wide Innovation

Thomas Cueni, director general of IFPMA, shared insights from his experience in the pharmaceutical industry on the particular challenges of AMR, highlighting political impediments to action despite industry engagement with the issue. According to Cueni, "The problem with AMR is that it doesn't have a face." To illustrate, he compared progress made in the area of antimicrobials versus pandemic influenza preparedness from the time they were both identified as top areas for research by the World Health Organization's (WHO's) *Priority Medicines for Europe and the World* report to now.[3] Cueni argued that society has seen galvanization since the 2009 H1N1 pandemic, including the formation of the Pandemic Influenza Preparedness Framework, but he said there has been no equivalent for AMR, seen as a "silent potential killer." Along with other speakers in the workshop, Cueni remarked on the conundrum of investing in standby med-

[3] WHO's *Priority Medicines for Europe and the World* was commissioned in 2004 and updated in 2013 (WHO, 2013).

icines that will not generate enough revenues to incentivize development. He noted that until the costs and effects of AMR are felt by individuals and policy makers, it will continue to be difficult to raise the necessary resources to meaningfully address the problem.

Furthermore, Cueni asserted that the global call to action for AMR has not been matched by sufficient investments from governments.[4] The private sector invested four times as much as all government budgets combined in AMR-related research. The estimates show that the private sector has spent more than $2 billion over the past decade on AMR-related research, compared with government initiatives amounting to $500 million over the same period (AMR Industry Alliance, 2018). Cueni was emphatic that this level of government spending would not be enough to generate one new antimicrobial. While public–private partnerships like BARDA, IMI, and the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) have helped push private-sector investment in this field to current levels, he deemed even $2 billion as insufficient to develop the necessary antibiotics. Cueni reiterated the urgency of combating AMR and the inadequate progress made to date if ultimately nothing has changed since 2004.

Cueni concurred with the need for both push and pull incentives and added that he believed there was no one-size-fits-all optimal package of incentives. He said that sustaining research is high risk, and push incentives are not enough to overcome the regulatory and scientific challenges to antimicrobial development. Cueni saw potential in a number of pull incentives while being cognizant of their individual drawbacks. Market entry rewards would guarantee income for pharmaceutical companies for bringing products onto the market as standby drugs designed for low volume of use; however, Cueni has yet to see any entity provide adequate funding in market entry reward initiatives.

Transferable market exclusivity (TME) is another pull incentive for consideration, though Cueni said it was more politically challenging, since it would provide pharmaceutical companies with patent extensions in wealthy countries on their existing legacy products in exchange for the successful release of a new antimicrobial product (Kesselheim, 2010). Companies can then use the additional revenues associated with the patent extension to offset the costs associated with the new product's development. He also highlighted drug reimbursement reform as a promising strategy to spark new antimicrobial development, though again he cautioned against pursuing any single strategy. To illustrate this, he said the price of new cancer

[4] Cueni referenced the fact that AMR was on the agendas for the Global Call to Action on Antimicrobial Resistance, organized by the Wellcome Trust, the United Nations Foundation, and the governments of Ghana, Thailand, and the United Kingdom, and the Berlin Declaration of the Group of Twenty Health Ministers, both in 2017.

immunotherapy can cost up to $475,000 per treatment, which would not be possible for antimicrobials (Dolgin, 2018). Cueni emphasized that it is important to move from talk to action in addressing AMR, and noted that even when the pharmaceutical industry is aware of the low profitability in producing new antimicrobials, they are open to being allies in public health and offering support to meet the needs of society.

Leveraging Existing Models and Pursuing Diagnostics

Jonathan Kfoury, managing director of L.E.K. Consulting, shared his observations from prior experience in clinical development of antimicrobials at Cubist and his work with other small biopharmaceutical companies. He noted that both large and small pharmaceutical companies are lowering their investments in antimicrobial research, despite the growing global need for new products. He agreed with Wolkowski that the major challenge impeding antimicrobial product development relates to negative forecasted returns on investment. Large companies in particular have to decide whether to invest in antimicrobials that address resistant infections, when faced with opportunities to invest in a range of other, potentially more profitable products. Kfoury also agreed with the other panelists that current incentives are not enough to pursue antimicrobials to the extent necessary in the next few decades.

While existing push incentives have been valuable to stimulating early-stage R&D efforts, more pull incentives are needed to specifically draw in midsize and large companies facing a range of investment decisions, he said. Kfoury emphasized the need for developing a suite of incentives versus a single pathway solution. This would help companies plan through their product development process and identify the best incentive to tap into at different stages. He also noted that different companies may need assistance at various stages of product development as the economics and operations behind the incentives for early-stage R&D are different from preclinical stage; phase 1, 2, and 3 trials; registration; and commercialization. Kfoury proposed incorporating strategies that leverage existing models, such as reimbursement "carve-outs" from DRG payments to ensure revenue streams from new antimicrobials. Under this strategy, all of the patient's treatment services for a resistant bacterial infection would be covered by the DRG payment, except the new antimicrobial (Kfoury, 2014). Hospitals that appropriately apply the new antibiotics to treat the infections would be fully reimbursed for the cost of the drug. In other words, a carve-out would avoid penalizing hospitals if they used a new drug that is more expensive than alternatives to treat a certain condition if the scenario met appropriate guidelines, he said.

Kfoury concluded by highlighting the lack of rapid diagnostics for resis-

tant infections and the challenge for physicians to decide on appropriate therapies at a given point in time, which further limits the use of targeted drugs. With current practices relying on clinical judgment and blood cultures, resistant infections may take several days to diagnose after the initial clinical presentation. To address this overall crisis within public health but also within industry, Kfoury called for greater collaboration on diagnostic innovation among pharmaceutical companies, diagnostic companies, governments, and nongovernmental partners to bring about novel products capable of addressing specific resistant pathogens.

DISCUSSION

The discussion began with Anas El Turabi, Frank Knox fellow in health policy at Harvard University, who asked the panelists if they have seen any evidence of more drug effectiveness and shorter hospital stays in cases where institutions have shifted to a value-based purchasing paradigm and incentivized the use of more appropriate, albeit expensive, medications. Schaper responded that the evidence needed to establish these reimbursement incentives does not exist yet, because clinical trials are designed to evaluate a new product's noninferiority compared with generic alternatives. As he referenced in his presentation, Schaper said another challenge is DRG payments for hospitals, when they favor the use of cheaper, broad-spectrum generic antimicrobials and create impediments for physicians to prescribe a more expensive and targeted drug. He also highlighted a gap in diagnostics and the potential effect of including new drugs in automated antimicrobial susceptibility testing. Schaper asserted that to promote antimicrobial development, hospital systems and payers must not let cost be the predominant driver for drug choices; they must be willing to pay more for a novel drug over cheaper alternatives.

The discussion turned to specifics on the use of pull incentives. Jay Siegel, former head of scientific strategy and policy for Johnson & Johnson, asked about the feasibility of designing sufficient TMEs and other intellectual property-based incentives that could overcome political and public perception barriers in order to promote standby drug development. Siegel underscored his point by sharing his experience at Johnson & Johnson, where he said the U.S. Food and Drug Administration's (FDA's) priority review voucher program for neglected tropical diseases was a factor for investing in programs for bedaquiline, a new drug to treat drug-resistant tuberculosis (TB); he further argued that altruism was another main driver for their investments especially at the preclinical stage. Cueni believed that different political systems will need to experiment with different strategies for incentives. Based on his experience in Europe, for example, he was skeptical of reimbursement reform alone being the solution because of the

noninferiority challenge. Cueni acknowledged the potential of TMEs and other intellectual property-based innovations to spur new drug development and the benefit to investors of not disbursing funds up front.

Elaborating on the issue of public perceptions, Cueni noted that he had observed from industry discussions that companies were aware of the public perception that companies would benefit from a "free ride," notwithstanding that they would still bear a significant risk themselves. He reported that companies have been open-minded and willing to combine different strategies and take on guardrails such as antimicrobial stewardship provisions. Future initiatives could be based on a combination of market-based incentives, in particular pull incentives, he said, to stimulate R&D investment with provisions on antimicrobial stewardship and access to medicines to ensure the delivery of new drugs to developing countries. Wolkowski reiterated Cueni's approach to employing a combination of strategies and stated that these types of incentives can benefit both large and small companies alike. With TMEs, for example, small companies that invest in necessary antimicrobials can potentially sell that exclusivity to larger partners that have more suitable products for patents.

Mark Pearson, deputy director for employment, labor, and social affairs at the Organisation for Economic Co-operation and Development, asked the panelists if there is a clear consensus from industry on their desired pull incentives. He cited several potential areas of focus that may confuse investors, such as whether investments should be in broad- or narrow-spectrum drugs or first-in-class versus non-first-in-class drugs. He also raised the concern that market entry rewards and TMEs could lead to double payment for new drugs, a payment for the award or extended patent in addition to a high price for the new product itself. Kfoury responded that Pearson's question depends on the type of model being engineered and for what purpose. If the funding structure is based on the most pressing needs in terms of pathogens and is designed from a scientific and a stewardship perspective, he said, then that will drive a different set of numbers and solutions. He argued that there is intrinsic value for a portfolio approach that considers the pathogen perspective and addresses questions that consider the most pressing needs from a global perspective.

Cueni reiterated that there can be multiple regional approaches to pull incentive strategies and magnitudes. He argued that the key challenge is that there is no market for new antimicrobial products, citing clear opportunities for profit from new products for diseases like Alzheimer's; this means that industry is likely to lower their future investments in antimicrobials in the coming years. To clarify, Wolkowski laid out a pharmaceutical company's portfolio perspective in making investment decisions, which can come down to investing in a novel antimicrobial to combat AMR versus pursuing an oncology indication versus a rare disease for which there are

no existing treatments. While the need for novel antimicrobials is clear from the perspective of patients and rising rates of AMR, the uncertainty related to the return on investment of antimicrobials and the current commercial landscape discourages investing in them, she said. In fact, Wolkowski said that investments in antimicrobials have demonstrated a negative return of one-eighth of the weighted average cost of capital. She agreed that there is a need to not only implement a mechanism to keep the economics neutral but also establish up front that pull incentives will be available several years into the product life cycle.

Kfoury highlighted that in hopes to address some of these issues, FDA set out a few initiatives with the potential to improve net present values of antimicrobial products, including a licensing structure and the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD). The LPAD program allows for expedited approval of antimicrobials that are designed to treat life-threatening infections in limited populations with unmet needs.[5] Though specific details are forthcoming, Kfoury argued that a combination of these and other ideas put forth by FDA can be valuable to shaping different types of models that can apply to different companies as they evaluate their portfolio investments at various stages of antimicrobial R&D.

Kimberly Thompson, president of Kid Risk, Inc., asked panelists to comment on the idea of limited trust and understanding among industry and health systems on the value of medical products, and specifically what happens when the market appears uninterested in paying for the full value of the product. She cited MenAfriVac as a successful public–private partnership that was able to make an investment case for manufacturers by anticipating demand for the group A meningococcal conjugate vaccine and bringing a new product to market.[6] She noted that the anticipated demand may not be there for antimicrobials, yet the challenge is to overcome the "valley of death" in getting stakeholders to understand the full value of developing antimicrobials. Thompson wondered whether this involved brainstorming new incentives that best accommodate multiple stakeholders or rather, aligning the right incentives with the right stakeholders. She also noted that different country markets have different attitudes toward

[5] At the time of the workshop on June 12, 2018, a statement from FDA Commissioner Scott Gottlieb was released on FDA's efforts to foster discovery and development of new tools to fight antimicrobial-resistant infections. For more information on the LPAD program and other efforts, see www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm610503.htm (accessed August 20, 2018).

[6] MenAfriVac was the initiative funded by the Bill & Melinda Gates Foundation that developed a group A meningococcal conjugate vaccine for use in "meningitis belt" countries in sub-Saharan Africa; this product was the first internationally qualified vaccine developed outside of the mainstream pharmaceutical industry.

paying for innovations and asked panelists if this factors into development of products that are seen to be more globally oriented. For example, the United States is typically seen as a favorable market for innovations, so the United States may potentially be less interested in investing in products to address the needs of developing countries; in light of that, she wondered if other countries are inclined to step up in lieu of U.S. investments.

Cueni voiced his support for public–private partnerships and added that the rollout of bedaquiline was possible through such a partnership. Cueni cautioned about the difference between developing a vaccine against a single disease and tackling the larger issue of AMR, which requires a continuous supply of many antimicrobials and vaccines to tackle future resistance patterns. Developing these products will require trust, he said. He shared examples of willing collaborators in public–private partnerships, including the Global Antibiotic Research and Development Partnership, a joint initiative of WHO and the Drugs for Neglected Diseases Initiative, and other initiatives borne out of Wellcome Trust, as well as the German R&D Hub and the United Kingdom. According to Cueni, these stakeholders recognize that these partnerships are not sufficient to develop the number of products needed for the future, and thus new pull incentives are necessary in light of this shortfall.

Also responding to the question about trust among stakeholders, Schaper stated that solutions and incentives need to consider a balance of risks across both the public and private sectors. He reminded that a suite of incentives would help achieve this goal through the stages of product development. Schaper envisioned a level of trust where governments can establish a mechanism that would assure companies of incentives for successfully bringing a product to market that targets an established resistant pathogen.

Anna Vassall, professor of health economics at the London School of Hygiene & Tropical Medicine, asked about experiences with push and pull mechanisms in BRICS countries,[7] specifically related to new drugs targeting drug-resistant TB. She was concerned about countries that would be falling out of reliable donor funding eligibility for TB drugs, yet did not have adequate health systems and funds to invest in the drugs themselves (e.g., bedaquiline in South Africa). In response, Schaper referred to a distinction between TB and AMR—the effect of push incentives is limited for TB because the disease is not prevalent in developed countries, while antimicrobials are needed by developed and developing countries alike. However, he saw the potential for BRICS countries to combine their purchasing power to develop mechanisms that would stimulate R&D targeted at developing countries. He agreed that most BRICS countries face a particular challenge

[7] BRICS refers to the countries of Brazil, Russia, India, China, and South Africa.

for falling out of funding eligibility because the Global Fund and other development partners are focused on the highest disease burden and lowest country financing capability.

The discussion wrapped up with Ramanan Laxminarayan, senior fellow and director of the Center for Disease Dynamics, Economics & Policy, offering his perspective on several fundamental challenges he saw fueling the difficulty among industry to generate return on investments in antimicrobials. First, he noted that AMR is perceived as a continuous, long-standing problem, so there is no urgency to actively innovate or make any decisions that have not already been made. In addition, Laxminarayan believed that there is insufficient price signaling from industry of the future high costs of new antimicrobials to users. Thus, users or prescribers of antimicrobials such as physicians are not taking the appropriate steps to conserve existing cheaper products, which parallels the negative effect of cheap gasoline prices on fuel conservation, he said. Finally, Laxminarayan emphasized the challenge of feasibly delivering a new antimicrobial, even once it has been developed, to determine which of the billions of people who contract a bacterial infection every year will die from a resistant strain. He concluded that new antimicrobials alone are not sufficient to address AMR and that industry could provide more guidance and leadership to "owning the problem."

Cueni agreed that other interventions are needed to complement antimicrobial development, and mentioned the AMR Industry Alliance is an example of cross-sector collaboration between private companies from the pharmaceutical, diagnostics, and biotechnology industries. He further commented on Laxminarayan's observations by illustrating the situation of bedaquiline. Cueni argued against recent proposals to license bedaquiline for TB treatment, stating such licensing would lead to inappropriate use of the drug. He added that TB's current stewardship mechanism of providing access to bedaquiline only from Global Drug Facility certified hospitals would not be applicable to other antimicrobials. However, Cueni highlighted efforts from GlaxoSmithKline, Novartis, and Pfizer to experiment with remuneration systems for sales representatives that reward for educating appropriate use rather than maximum sales. Cueni concluded with the need for industry to expand the discussion beyond human use of antimicrobials to include livestock and other industries. He mentioned that the AMR Industry Alliance had begun addressing the issue of environmental discharge related to antimicrobial production, particularly in China and India, and stated that industry response will require a One Health approach. He also highlighted the importance of transparency, not only among industry, but also for consumers who have to make decisions about buying food that has been exposed to antimicrobials.

8

Reimagining Sustainable Investments to Counter Microbial Threats

Session III, part A, examined ways to invest in sustainable solutions to combat microbial threats globally and in resource-limited settings. The session was moderated by Peter Sands, executive director of The Global Fund to Fight AIDS, Tuberculosis and Malaria. The session featured two presentations: Dean Jamison, professor emeritus in global health at the University of California, San Francisco, presented on the economics of international collective action to control microbial threats, focusing on the landscape of development assistance for country-specific and global health functions. Tania Zulu Holt, partner at McKinsey and Co., discussed economic bottlenecks in delivering medical products across Africa and the role of human-centered costing to ensure supply chain sustainability in resource-limited settings.

ECONOMICS OF INTERNATIONAL COLLECTIVE ACTION TO COUNTER MICROBIAL THREATS

Dean Jamison, professor emeritus in global health at the University of California, San Francisco, began by describing two realms of decision making brought about by international aid that aims to counter microbial threats: country-specific decisions by national governments and international collective action by global institutions. The two are interrelated and often part of a two-stage decision process, since national governments respond with resource allocation decisions based on aid disbursement and policy decisions of international agencies. Jamison described the potential issues of the two-step process of aid flow and recalled Lawrence H.

Summers's remarks on fungibility of aid (see Chapter 2). For example, once a donor allocates $10 million designated for tuberculosis (TB) control to a country, the country's government then responds by using donor funds on TB control but potentially reallocating its domestic TB budget elsewhere in the health sector or outside of health altogether.

Decision Making About International Aid for Health at the Country Level

As for decision-making dynamics within a national government, Jamison described how health investment decisions are made. He specified that ministries of finance are often the ones responsible for allocating funds. When making such decisions, he said, ministries of finance are concerned with identifying the resource needs, weighing the specific value of different kinds of investments in activities such as pandemic preparedness to their country, and determining what fraction of the value of that investment will fall outside of the country. He argued that ministries of finance tend to be primarily concerned with maximizing the fraction of funds that will remain in the country.

Jamison mentioned four broad motivations of international aid agencies to influence decision making in recipient countries. First, he noted the aid agencies may be motivated to ease resource constraints. For the poorest countries, he said easing resource constraints is the primary goal of aid, but for middle-income countries where the goals shift, the issue of fungibility surfaces more prominently. Second, Jamison said aid flow has effects on national prices and incentives faced by governments when making budgetary allocation decisions, noting that incentives may change the ease of conducting certain activities because of the addition of donor funds. He added that the third motivation may be to change the information environment. When aid is done well, he clarified, a substantial amount of technical information and knowledge learned in one country or from a scientific community is transferred to another country. Finally, he noted that the international system adopts shared risks facing individual countries when donor agencies provide aid.

Country-Specific Versus Global Functions in International Aid for Health

Jamison explained that there are functions of international aid for infectious disease management that can be divided into two categories. One is country-specific functions that strengthen national disease control and health systems, and the other category is global functions that aim to meet global goals, such as those supporting core global public goods (e.g., research and development [R&D]), managing cross-border threats (e.g., outbreak and antimicrobial resistance response), and fostering leadership

and stewardship. Currently, country-specific investments are the predominant way development aid for health is used (see Figure 8-1). He specified that the focus of investments for country-specific or global functions are different in low- and middle-income countries versus high-income countries. For example, the majority of donor funds for country-specific functions in low- and middle-income countries are focused on financing health services delivery, whereas in high-income countries they are focused on training health workers from low- and middle-income countries. He added that investments for global functions in low- and middle-income countries assist with national efforts in transnational activities, such as pandemic preparedness. In high-income countries these investments also target management of cross-border externalities, as well as global public goods, leadership, and stewardship initiatives.

Jamison pointed to some of the problems of investments for country-specific functions. He reiterated the disposition of some finance ministers, who would be reluctant to invest in domestic preparedness activities if

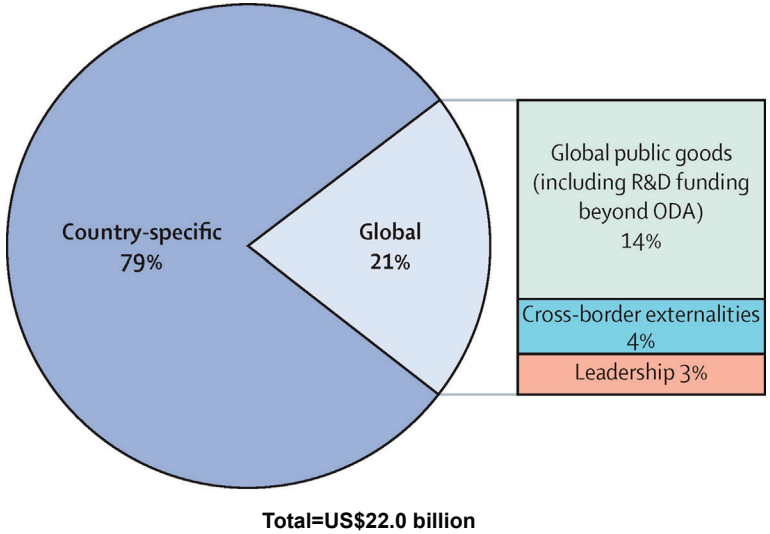

FIGURE 8-1 The distribution of health aid across country-specific and global functions in 2013.
NOTE: ODA = official development assistance; R&D = research and development.
SOURCES: Jamison presentation, June 13, 2018; Schäferhoff et al., 2015. Reprinted from The Lancet, Vol. 386, Schäferhoff, M., S. Fewer, J. Kraus, E. Richter, L. H. Summers, J. Sundewall, G. Yamey, and D. T. Jamison, "How much donor financing for health is channelled to global versus country-specific aid functions?", Pages 2436–2441, Copyright (2015), with permission from Elsevier.

the value of the investment is seen as more beneficial on the transnational level and particularly if external aid will make up the difference. Jamison also highlighted the spectrum of aid fungibility among the country-specific functions, where pandemic preparedness is less fungible than health system strengthening and disease control investments. On the other hand, he said aid for global functions toward R&D of health tools and managing cross-border externalities are considered nonfungible.

To conclude, Jamison drew attention to two main gaps in the $22 billion in overall annual health aid across country-specific and global functions. First, he said existing international systems are likely preventing donor funds from effectively benefiting the poor in middle-income countries; the more fungible the aid funding, the less likely it is to reach the poor. Thus, funding more R&D and other global functions as opposed to country-specific functions may be a better strategy to ensure that donor support reaches poor individuals in middle-income countries more directly (Schäferhoff et al., 2015). In addition, Jamison prioritized several key global functions that continue to be underfunded, including development of better drugs and vaccines for TB and influenza pandemic preparedness. Shifting aid away from country-specific purposes toward these global function priorities is what Jamison believes economic analyses is increasingly pointing toward as a desirable path.

OVERCOMING ECONOMIC BOTTLENECKS IN DELIVERING MEDICAL PRODUCTS TO ADDRESS MICROBIAL THREATS ACROSS AFRICA

Tania Zulu Holt, a partner at McKinsey and Co., presented on the realities she has observed on the ground of supply chain bottlenecks in delivering medical products across Africa. She began with a vignette of a nurse named Amina in Nigeria and her struggle to provide vaccination, reproductive health care, and other services at clinics because of inconsistent access to medical products (see Box 8-1). Holt noted that this portrayal is not representative of the country or continent but provides context for the complicated layers of supply chains that can run through one facility, which is magnified to thousands of facilities nationally and relies on dozens of data systems tailored to different donors.

Holt described how medical products are often delivered through vertical, disease-specific supply chains that operate through different mechanisms, funding streams, and resources (see Figure 8-2). She noted that different commodities can be delivered twice per year, three times per year, quarterly, bi-monthly, or monthly. While some products pass through state and local government warehouses, others bypass these levels and are delivered directly to clinics. According to Holt, this leads to multiple inefficien-

BOX 8-1
Hidden Economic Costs and Bottlenecks for Amina Across Supply Chains

Holt portrayed Amina as a nurse working in rural Sokoto in northern Nigeria, where she sees 50 to 100 clinic patients daily. One of Amina's persistent challenges is receiving commodities on a regular basis, which results in her sometimes turning away patients. For example, she can only provide vaccines once per week. In addition, Amina does not have a functional refrigerator for vaccine storage in her facility, which forces her to add commute time and delay seeing patients, in order to pick them up from a larger health facility. The costs for bus transportation to pick up vaccines are paid out of pocket by Amina. Though Amina has to return unused vaccines to the larger health facility at the end of the day, she is likely tired from problem solving the difficult issues that had arisen from that day and discards them without cold storage onsite.

As part of providing reproductive health services, Amina faces similar challenges when she is required to attend monthly offsite meetings and share relevant data on her patients. These meetings attempt to quantify commodities received and dispensed to different patients, but there may be a potential frustration with time spent and inefficient data tracking as Amina is most of the time receiving the same amount of commodity every month.

The situation differs for Amina's delivery of HIV and tuberculosis (TB) commodities, malaria nets, and essential medicines. HIV and TB commodities are consistently delivered through donor supply chains and tracked by a computerized system. The nongovernmental malaria campaigns deliver nets once or twice a year and tend to engage more with the communities. As for essential medicines, Amina has not received a shipment from the government for years. Along with her fellow nurses, she contributes her own money to an informal revolving drug fund to purchase substandard medicines. Although these medicines are meant to be offered for free at government run clinics, she must sometimes charge patients for visits in order to replenish the fund or turn away patients.

SOURCE: Holt presentation, June 13, 2018.

cies and economic bottlenecks that lead to significant costs and barriers to effective service delivery. Frontline health workers, like Amina, are expected to manage these overlapping systems by devising their own unique coping strategies in order to deliver health services.

Human-Centered Approach in Costing Medical Product Supply Chains

Holt described the high costs typically accounted for in systematic planning of medical product delivery to health facilities, including the costs associated with procurement, warehousing, and delivery. She argued that

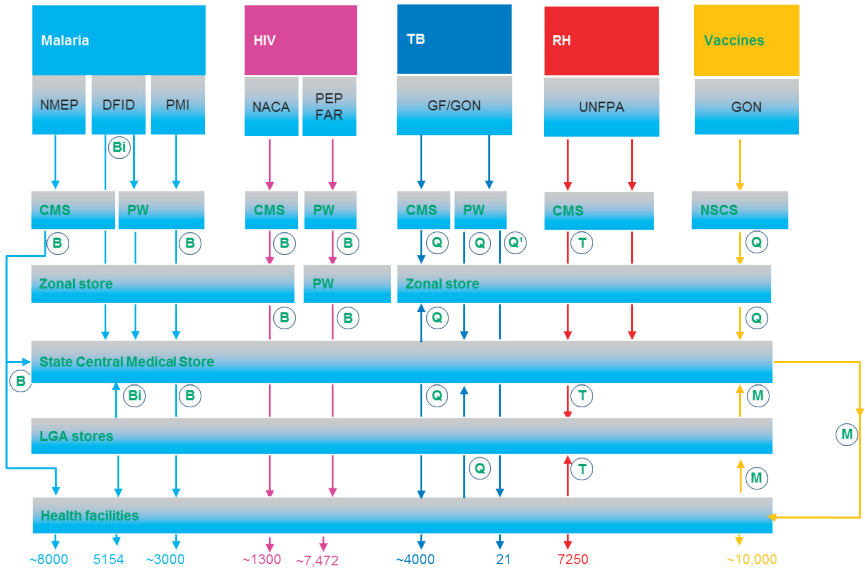

FIGURE 8-2 Multiple overlapping supply chains for medical products in Nigeria.
NOTES: Medical products for malaria, HIV, tuberculosis (TB), reproductive health (RH), and vaccination are delivered through various pathways through the Nigerian health system.
B = bi-monthly; Bi = twice per year; CMS = Central Medical Store; DFID = U.K. Department for International Development; GF = The Global Fund to Fight AIDS, Tuberculosis and Malaria; GON = Government of Nigeria; LGA = local government area; M = monthly; NACA = National Agency for the Control of AIDS; NMEP = National Malaria Eradication Program; NSCS = National Strategic Cold Store; PEPFAR = The President's Emergency Plan for AIDS Relief; PMI = President's Malaria Initiative; PW = private warehouse; Q = quarterly; T = three times per year; UNFPA = United Nations Population Fund.
SOURCE: Holt presentation, June 13, 2018.

this approach ignores the last mile costs, which are often out-of-pocket payments made by nurses, doctors, and health extension workers who travel to higher-level facilities to pick up supplies. Additionally, the opportunity cost for patient care is unaccounted when skilled health care workers are traveling to get medical supplies when they could be seeing patients. Another cost occurs when patients visit a clinic for health services and are turned away because of stock outs. These patients also spend money to travel to these facilities in addition to time and wages that they forgo by

missing work. Holt stated that in higher levels of government, supply chain managers and program officers often use their own resources to sponsor operational funds or to coordinate logistics since government funding is not necessarily released to align with supply chains. According to Holt, these "human-centered costs" are not adequately accounted for in supply chain evaluations and require looking beyond on-the-surface warehousing and fuel costs. She argued that this oversight leads to underperforming systems, supply shortages, and other inefficiencies.

Potential Strategies for Reducing Economic Bottlenecks

Holt described four strategies to reduce economic bottlenecks in the medical product supply chain, despite the challenge in distilling the exact costs of integrating supply chains and investing in other potential solutions. Firstly, zero-based budgeting, where all economic costs are reevaluated bottom up and justified for each new time period, can help to better account for human-centered costs and provide a more accurate baseline in countries and remove hidden costs. Second, she noted that there are many inefficiencies associated with multiple vertical supply chains for warehousing and last mile delivery, and that these should be better integrated to reduce costs. Outsourcing of supply chain operations to the private sector is another strategy that can also increase efficiency, reducing costs by 5 to 15 percent, Holt said. She acknowledged that outsourcing is not an easy option for governments to consider, but it can overcome many last mile economic bottlenecks by distributing commodities directly to facilities. The fourth strategy she highlighted is investing in better, single platform data systems to reduce waste and improve quantification at the facility and central levels.

Holt provided an example of cost savings on integrating last mile delivery of health commodities for potentially addressing these bottlenecks. From a McKinsey analysis of overlap in last mile delivery across 1,121 primary health facilities and 5 donor programs in a Nigerian state, Holt noted that only 12 percent of facilities were delivering the full complement of services being evaluated. However, the calculated annual savings could potentially reach $10.6 million if full last-mile integration of health commodity supply chains across the various service delivery programs were applied to the entire country (see Box 8-2).

Holt concluded by highlighting the need to invest in country-level supply chain systems that can be leveraged for both routine services and for future emergencies. While international donors are spending billions of dollars on health commodities in Africa, she noted that there is not nearly enough spending on product delivery. Conversely, the pharmaceutical industry spends between 4 and 11 percent of their commodity value on supply chain, she said. Holt argued that if between 2 and 3 percent of

BOX 8-2
Selected McKinsey & Co. Findings on Cost Savings (in U.S. dollars) on Last Mile Delivery of Health Commodities Across 1,121 Primary Health Facilities in a Nigerian State

1. Up to 16 million naira ($80,000) of the combined annual cost of delivery in the state can be saved by consolidating last mile delivery to those facilities offering all five program services (reproductive health, HIV, tuberculosis, malaria, and routine immunization).
2. Integrating last mile delivery for facilities with three- and four-program overlap could save an annual total of 76 million naira ($380,000).
3. Full delivery integration in the state could save 120 million naira ($605,000) annually.
4. Extrapolating nationally, full last mile integration could save 2.13 billion naira ($10.6 million) annually.

SOURCE: Holt presentation, June 13, 2018.

health commodity value in Africa was directed toward this goal, it would equate to nearly $1 billion available to strengthen supply chains and interagency collaboration.

DISCUSSION

The discussion began with two questions on health systems strengthening, focusing on country ownership and cost-effectiveness of health interventions. Kimberly Thompson, president of Kid Risk, Inc., asked about the difficulties of tracking fungible health systems investments and the need for more transparency to understand the full costs embedded in systems, in order to build local capacity. She inquired about holding countries accountable for service delivery performance across disparate national health systems. Jamison responded that despite the traction behind health systems strengthening, aid is still predominantly spent on disease-focused programs since broader systems-focused programs are more difficult for donors to evaluate and attribute health outcomes to their funds. In his opinion, country-specific efforts that are tightly focused on health objectives such as mortality reduction, will preserve accountability and avoid the fungibility issue.

Katharina Hauck, senior lecturer at the Imperial College London, observed the scope of the McKinsey analysis of primary health facilities in Nigeria and asked about the methodological challenges of evaluating the cost-effectiveness of health systems strengthening initiatives, particularly

with the economies of scope for clinics delivering multiple services. Holt highlighted the need for more cost-effectiveness analyses at the country level despite the challenges, in order to evaluate current inputs into health systems, performance level, and benefits from investments in one area over the other. Without understanding the trade-offs, she said it would be difficult for payers within the system to direct program design and make future investments. On the issue of aid accountability, Holt commented that some countries are too fragile to consider health systems strengthening initiatives, while others are economically developed enough to aim for service delivery beyond traditionally donor-funded diseases. In this second category of countries, there is an opportunity to engage and support them in transitioning from vertical programs to a systems approach though there will be challenges with accountability, she said.

The discussion transitioned to specific questions about Jamison's presentation. Jonna Mazet, executive director of the One Health Institute at the University of California, Davis, asked about the relative benefits of country-specific versus international collective action approaches and wondered about the potential for hybrid programs. For example, U.S. Agency for International Development programs invest in both global functions, such as R&D, with country-specific aims to build local capacity for national pandemic preparedness. Jamison responded that the hybrid program she described was the political "sweet spot" of funds advancing a global public good while actually being spent within countries. He noted that spending to advance international collective action such as pandemic preparedness can be done at any level—within low- or middle-income countries, high-income countries, or in agencies.

Finally, Mukesh Chawla, advisor for health, nutrition, and population at the World Bank, asked Jamison how to better bridge the political and economic incentives behind investments for global public goods in conversations among countries, donors, and the international community. Jamison noted that a major motivation yet challenge of aid is translating international experiences to local contexts. Jamison stated that both politics and economics are important considerations, but that the international community "often has little to say about domestic politics and a great deal to say about economics. I think we, on the outside, should probably focus on the economics." Similarly, he said while health systems are unquestionably important, they are domestic issues, about which the international community does not always have robust knowledge and understanding. Rather, the international community has the technocratic capacity for disease control such as for HIV and TB, and some supply chain management issues that could bring value to countries, he said. Jamison argued for the international community to focus on areas where it has clear capacity and knowledge to bring value to countries.

9

Looking to the Future: Potential Next Steps for Using Economics to Manage Microbial Threats

Session III, part B, of the workshop considered potential next steps for applying economics to manage microbial threats. The session was moderated by Suerie Moon, director of research at the Global Health Centre of the Graduate Institute of International and Development Studies, Geneva. During the session, workshop organizers asked forum members, speakers, and attendees to break into three groups organized around three themes. A member of the Forum on Microbial Threats or a speaker of the workshop was assigned to moderate and report on the discussions that emerged from each breakout group. Peter Daszak, president of EcoHealth Alliance, reported on modeling the economics of emerging infectious diseases (EIDs) (group 1). Ed Whiting, chief of staff and director of policy at the Wellcome Trust, focused on creating a sustainable economic model to stimulate research and development (R&D) of antimicrobials (group 2). Anas El Turabi, Frank Knox fellow in health policy at Harvard University, reported on incentivizing national governments to invest in preparedness (group 3). This chapter summarizes some of the challenges and suggested actions that emerged from the group dialogue, including reflections by workshop participants during the final synthesis discussion of the workshop. The ideas presented herein should not be construed as collective conclusions or recommendations, and do not necessarily represent the views of the workshop participants, the forum members, or the National Academies of Sciences, Engineering, and Medicine.

MODELING THE ECONOMICS OF EMERGING INFECTIOUS DISEASES

Peter Daszak, president of EcoHealth Alliance, reported for the breakout group on modeling the economics of EIDs. He stated that the group discussed approaches to improve these types of models through incorporating behavioral responses to fear associated with outbreaks as well as filling in knowledge gaps in EIDs, and communicating about models more effectively.

Potential Next Steps to Improve Economic Models of Emerging Infectious Diseases: Incorporating Behavioral Responses to Fear

Daszak stated that many members of the group spoke about the knowledge gaps in understanding the economics of fear associated with outbreaks. Wherever on the spectrum of fear—from excess to lack of fear, he said, different levels of fear at different population levels, including the household, national, and global levels, at different times can affect the course and the costs of an outbreak. The level of fear may also depend on the type of disease, as experienced in Ebola in the United States (high levels of fear) versus Zika (low levels of fear). Therefore, collecting data to gain a deeper understanding of these factors is crucial, he said.

While gathering such data on fear would be helpful, members of the group also recognized the challenge to incorporate this kind of data into models. Some participants pointed to the challenge of synergizing qualitative and social science data into predictive infectious disease models and to model social and biological systems at the same time. He added that data on human behavior, which tend to be context specific, are difficult to incorporate into larger scale, population-level models. For example, not only can individual responses to a single outbreak differ within the same region, but also data are specific to different types of outbreaks (e.g., short-term versus long-term endemic outbreaks and antimicrobial resistance [AMR]). Many members discussed that a key challenge is to identify which existing datasets and findings could be generalizable for global models.

Some types of models, Daszak said, may be more amenable to incorporate such behavioral data. Members of the group discussed the possibility of using game theory and stochastic dynamic approaches, which could incorporate the effect of fear and trade-offs. Other participants thought that behavioral economics could illuminate individual preferences with respect to risk, time, and altruism associated with an outbreak. System dynamics models was another type that a few members thought could provide an intermediate approach between behavior-rich analyses and oversimplified economic models that lack behavioral parameters.

Daszak explained that several members of the group identified stakeholders who should be involved in developing these types of economic models to ensure the behavior component is included. These stakeholders include people with expertise in public health and outbreak response, insurance, economics and finance, trade and travel, and social sciences. Specifically, he noted that outbreak responders could be involved in surveys to evaluate how fear changes over the course of the epidemic. He stated that social scientists could be particularly helpful if they are able to determine what data are generalizable for use in models from the context-specific datasets they usually collect.

Other Potential Considerations: Filling in Additional Data Gaps and Effectively Communicating About Models

Besides the fear factor, Daszak reported on other ways to improve these types of models. He said that the group discussed the lack of knowledge on the geography of risk to identify disease reservoirs and regions with potential for EIDs. Daszak noted that geographical disease data can shift rapidly when there are changes in the environment. Some of the group members argued that the gap in geographical data can make it difficult to set up clinical trials to control outbreaks at the right place and time. Additionally, Daszak reported that there is a knowledge gap in understanding the economic damages of EIDs. Some participants suggested that more objectivity and clarity is needed with regard to cost measurements that seem to range from millions to trillions of dollars. Daszak also pointed out to the importance of incorporating the issue of temporality more carefully into models. To better understand infectious diseases that are slow moving or infrequent, modelers could possibly learn and adapt their models from other fields such as climate change, he said.

Finally, Daszak shared the group's discussions on the difficulty of communicating the results of models to policy makers. He noted that while some policy makers might rely too much on models without understanding their underlying uncertainty, others might suffer from "model fatigue," and believe that models lack value. Daszak emphasized that the equations underlying models could be shared, but the models should then be described to decision makers in a way that better highlights both their usefulness and uncertainty.

STIMULATING RESEARCH AND DEVELOPMENT FOR ANTIMICROBIALS

Ed Whiting, chief of staff and director of policy at the Wellcome Trust, shared insights from the breakout group that discussed how to stimulate

R&D of antimicrobials. Without incentives and resolving the market failure issues, many companies are likely to withdraw from antimicrobials over the years. With the aim of increasing the number of available antimicrobials to fight infectious disease threats, the group discussed approaches to spur drug development including issues related to incentives, and other considerations including filling data gaps and strengthening coordination between national and global level efforts.

Potential Next Steps to Stimulate Antimicrobial Development: Addressing Challenges of Incentive Design

Whiting shared that many of the participants recognized the need for incentives, particularly pull incentives to accelerate antimicrobial development. He suggested, however, that the specifics on what pull incentives might entail continue to be nebulous. Some participants acknowledged that even though the specific incentives needed by different types of companies and national markets would be distinct, a general degree of consensus on what the incentives may look like would be useful to push this field forward. Whiting noted that the work of the International Federation of Pharmaceutical Manufacturers & Associations has moved the industry closer toward a consensus on this issue.

In terms of specific incentives, the group debated the use of reimbursement incentives and market reward incentives. Many of the members of the group thought that while reimbursement reforms would be helpful, they are not sufficient. Furthermore, a few participants highlighted that cost-plus models may be a dead end, as they do not take into account the riskiness of antimicrobial drug development.[1] Whiting said that many members believed that market entry awards, paid for by transferable exclusivity and intellectual property–based incentives, are critical as well. With this recognition, a member noted that legislation had been recently introduced in the United States to provide for a 1-year transferable exclusivity voucher to incentivize the development of new antibiotics, vaccines and other medical products that could mitigate the effects of AMR.[2]

To accelerate progress in this area, Whiting noted the need to help policy makers make well-informed decisions and boost political will through transparent information sharing. Some members pointed out that policy makers are confronted with challenging questions and face difficulty in

[1] A cost-plus model makes products from R&D available at the cost of manufacture plus a small margin to try to ensure the sustainable production of the products.

[2] As of June 2018, U.S. Representatives John Shimkus (R-IL) and Tony Cardenas (D-CA) introduced the Re-Valuing Antimicrobial Products Act of 2018 (REVAMP Act), which also includes provisions on stewardship and the development of an innovation fund for unmet antimicrobial R&D needs.

understanding the complex and multistage R&D process (e.g., financial flows, intellectual property flows, and licensing arrangements), which stalls progress in the discussion on incentives. Drug noninferiority studies is a particularly challenging issue that is debated among the companies and policy makers. To approve new antimicrobial drugs, he said policy makers have to grapple with tough questions:

> Will new drugs be better? If we are going to put more money into this, how can we get to a place where drugs are brought through the regulatory pathways quickly, but at the same time, are going to be good enough to justify the extra investment that would be made from either a public or payer purse?

Policy makers must balance the cost of higher drug prices against other AMR interventions, Whiting added, underscoring that policy makers as well as decision makers in private-sector companies work with "a finite pie." That is, if the pie is cut one way and makes one part bigger, another part of the pie will inevitably be smaller; therefore, equipping decision makers with information to make the best choices is a critical yet grand, "human" challenge, said Whiting.

To better inform policy makers, a member suggested that companies could commit to providing the profit margins they need and outline what the market rewards need to be in order to dispel concerns about unjustified rewards. Another member suggested that economists need to be more involved in building the case on why governments should invest in incentives. Others pointed out that this issue should be seen as a risk-shared benefit and not count only on governments and the industry to bear the burden to solve the problem.

Other Potential Considerations: Filling in Data Gaps and Coordinating National and Global Efforts

Whiting reported that the group discussed data gaps in this field. Some members argued for the need of real-time monitoring for the development of new antimicrobials, incentives, and degree of access to antimicrobials. Others called for the incorporation of patient voices in filling knowledge gaps related to AMR. He specified that adding a human face to the issue could bring more trust and empathy to the debate over incentives. Whiting reported that a few group members also suggested that experiences from outside the human health sector could direct efforts aimed at understanding what further measures and analyses could be examined to enhance conservation of currently available drugs. He noted that the plant community has demonstrated lessons related to the preservation of fungicides,

and the agricultural community has led efforts to reduce antimicrobial use for animal husbandry.

As more data are identified, he said, some members recognized the importance of data sharing. He clarified that sharing means not only the cost of research and data, but also what the research and interventions are achieving and not achieving, and the new products that are in the pipeline. Whiting noted that The Pew Charitable Trusts has helped to partially fill these gaps by tracking the pipeline of antimicrobials in development. This type of sharing and real-time monitoring could build transparency and trust and positively affect other global health challenges, he said.

Finally, he emphasized the need for better coordination between national and global efforts on AMR. Some group members thought there needs to be more opportunities and support for countries to engage in national experiments and trials in R&D of antimicrobials that would allow them to succeed in this arena. Whiting also noted the importance of documenting and linking these national experiments to global efforts in AMR. He stated:

> If we have national-level experiments, we need to have clarity about how global coordination on stewardship and access would work to ensure that if you are producing something new that is going to attack infections that happen all around the world, it can be made available to people who need it most in the simplest way possible.

Whiting suggested that such organizations as The Global Fund to Fight AIDS, Tuberculosis and Malaria and the United Nations Children's Fund could play a role in ensuring access of antimicrobials to populations who need it the most.

INCENTIVIZING NATIONAL GOVERNMENTS TO INVEST IN PREPAREDNESS

Anas El Turabi, Frank Knox fellow in health policy at Harvard University, reported for the breakout group focused on incentivizing national governments to invest in preparedness. El Turabi stated that the group discussed specific strategies including synergizing preparedness investments with existing health expenditures and connecting disease risk to foreign direct investment. Crosscutting considerations were also discussed including enhancing local capacity and political will.

Potential Next Steps to Invest in Outbreak Preparedness: Synergizing with Existing Health Expenditures and Linking Disease Risk to Foreign Direct Investment

El Turabi reported that many of the group members recognized the current language on outbreak preparedness is not working to convince governments to invest in this issue. Some members pointed out that governments still do not understand the actual risks of infectious disease outbreaks, and even if they do, they recognize that preparedness is a long-term issue that may not coincide with political terms and cycles and is not worth investing in. Preparedness is a long-term issue that requires short-term investments, El Turabi stated, so unless this fact is not made more salient to governments and the development partners, preparedness efforts will continue to be inadequate.

To convince policy makers, many group members discussed that outbreak preparedness could be connected to investments that are needed in the short term. Specifically, technical assessments on outbreak preparedness could align with short-term, local priority needs, El Turabi said. Rather than start with a blank piece of paper to understand the future cost of pandemic and pandemic preparedness investments, some participants discussed that existing initiatives that already invest in disease control activities could be leveraged. He noted that the group discussed if it were possible to calculate the added spend, or the built-on expenditure that would be needed for an existing health program to also start meeting some of the specific day-to-day preparedness functions required by the Joint External Evaluation (JEE). As an example, he noted that The Global Fund to Fight AIDS, Tuberculosis and Malaria could make a variety of preparedness investments that synergize with its disease-specific programs. Building on existing health expenditure streams would require a different type of economic and cost analysis than what has been previously done, but he said it could be an important shift to encouraging governments to invest in pandemic preparedness.

Another strategy raised by some participants involves the private sector, which can be substantially exposed to economic risks from infectious disease threats yet are often excluded as partners from these conversations. A few group members discussed that connecting the effects of outbreaks on commercial and investment activity, particularly foreign direct investment and country credit rating assessments, could motivate governments to pay more attention to outbreak preparedness to protect their self-interests. This could also mobilize the private sector as a partner, holding governments who do not invest in preparedness accountable for their inaction. One member suggested that a potential avenue for analysis could be to assess the response in foreign direct investments in Paraguay, as a result of it declaring

malaria elimination. However, several members of the group cautioned that this tactic could work for countries where foreign direct investment is a major political lever; thus, this may not work for low-income countries. For these situations, the Global Heath Security Index,[3] which is in the process of being created by the Nuclear Threat Initiative, Johns Hopkins Center for Health Security, and Economist Intelligence Unit, might be particularly helpful, El Turabi said.

Other Potential Considerations: Strengthening Local Capacity and Political Will

El Turabi highlighted crosscutting considerations that could incentivize national-level preparedness. Many members called for more microlevel data at the local level to refine the technical assessments of outbreak preparedness and help local and country decision makers evaluate preparedness investments. A few members also called for the need for better data to understand the logic underlying how policy makers perceive issues and make choices to help frame the argument for the economics of EIDs and outbreaks at the local and national level. He also commented on the need for greater local capacity development and the importance of local and national government partnerships to ensure sustainability of preparedness efforts. He stated that the recent establishment of the Africa Centers for Disease Control and Prevention was a positive step forward in the development of regional public health capacity. He hoped these types of investments in public health infrastructure also allow the capacity to perform economic analyses.

Finally, El Turabi emphasized the importance of political will. Some group participants had raised the need to capitalize on the political interest that typically follows outbreaks to build sustainable solutions that become engrained in institutions in a way that outlives political leadership. As a success story, a group member cited the severe acute respiratory syndrome epidemic in China, which was followed by a variety of improved surveillance initiatives and sustained workforce changes that conferred long-term, broader health benefits (Braden et al., 2013). El Turabi concluded:

> If we can find ways to convert those short, intense bursts of political interest into something that develops new structures and capacity of preparedness in bureaucracies, what we might actually find is there are functions and capacities to demonstrate these arguments [on the value of preparedness] that build up over time and move us in the right direction.

[3] The Global Health Security Index will assess countries' capabilities to prevent, detect, and respond to high-consequence biological events. This index will rely on publicly available data and be measured by an independent entity. The first Global Health Security Index is expected to be released in 2019.

SYNTHESIS AND GENERAL DISCUSSION

After the panelists reported on the discussions that emerged from the breakout groups, several workshop participants provided reactionary comments during the final discussion of the workshop. The final discussion focused on three areas: communicating about and building models, filling in data gaps, and addressing issues related to R&D of drugs to counter microbial threats.

First focusing the discussion on communicating about models, Jay Siegel, former head of scientific strategy and policy for Johnson & Johnson, agreed with Daszak's summary on the challenges of presenting models, especially to avoid the dual risks of overconfidence in and underacceptance of economic models among decision makers. From Siegel's perspective, it is not only important to communicate uncertainty in models in a way that users understand, but also to convey the sensitivities around changing assumptions in models. He argued that it is key to understand the assumptions driving a model. A shift in assumptions can lead to minor or massive changes in results, so Siegel said communicating those would help decision makers interpret results more accurately and increase their confidence in the model's utility.

Carlos Castillo-Chavez, professor of mathematical biology at Arizona State University, also illustrated the importance of communicating models, even within research communities, with an example of Nobel Laureate Ronald Ross's discoveries on mosquito control effects on malaria's incidence at the population level. Ross had devised conceptual models that he shared in his publication's appendix, detailing his questions, descriptions, conclusions and their underlying equations, so that other researchers and the broader community could learn from those models (Ross, 1915). As more types of models are being applied to the field of public health, Castillo-Chavez said this type of communication is critical.

Martin Meltzer, senior economist and distinguished consultant at the U.S. Centers for Disease Control and Prevention, elaborated on communicating realistic expectations of model results and the role of proxies. In communicating with the multidisciplinary stakeholders involved in infectious disease response and pandemic preparedness, Meltzer asserted that simple models could be better to avoid creating "black boxes" of information. He noted that although a simple model would not capture all of the social interactions and utilities that policy makers in particular are interested in capturing, some proxies for human behavior, such as compliance to public health measures, could be programmed as a variable changing over time in a simple model, while capturing multiple aspects of behavior. Meltzer posited that the value of models to public health policy is not from actual number results but rather from identifying which variables will produce changes that decision makers should consider priorities. Because pub-

lic health responses can take broad approaches, he argued that improved accuracy of models do not necessarily improve policy, while getting a better ballpark view may be more important for improving models as prioritization tools for decision making. He emphasized that models should be used as a teaching tool.

Castillo-Chavez agreed that models can be used for teaching, but he added they can also reveal a way of understanding science, whether that means to understand the interactions of macro- or micro-level phenomenon. As Meltzer observed, Castillo-Chavez also pointed to the problem of thinking about models as a direct reflection of reality. Models that aim to do that tend to become complicated, and can be more complicated than reality, Castillo-Chavez said; consequently, he added, they tend to not necessarily increase understanding of the real world. He reiterated that models have to be tied to specific questions. He said, "There is no model that is right, but it can help us understand a question. In particular, it adds understanding or generates new hypotheses."

El Turabi also emphasized that models should be fitted for their purposes, whether to predict the probabilities of future outcomes or inform policy decisions, and should focus on actual decision-making functions and needs. This requires concerted efforts to better understand the "customers" of these models, he noted, which include decision makers who allocate resources to manage microbial threats. He said that researchers need to understand the customers' inputs in the decision-making process and produce models that allow for analyses that will influence those inputs.

Daszak highlighted that there is a range of customers and vested interests that modelers need to tailor to. In global health, he said, customers of models can run the gamut of governments, drug companies, and insurance companies, among others. While there are a range of customers, Daszak posited that decision makers are the ultimate end users of these types of models, but modelers in academia might be developing a model to an interesting question that is not the exact question that the ultimate decision maker needs to have addressed. This mismatch, he said, may result in a problem because the decision maker wants to make decisions based on that model, which may not be appropriate. To avoid this from happening, he suggested that customers should engage with modelers to ensure that the appropriate models are developed. Daszak specified that customers could prepare requests for proposals to bring in modelers who can do work specific to their questions. He added that it is necessary for modelers to work with the customer in an iterative process that allows adaptation and refinement of models, in order to adequately answer key questions asked by the customers.

Mukesh Chawla, advisor for health, population, and nutrition at the World Bank, pointed to his experience managing their Pandemic Emergency

Financing Facility (PEF),[4] where he argued that precision in modeling is, in fact, crucial in certain situations, particularly for funding decisions. Chawla explained the facility holds $500 million, and when a qualifying outbreak reaches a threshold set by the World Bank, the insurance is triggered, and he is responsible for disbursing funds to resource-constrained countries based on certain formulas and parameters for disbursement. He illustrated the need for precision for PEF by laying out a case for modeling the probability of the event reaching a particular threshold, such as 100 deaths from Lassa fever. He said the modelers have to figure out how to model the probability that there would be Lassa fever anywhere in the world in the next year that gets to the level of 100 deaths; this is multiplied by the expected payout in order to arrive at the premium. Thus, a lack of precision by 0.1 percent probability can translate to multiples of millions of dollars at stake, according to Chawla. He reflected that to develop PEF, he was struck by the lack of development and accessibility of these models, with the exception of influenza models. He said, however, that the World Bank has been trying to incubate this kind of work and hoped that universities and development partners take the lead on socializing and demystifying these models for pandemic response, possibly mirroring how the automobile insurance industry has demystified the calculations for the probability of an individual's next automobile collision.

Anna Vassall, professor of health economics at the London School of Hygiene & Tropical Medicine, emphasized the importance of building capacity in mathematical modeling and health economics in low- and middle-income countries and remarked that not enough progress has been made in the past 20 years. She said the main challenge is that while efforts to build capacity are occurring, methods for models continue to change, and most modeling, which is still done in European universities, will be rolled out to countries as user-friendly models that ultimately undermine local capacity. Vassall urged the global health community to rethink their approach to modeling and learn from the mistakes from the health economics field. El Turabi concurred with Vassall on the risk of tools used by local workforces becoming irrelevant by the time that capacity is functional. El Turabi called for programs that cultivate more health economists and computational data scientists specifically for pandemic security and become mainstream in existing development activities.

The discussion transitioned to the need for more data, with El Turabi mentioning more efforts are needed to collect more microlevel data to make

[4] PEF is a quick disbursing financing mechanism that provides surge funds to enable a rapid response to a major infectious disease outbreak. For more information on PEF, see http://www.worldbank.org/en/topic/pandemics/brief/pandemic-emergency-facility-frequently-asked-questions (accessed August 16, 2018).

better economic cases to governments. He suggested the need to think through how to leverage and pull together existing datasets. The World Bank gathers a wealth of granular data, he added, but researchers could curate the data better and make the data more accessible to groups that are engaging in local level analyses. El Turabi also highlighted the lack of empirical data on causal relationships among investments, trade outcomes, and disease activity more broadly.

Nita Madhav, vice president of data science at Metabiota, focused on the specific gap of analyses in low-frequency, high-consequence events. She noted that analyses of infectious disease events are easier to conduct when there is data to inform it, such as for high-frequency events like influenza. For high-frequency events, she said there tends to be existing datasets where the disease is well characterized, especially in well-resourced areas and would encourage more types of analyses to be done leveraging the data. However, low-frequency, high-consequence events such as novel coronavirus outbreaks, which have occurred twice in the past 15 years, rely heavily on assumptions and limited datasets, Madhav said. Thus, to model these types of events, she stated that modelers have to make general assumptions and make the most of the scant data that are out there until more data are collected.

Daszak agreed on the insufficient data and weak analyses for sporadic disease outbreaks and mentioned that the response for emerging diseases is not focused on understanding in depth the drivers of its emergence, geographical origins, and triggers at various points of disease spillover that may lead to global spread—all of which have different parameters involved in modeling. Daszak said that there are lessons to be learned from more common individual spillover events, which are generally poorly understood but ultimately feasible for data collection. He suggested for groups to gather more data on emerging diseases in order to stop them before they reach pandemic potential, not only in other countries, but also in the United States where the focus can be on a better understanding of where foodborne infections and drug-resistant strains originate, for policy makers to allocate resources accordingly. Daszak emphasized that next steps should center on gathering different types of data to support modeling—both disease data on individual spillover events that will inform different scale outbreaks, and social and behavioral science data that can be generalized using appropriate proxies.

The discussion ended with a conversation about the economics and costing issues of medical products to counter infectious diseases. Vassall raised ongoing challenges she has observed with predicting the market price of tuberculosis (TB) drugs. To predict the market price, she said several difficult questions need to be addressed. For example, how might a new drug or regimen affect the health system costs, and how do these entities

interact with one another? How does spending on a new drug affect spending on other areas of health improvement? What is the opportunity cost of investing in TB drugs and forgoing other health interventions? And to what extent should other complementary health interventions be developed, whether that means drug susceptibility testing or the introduction of a new vaccine, and how does that affect drug pricing commitments? Vassall noted that there are not enough cost data yet to robustly model these questions.

Whiting commented on the role of industry in the world of AMR. He hoped that the pharmaceutical industry continues to generate and refine its consensus on the resources needed to develop new antimicrobials and make this consensus as public as possible. In doing so, he noted industry stakeholders and policy makers might have a better understanding of the decisions that need to be made. Whiting also added the need to have granular analysis on the choices decision makers face in order to provide them with more detailed guidance. Finally, he suggested that more information is needed in the areas of antimicrobial stewardship and access initiatives. He acknowledged the growing literature and community of practice in these areas and believed that it would help generate new solutions about the economic case of antimicrobials in the future.

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Closing Remarks

The workshop discussions over the 1.5 days allowed participants to understand some of the challenges and opportunities of using economics to manage microbial threats, and to identify potential strategies to leverage economic tools to counter infectious diseases, ranging from endemic to emerging infectious diseases to antimicrobial resistance (AMR). At the end of the workshop, three participants summarized what they believed were the lessons learned from the discussion. First, Suerie Moon, director of research at the Global Health Centre of the Graduate Institute of International and Development Studies, Geneva, began with her reflections based on the breakout group discussion. Peter Sands, executive director of The Global Fund to Fight AIDS, Tuberculosis and Malaria, followed with his thoughts on the key points from the workshop and the challenges that need to be overcome to push the field forward. Peter Daszak, president of EcoHealth Alliance, provided closing comments at the end the workshop.

RESEARCH, CONVENINGS, AND POLICY

Suerie Moon, director of research at the Global Health Centre of the Graduate Institute of International and Development Studies, Geneva, reflected on three overarching categories for action steps she observed from the final discussion: research, convenings, and policy. She said research needs to move from broad, global-level impact estimates to creating more specific data that are targeted and relevant to policy makers. She flagged the potential for this type of research and economic analyses to serve as an accountability tool for policy makers to measure actions taken by

responsible parties. To conduct these economic analyses, Moon raised participants' questions on who should be involved and whether the group of stakeholders should be broadened. In all cases, she observed, communication among researchers themselves and with the broader policy community will remain crucial.

In terms of convenings, Moon observed repeated calls among some workshop participants for opportunities for research and policy communities to come together to better address issues, make decisions, and implement policies. To illustrate this point, she mentioned the crossroads for decision making with the available economic analyses and tools, particularly in light of the urgency with AMR, and the need for research and policy communities to convene to review the analyses, make a decision, and move on.

Finally, Moon stated the need to implement policy changes. She said that making policy changes would require expanding the usefulness of economic analyses for stakeholders who tend to exist in academic and policy silos, as well as crossing those silos, both within and outside the health sector. Doing so will contribute to improving the global capacity to manage microbial threats, asserted Moon.

FINAL THOUGHTS

Peter Sands, executive director of The Global Fund to Fight AIDS, Tuberculosis and Malaria, provided his main points from the workshop's 1.5 days of discussions, and he highlighted the continued challenges that the global community must grapple with. He observed that building an investment case for managing microbial threats is vital in a climate of increasing economic vulnerability as the world is more interconnected by social media and increased communication, transportation, and trade. The investment case, according to Sands, needs to be rooted in an analysis of the burdens and risks of microbial threats. Furthermore, he reflected that economic tools, whether they be models or behavioral economic frameworks, can be helpful in designing optimal interventions and making the inevitable trade-offs in resource-constrained environments. In his current role, he noted that this analysis will be necessary to build a compelling investment case to underpin the Global Fund's next replenishment in 2019. Sands also mentioned that economics needs to be leveraged more in global health. To make this point, he shared two examples from the HIV field.

In his first example, he shared that in some countries, an HIV-diagnosed person must pay a small fee before getting on antiretroviral therapy (ART). He noted that the act of having to pay a fee typically leads to a high fall-off of HIV-diagnosed people receiving therapy. Even relatively small amounts

of money, he explained, can create an impediment to prompt treatment, a phenomenon that can be explained by behavioral economics. In his second example, Sands reported that while the largest proportion of new HIV infections is among adolescent girls and young women, qualitative data suggest that they have decreased fear of contracting HIV partly as a side effect of the availability of effective ART and treatments. Sands remarked that the development of effective ART is an enormous achievement that has been able to manage what was a fatal disease into a more chronic condition, but urged the global community to also think through the incentive structures to address the unintended consequences of the achievement.

Sands moved on to reviewing challenges that surfaced during workshop discussions. He noted the market failure of incentivizing research and development for new antimicrobials, which is reflected in industry debates over reimbursement reform, procurement, and what constitutes the suite of incentives. He also pointed out that investments in preparedness in low- and middle-income countries remain low. As an example, Sands cited the disparity between participation in the Joint External Evaluations (JEEs), which is high, and the few countries that have committed actual funding to implement plans addressing the gaps identified by those JEEs. He also expanded on the challenge of breaking through multiple silos, noting that they exist between economics and public health, scientific and clinical worlds, and also within the infectious disease realm among endemic diseases, emerging outbreaks, and AMR, in which different approaches are often used to calculate and communicate the economic impact. While this might reflect the intrinsic differences of the various diseases, he argued there could be more cross-fertilization among the diverse approaches. These communities are incrementally being bridged by convenings such as this workshop, but he said more progress is necessary to make approaches to economic analysis across domains more consistent, grounded in empirical evidence, and specific for policy makers on the national level.

As the breakout reports suggested, Sands said more work needs to be done to build the knowledge base for such rigorous analyses and to address data gaps. In particular, he highlighted the intellectual challenge of examining the economics of fear. In addition, Sands agreed with the need to build both local and global capacity and noted that there is a global shortage of the necessary economic expertise especially dedicated to tackling diseases with high mortality, such as tuberculosis. He hoped that the topic of economics of microbial threats becomes more attractive to young professionals and academics to boost this capacity. Finally, Sands urged better incorporations of rigorous and empirical economic considerations into health strategies, and for macroeconomic analyses to more effectively weave in health considerations. However, these economic analyses, he cautioned, cannot be too narrow and focus only on the technical aspects. He concluded:

> The economics we are most interested in here is political economy. It is economics attached to political decision making. We need to keep our scope broad enough. Ultimately, if we want to affect policy making and policies, we have to weave in that political consideration.

Peter Daszak, president of EcoHealth Alliance, provided closing remarks for the workshop. He observed that the meeting had been an effort itself in breaking down silos and engaging communities across emerging and endemic infectious diseases, the biological and social sciences, the private and public sectors, and security with public health. Though bridging these disciplines will require compromises all around, Daszak said they will also provide opportunities to move the agenda forward to implement policy changes.

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Appendix A

Workshop Statement of Task

An ad hoc committee under the auspices of the National Academies of Sciences, Engineering, and Medicine will plan a 1.5-day public workshop that will examine the interaction of economic activity and microbial threats, including infectious disease outbreaks and antimicrobial resistance. A critical focus of the workshop will be to discuss the need for key metrics of risk and analytical tools to provide a comprehensive understanding of the economic risk that microbial threats pose. The workshop will also focus on exploring approaches to incorporate estimates of infectious disease risk to overall macroeconomic assessments of economic growth in countries to incentivize action that minimize these threats. Specifically, this workshop will feature invited presentations and discussions on topics, including

- Economic costs from infectious diseases that may place a disproportionate burden on low- and middle-income countries but affect regional and global stability because of interconnected financial systems worldwide
- Gaps in assessing economic costs of microbial threats through multiple channels of disruption, including dynamics of fear-based behavioral change
- Critical opportunities and challenges to model and develop metrics of risk, including identifying and using appropriate data and dealing with uncertainty, and to build analytical tools to understand the potential economic consequences of infectious diseases in the short, medium, and long term

- Strategies to incorporate estimates of infectious disease risk to overall macroeconomic assessments of economic growth to ensure the risks are reflected in financial markets and business investment decisions or influence flows of development assistance, and to link these assessments to incentives for action to minimize the threats
- Implications for the International Health Regulations, particularly on trade and travel measures, as well as for upstream and downstream strategies, policies, and interventions—such as effective communication messages, simulation exercises, investment decisions, and One Health approaches—that various sectors of government, multilateral institutions, and others may carry out in preventing and mitigating the economic costs
- Collaboration and coordination mechanisms among various stakeholders and across sectors in public health, animal health, economics, travel, trade, commerce, and agriculture, among others

Workshop speakers and discussants will contribute perspectives from government, academia, private, and nonprofit sectors. The committee will plan and organize the workshop, select and invite speakers and discussants, and moderate the discussions. A proceedings of the presentations and discussions at the workshop will be prepared by a designated rapporteur in accordance with institutional guidelines.

Appendix B

Workshop Agenda

TUESDAY, JUNE 12, 2018

8:30 am ET Welcome Remarks
Peter Daszak, Chair, Forum on Microbial Threats

The Neglected Dimension of Economic Security: Managing Microbial Threats (by video)
Lawrence H. Summers, Harvard University

Workshop Overview and Goals
Peter Sands, The Global Fund to Fight AIDS, Tuberculosis and Malaria

Session I: The Economic Cost of Microbial Threats

Part A: The Economic Risk of Endemic Infectious Diseases
Thomas Inglesby, *Moderator*

9:10 am The Economic Case for Eradicating Polio
Kimberly Thompson, Kid Risk, Inc.

Epidemic to Endemic—The Economic Impact of HIV/AIDS
Katharina Hauck, Imperial College London

Costing of Tuberculosis Control
Anna Vassall, London School of Hygiene & Tropical Medicine; University of Amsterdam

9:45 am Discussion

10:20 am Break

Part B: Economics and Modeling of Emerging Infectious Diseases and Biological Risks
Rebecca Katz, *Moderator*

10:35 am The Cost of Pandemic Influenza—What Has Changed and What Have We Learned 100 Years Later?
Martin Isaac Meltzer, U.S. Centers for Disease Control and Prevention

Assessing Economic Vulnerability to Emerging Infectious Disease Outbreaks—Ebola Versus Zika
Anas El Turabi, Harvard University

Epidemic Risk Modeling—How Can We Measure the Impact of Aversion Behavior and Cascading Social Responses?
Carlos Castillo-Chavez, Arizona State University

The Global Catastrophic Biological Risks
Thomas Inglesby, Johns Hopkins Bloomberg School of Public Health

11:30 am Discussion

12:00 pm Lunch

Part C: The Cost of Antimicrobial Resistance (AMR)
Keiji Fukuda, *Moderator*

1:00 pm Considerations for Estimating the Cost of AMR—Direct Versus Indirect Costs
Mukesh Chawla, World Bank

Cost-Effectiveness of Interventions to Limit the Spread of AMR—A Perspective from the Organisation for Economic Co-operation and Development (OECD)
Mark Pearson, OECD

The Impact of AMR Beyond the Health Sector—How to Make the Investment Case for Controlling AMR?
Ramanan Laxminarayan, Center for Disease Dynamics, Economics & Policy

1:40 pm Discussion

Session II: The Economic Cost of Preparedness for Microbial Threats

Part A: National Preparedness
Beth Cameron, *Moderator*

2:10 pm Economics of National Preparedness to Fight Against Microbial Threats
Tolbert Nyenswah, National Public Health Institute of Liberia

Cost-Benefit Analysis of Outbreak Response in the Context of the Monitoring and Evaluation of the International Health Regulations
Andreas Gilsdorf, Consultant for Public Health Security

Economic Impacts of Financing Performance of Veterinary Services Gap Analysis
Franck Berthe, World Bank

The Cost of Implementing a One Health Approach to Combat Microbial Threats
Katherine Lee, University of Idaho

3:00 pm Discussion

3:40 pm Break

Part B: Accelerating Research and Development of Medical Products
Jami Taylor, *Moderator*

3:55 pm	Panel Discussion **Paul Schaper,** Merck & Co., Inc. **Joanna Wolkowski,** Pfizer Inc. **Thomas Cueni,** International Federation of Pharmaceutical Manufacturers & Associations **Jonathan Kfoury,** L.E.K. Consulting
4:20 pm	Discussion
5:25 pm	Wrap Up **Peter Sands,** Workshop Chair
5:35 pm	Reception

WEDNESDAY, JUNE 13, 2018

8:30 am ET	Welcome and Recap Day 1 **Peter Sands,** Workshop Chair

Session III: Investing in Preparedness for Microbial Threats

Part A: Investing in Sustainable Solutions
Peter Sands, *Moderator*

8:40 am	Development Assistance for Health: Economic Perspectives to Counter Microbial Threats **Dean Jamison,** University of California, San Francisco; University of Washington Overcoming Economic Bottlenecks in Delivering Medical Products to Address Microbial Threats Across Africa **Tana Zulu Holt,** McKinsey and Co.
9:05 am	Discussion

Part B: Breakout Session

9:25 am	Introduction to Session **Suerie Moon,** The Graduate Institute, Geneva
9:30 am	(mobilize to breakout room)
9:35 am	Breakout Session
	The purpose of the breakout session is to identify priority next steps and develop actionable strategies to achieve those next steps across the three topics below.
	Group 1: Modeling the Economic Risks of Emerging Infectious Diseases **Peter Daszak,** EcoHealth Alliance
	Group 2: Creating a Sustainable Economic Model to Stimulate Research and Development for Antibiotics **Ed Whiting,** Wellcome Trust
	Group 3: Incentives for National Governments to Invest in Preparedness: Incorporating Economic Risks of Outbreaks into Macroeconomic Assessments **Mukesh Chawla,** World Bank
10:50 am	Break
11:30 am	Breakout Group Reports **Suerie Moon,** *Moderator*
	Group 1: Modeling the Economic Risks of Emerging Infectious Diseases **Peter Daszak,** EcoHealth Alliance
	Group 2: Creating a Sustainable Economic Model to Stimulate Research and Development for Antibiotics **Ed Whiting,** Wellcome Trust
	Group 3: Incentives for National Governments to Invest in Preparedness: Incorporating Economic Risks of Outbreaks into Macroeconomic Assessments **Anas El Turabi,** Harvard University

11:30 am	Synthesis and General Discussion **Suerie Moon,** *Moderator*
12:15 pm	Closing Remarks
	Peter Sands, Workshop Chair
	Peter Daszak, Chair, Forum on Microbial Threats
12:30 pm	Adjourn

Appendix C

Biographical Sketches of Workshop Speakers and Moderators

Franck Berthe, D.V.M., Ph.D., is a senior livestock specialist in the Agriculture Global Practice of the World Bank and the coordinator of the Livestock Global Alliance since March 2016. The Alliance brings together the Food and Agriculture Organization of the United Nations, the International Fund for Agriculture Development, the International Research Institute on Livestock, the World Organisation for Animal Health (OIE), and the World Bank—five global public institutions committed to safer, fairer, and more sustainable livestock. Dr. Berthe was previously head of the Animal and Plant Health Unit at the European Food Safety Authority based in Parma, Italy. His core activity was to assess animal and plant production systems and practices with respect to primary production, ecosystems, and public health. Dr. Berthe's job was to provide scientific advice to the EU risk managers and decision makers on a wide range of risks at the human–animal–ecosystem interface. Prior to coming to Italy in 2007, Dr. Berthe was associate professor at the Atlantic Veterinary College (UPEI) and Canada Research Chair in aquatic health sciences, exploring host pathogens relations in their environment. From 1994 to 2004 Dr. Berthe led active research in aquatic animal health at the French institute for the exploitation of the sea (IFREMER) in France and overseas territories. Dr. Berthe is vice president of the Biological Standards Commission of OIE. He has served on OIE specialized commissions since 1996. A native of France, Dr. Berthe received a doctorate of veterinary medicine and a Ph.D. degree in molecular parasitology. He has a diploma in bacteriology from the Pasteur Institute.

Elizabeth Cameron, Ph.D., is the Nuclear Threat Initiative's (NTI's) vice president for global biological policy and programs. Dr. Cameron previously served as the senior director for global health security and biodefense on the White House National Security Council staff, where she was instrumental in developing and launching the Global Health Security Agenda and addressed homeland and national security threats surrounding biosecurity and biosafety, biodefense, emerging infectious disease threats, biological select agents and toxins, dual-use research, and bioterrorism. From 2010 to 2013, Dr. Cameron served as office director for Cooperative Threat Reduction (CTR) and senior advisor for the Assistant Secretary of Defense for nuclear, chemical, and biological defense programs. In this role, she oversaw the implementation of the geographic expansion of the Nunn-Lugar CTR program. For her work, she was awarded the Office of the Secretary of Defense Medal for Exceptional Civilian Service. From 2003 to 2010 Dr. Cameron oversaw the expansion of U.S. Department of State Global Threat Reduction programs and supported the expansion and extension of the Global Partnership Against the Spread of Weapons and Materials of Mass Destruction, a multilateral framework to improve global chemical, biological, radiological, and nuclear security. Dr. Cameron served as an American Association for the Advancement of Science fellow in the health policy office of Senator Edward M. Kennedy where she worked on the Patients' Bill of Rights, medical privacy, and legislation to improve the quality of cancer care. From 2001 to 2003, she served as a manager of policy research for the American Cancer Society. Dr. Cameron holds a Ph.D. in biology from the Human Genetics and Molecular Biology program at Johns Hopkins University and a B.A. in biology from the University of Virginia. Dr. Cameron is a member of the Council on Foreign Relations.

Carlos Castillo-Chavez, Ph.D., M.S., is a Regents professor; the Joaquin Bustoz, Jr., Professor of Mathematical Biology; a distinguished sustainability scientist; and the founding director of the Simon A. Levin Mathematical and Computational Modeling Sciences Center (SAL-MCMSC) at Arizona State University (ASU). He has co-authored more than 250 publications and a dozen books, textbooks, research monographs, and edited volumes. He was born in Mexico City, immigrating to the United States in 1974. Dr. Castillo-Chavez received his bachelor's, master's, and Ph.D. degrees from three campuses of the University of Wisconsin (UW) Stevens Point, Milwaukee, and Madison, respectively. He reached the rank of full professor at Cornell University in 1997 where he spent 18 years before moving to ASU in 2004. During his 30 years in academia, he has mentored 25 postdoctoral students. His 46 Ph.D. students include 21 women, 26 from U.S. underrepresented groups, and 7 from Latin America. He has been a research co-mentor to nearly 500 undergraduates. According to the

mathematics genealogy project, Dr. Castillo-Chavez is among the top 200 mentors of Ph.D. students in the history of mathematics. Recognitions to his work include: three White House awards (1992, 1997, and 2011), the 12th American Mathematical Society Distinguished Public Service Award in 2010, the 2007 American Association for the Advancement of Science (AAAS) Mentor award, and the 17th recipient of the Society for Industrial and Applied Mathematics (SIAM) Prize for Distinguished Service to the Profession and Distinguished Alumni by UW Stevens Point. He is a fellow of the AAAS, SIAM, founding fellow of the American Mathematical Society (AMS), and American College of Epidemiology (ACE). He has held honorary professorships at Xi'an Jiatong University in China, the Universidad de Belgrano in Argentina, and East Tennessee State University. Past appointments include a Stanislaw M. Ulam Distinguished Scholar at Los Alamos National Laboratory, a Cátedra Patrimonial at the Universidad Nacional Autónoma de México in México, and a Martin Luther King Jr. Professorship at the Massachusetts Institute of Technology. He was a member of the Board of Higher Education at the National Academy of Sciences (2009–2015) and served on President Barack Obama's Committee on the National Medal of Science (2010–2015). He holds external current faculty appointments at Cornell University (since 2004), Santa Fe Institute (since 2005), and Universidad de Los Andes, Colombia (since 2016). His research lives at the interface of disease evolution, behavioral epidemiology, social dynamics, homeland security, epidemiology, addiction, and sustainability. He is the recipient of the inaugural Dr. William Yslas Outstanding STEM in Higher Education Award in 2015, given by the Victoria Foundation and co-sponsored by the Pasqua Yaqui Tribe of Arizona. Dr. Castillo-Chavez was elected member-at-large of the Section on Mathematics of the AAAS (February 2016–February 2020). On February 24, 2016, the University Francisco Gavidia inaugurated the "Centro de Modelaje Matemático Carlos Castillo-Chavez" in the City of San Salvador, El Salvador. He has been appointed to the National Science Foundation's (NSF's) Advisory Committee for Education and Human Resources (2016–2019) and is a member of NSF's Advisory Committee for Cyberinfrastructure. He has been named George Polya Lecturer for 2017–2018. Dr. Castillo-Chavez has been the recipient throughout his academic career of grants by the NSF, the National Institutes of Health, Department of Defense, the Department of Agriculture (Hatch), and the Sloan Foundation. He also held the position of Rector of Yachay Tech University in Ecuador (2016–2018), an appointment made by former President Rafael Correa Delgado.

Mukesh Chawla, Ph.D., is advisor for health, nutrition, and population at the World Bank and coordinator of the Pandemic Emergency Financing Facility. He has worked for more than 20 years with governments and

international development partners in Africa, Asia, and Europe on a variety of health-sector issues. His current area of interest and responsibility is helping countries get better prepared to respond immediately and effectively to disease outbreaks that have the potential of assuming pandemic proportions. He has written extensively on the role of markets and marketlike institutions in the creation of incentives that strengthen health systems, fiscal space for health, innovations in health financing, design of health-sector reforms, and economics of aging populations. Prior to joining the Bank, he held a research faculty position at Harvard University. Before that, as member of the Indian Administrative Service in India, he held several key government positions between 1980 and 1998. He attended St. Stephen's College and Delhi School of Economics in India, and Boston University.

Thomas B. Cueni, M.A., has been director general of the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) since February 1, 2017. Prior to joining IFPMA he was secretary general of Interpharma, the association of pharmaceutical research companies in Switzerland. For many years Mr. Cueni has been involved in the work of the European Federation of Pharmaceutical Industries and Associations (EFPIA), where he most recently served as vice chair of the European Markets Committee and association representative on the board. He represented the industry on the European Union (EU) High-Level Pharmaceutical Forum, was chairman of EFPIA's Economic and Social Policy Committee, and chairman of the EFPIA Task Force on the EU Commission's Pharmaceutical Sector Inquiry. Mr. Cueni also represented Interpharma, which he successfully transformed from the association of Swiss Rx companies to the association of pharmaceutical research companies in Switzerland, on the Council of IFPMA. Prior to his appointment with Interpharma, Mr. Cueni had a career as a journalist, *inter alia*, as London correspondent for the *Basler Zeitung* and *Der Bund*, and he served as a Swiss career diplomat with postings in Paris (Organization for Economic Co-operation and Development) and Vienna (International Atomic Energy Agency, United Nations Industrial Development Organization). He studied at the University of Basel, the London School of Economics, and the Geneva Graduate Institute for International Studies, and has master's degrees in economics (University of Basel) and politics (London School of Economics).

Peter Daszak, Ph.D., is president of EcoHealth Alliance, a U.S.-based organization that conducts research and outreach programs on global health, conservation, and international development. Dr. Daszak's research has been instrumental in identifying and predicting the effect of emerging diseases across the globe. His achievements include identifying the bat origin of SARS, identifying the underlying drivers of Nipah and Hendra virus

emergence, producing the first ever global emerging disease "hotspots" map, developing a strategy to find out how many unknown viruses exist that could become pandemic, identifying the first case of a species extinction attributable to disease, and discovering the disease chytridiomycosis as the cause of global amphibian declines. Dr. Daszak is a member and chair of the National Academies of Sciences, Engineering, and Medicine's Forum on Microbial Threats. He is a member of the National Research Council (NRC) Advisory Committee to the U.S. Global Change Research Program, the Supervisory Board of the One Health Platform, the One Health Commission Council of Advisors, the Center of Excellence for Emerging and Zoonotic Animal Diseases External Advisory Board, the Cosmos Club, and the Advisory Council of the Bridge Collaborative. He served on the Institute of Medicine committee on global surveillance for emerging zoonoses, the NRC committee on the future of veterinary research, the International Standing Advisory Board of the Australian Biosecurity Cooperative Research Centres, and has advised the Director for Medical Preparedness Policy on the White House National Security Staff on global health issues. Dr. Daszak is a regular advisor to the World Health Organization (WHO), World Organisation for Animal Health, and the Food and Agriculture Organization of the United Nations, and is actively involved in the WHO expert group on Public Health Emergency Disease Prioritization. Dr. Daszak won the 2000 Commonwealth Scientific and Industrial Research Organisation medal for collaborative research on the discovery of amphibian chytridiomycosis, is the EHA institutional lead for USAID-EPT-PREDICT, is on the editorial boards of *Conservation Biology*, *One Health*, and *Transactions of the Royal Society of Tropical Medicine & Hygiene*, and is editor-in-chief of the journal *EcoHealth*. He has authored more than 300 scientific papers, and his work has been the focus of extensive media coverage, ranging from popular press articles to television appearances.

Anas El Turabi, B.M.Ch.B., M.Phil., is a Frank Knox fellow and doctoral candidate in health policy at Harvard University and an honorary visiting fellow at the Department of Public Health and Primary Care at the University of Cambridge. He received his B.A. with honors in physiological sciences and his medical degree from the University of Oxford, and an M.Phil. with distinction in clinical science from the University of Cambridge, where he completed the academic residency program in primary care. He has held fellowships at the University of Cambridge, RAND Europe, and Harvard University and has worked in health policy and global health at the Department of Health in England and with the World Health Organization. His current research involves applying statistical and computational methods to large health and economic datasets to better understand the economics of infectious disease crises, with the goal of informing global responses to pan-

demic risk reduction. He has previously supported the National Academy of Medicine's Commission for a Global Health Risk Framework for the Future and the World Bank's International Working Group on Financing Preparedness, developing estimates of the expected economic impact of pandemics, working on methods to assess economic vulnerability to infectious disease crises, and developing the investment case for improving global and national preparedness functions. He is a practicing primary care physician and sits on the General Practice Reference Group of the United Kingdom's National Institute for Health and Care Excellence and the International Evaluation Advisory Committee of the Ontario Brain Institute.

Keiji Fukuda, M.D., M.P.H., is the director and a clinical professor at The University of Hong Kong School of Public Health. He previously worked at the World Health Organization (WHO) in several capacities including assistant director general (ADG) and special representative of the director general for antimicrobial resistance; ADG for the Health Security and Environment Cluster; and director of the Global Influenza Programme. Before that, he worked at the U.S. Centers for Disease Control and Prevention (CDC) as the Epidemiology Section chief, Influenza Branch, and as a medical epidemiologist in the Viral Exanthems and Herpesvirus Branch, National Center for Infectious Diseases. Dr. Fukuda has been a global public health leader in many areas including health security; emerging infectious diseases including seasonal, avian and pandemic influenza, severe acute respiratory syndrome, Middle East respiratory sydrome, and Ebola; antimicrobial resistance; development of the Pandemic Influenza Preparedness Framework; implementation of the International Health Regulations; food safety; and chronic fatigue syndrome. He has considerable experience in epidemiological research and field investigations, media communications, and international diplomatic negotiations including those held to establish a historic heads of state-level meeting on antimicrobial resistance at the United Nations in 2016. He has a B.A. in biology, an M.D., an M.P.H., was trained in the Epidemic Intelligence Service at CDC, and is certified in internal medicine by the American Board of Internal Medicine.

Andreas Gilsdorf, M.D., Dr.med., is an independent consultant on public health security. Until the end of 2017 he was the head of the Surveillance Unit and deputy head of the Department of Infectious Disease Epidemiology at the Robert Koch Institute (RKI), the German national public health institute. Dr. Gilsdorf is a physician with a specialization in occupational medicine and infectious disease epidemiology. From 2006 to 2008 he worked at the World Health Organization (WHO) Regional Office for Europe in Copenhagen, Denmark, on communicable disease surveillance and response. At RKI, he was responsible for the national infectious disease

surveillance system and represented the institute internationally, including at WHO as the focal point for the International Health Regulations (IHR), at the European Commission, and at the European Centre for Disease Prevention and Control. Dr. Gilsdorf was in charge of preparedness and response and built up and headed the Emergency Operations Centre at RKI. In 2017, his team had the technical lead at the G20 health ministers' emergency exercise during their summit in Germany. Since 2018, he has been working as a consultant for public health security, focusing on strengthening IHR, intersectoral collaboration, preparedness, and emergency response operations.

Katharina Hauck, Ph.D., is an expert in the economics of infectious diseases, with specific research interests in the economics of HIV/AIDS, economic impact of epidemics, evaluation of complex public health, and health care interventions; cost-effectiveness analysis and priority setting; health system performance; and the role of individuals' behaviors in the transmission of infectious disease. Dr. Hauck is a senior lecturer in health economics at the Department of Infectious Disease Epidemiology, Imperial College London. She is also a member of the "Global Health" and "Health Care Delivery Systems" Expert Networks of the World Economic Forum, co-chair for economics of the Global Fund Modelling Secretariat, and member of the International Decision Support Initiative.

Tania Zulu Holt, M.Sc., is a partner at McKinsey and Co. She started her career in the London office and subsequently relocated to Johannesburg in 2010 to pursue her passion for the continent and help expand McKinsey's activities in health care across Africa. She leads McKinsey's health care activities across Africa, motivated by a personal passion for extending access to affordable and high-quality health care services and products. She works at the intersection between private companies, governments, and social stakeholders across the whole continent, and has on-the-ground experience across 20 countries to date. Ms. Holt is passionate about diversity in organizations and is a co-author of McKinsey's highly acclaimed *Women Matter Africa* report that shows that companies with a greater share of women on their boards of directors and executive committees tend to perform better financially. Prior to joining McKinsey, she worked with the Danish Ministry of Health.

Thomas V. Inglesby, M.D., is the director of the Center for Health Security of the Johns Hopkins Bloomberg School of Public Health. The Center for Health Security is dedicated to protecting people's health from the consequences of epidemics and disasters. Dr. Inglesby is also professor in the Department of Environmental Health and Engineering in the Johns

Hopkins Bloomberg School of Public Health with a joint appointment in the Johns Hopkins School of Medicine. Dr. Inglesby's work is internationally recognized in the fields of public health preparedness, pandemic and emerging infectious disease, and prevention of and response to biological threats. He is chair of the Board of Scientific Counselors, Office of Public Health Preparedness and Response, U.S. Centers for Disease Control and Prevention (CDC). He is also chair of the National Advisory Council of the Robert Wood Johnson Foundation's National Health Security Preparedness Index. He was a member of the CDC Director's External Laboratory Safety Workgroup that examined biosafety practices of CDC, the National Institutes of Health (NIH), and the Food and Drug Administration (FDA) following high-profile laboratory incidents in federal agencies. He was on the 2016 Working Group assessing U.S. biosecurity on behalf of the President's Council of Advisors on Science and Technology (PCAST). He has served on committees of the Defense Science Board, the National Academies of Sciences, the Institute of Medicine, and in an advisory capacity to NIH, Biomedical Advanced Research and Development Authority, Department of Homeland Security, and Defense Advanced Research Projects Agency. Dr. Inglesby has authored or co-authored more than 115 publications, including peer-reviewed research, reports, and commentaries on issues related to health security and preparedness for epidemics, biological threats, and disasters. He is editor-in-chief of the peer-reviewed journal *Health Security*, which he helped establish in 2003. He was a principal editor of the JAMA book *Bioterrorism: Guidelines for Medical and Public Health Management*. He has been invited to brief White House officials from the past four presidential administrations on national biosecurity challenges and priorities, and he has delivered congressional testimony on a number of issues related to public health preparedness and biosecurity. He is regularly consulted by major news outlets for his expertise. He is a member of the Board of Directors of PurThread, a company dedicated to developing antimicrobial textiles. Dr. Inglesby completed his internal medicine and infectious diseases training at the Johns Hopkins University School of Medicine, where he also served as assistant chief of service in 1996–1997. Dr. Inglesby received his M.D. from Columbia University College of Physicians and Surgeons and his B.A. from Georgetown University. He sees patients in a weekly infectious disease clinic.

Dean T. Jamison, Ph.D., is emeritus professor in the Institute for Global Health Sciences at the University of California, San Francisco (UCSF). In addition to UCSF, Dr. Jamison has been with University of California, Los Angeles, and the University of Washington and served as the T & G Angelopoulos Visiting Professor in the Harvard Kennedy School and the Harvard T.H. Chan School of Public Health (2006–2008). He previously worked at

the World Bank as a research economist and as manager of the Education Policy Division and of the Health, Nutrition, and Population Division. He was lead author for the bank's 1993 World Development Report, *Investing in Health*. Dr. Jamison studied at Stanford (M.S., engineering science) and at Harvard (Ph.D., economics, under K. J. Arrow). In 1994 he was elected to membership in the National Academy of Medicine of the U.S. National Academies of Sciences, Engineering, and Medicine. Dr. Jamison served as co-chair with Lawrence H. Summers of the Lancet Commission on *Investing in Health* (*The Lancet*, December 2013). Most recently, he led work on the nine-volume *Disease Control Priorities* series from the World Bank and was lead author of its synthesizing publication (*The Lancet*, December 2017).

Rebecca Katz, Ph.D., M.P.H., is an associate professor of international health and co-director of the Center for Global Health Science and Security at Georgetown University. Prior to coming to Georgetown, she spent 10 years at George Washington University as faculty in the Milken Institute School of Public Health. Her research is focused on global health security, public health preparedness, and health diplomacy. Since 2007, much of her work has been on the domestic and global implementation of the International Health Regulations. Since 2004, Dr. Katz has been a consultant to the U.S. Department of State, working on issues related to the Biological Weapons Convention, pandemic influenza, and disease surveillance. Dr. Katz received her undergraduate degree from Swarthmore College, an M.P.H. from Yale University, and a Ph.D. from Princeton University.

Jonathan Kfoury, S.M., is a managing director and partner in L.E.K. Consulting's San Francisco office, focused on biopharmaceuticals, medical technology, and life sciences. He joined the firm in 2006, and since that time has led an extensive set of engagements with global biopharmaceutical, medical technology, and diagnostic clients across human health, animal health, and agribusiness markets. Mr. Kfoury advises clients on commercial strategy and life cycle management for inline products, market access, and commercialization planning for pipeline assets, and growth and partnering strategy. With an operating background in both clinical and business development at specialty biopharmaceutical companies, Mr. Kfoury brings a hands-on understanding of internal decision making needs to his advisory work with clients. In addition to significant experience in immunology, oncology, men's and women's health, and central nervous system pain management, Mr. Kfoury's interests include growth strategy for antibiotics and infectious diseases, biosimilars, and digital health opportunities. He has published and spoken extensively across the industry on the crisis of antimicrobial resistance, barriers to investment into novel antibiotics, public–private part-

nerships, and key opportunities for pharmaceutical, vaccine, and diagnostic manufacturers within anti-infectives more broadly. Prior to joining L.E.K., Mr. Kfoury was a business development executive for Acusphere and Purdue Pharma, and manager of global clinical development for Cubist Pharmaceuticals' (now Merck's) blockbuster antibiotic Cubicin—the most successful intravenous antibiotic launched in U.S. history. In addition to global management training at INSEAD, Mr. Kfoury earned an S.M. in health policy and management from Harvard University and graduated from Trinity College with a bachelor of science degree in neuroscience.

Ramanan Laxminarayan, Ph.D., M.P.H., is director and senior fellow at the Center for Disease Dynamics, Economics & Policy (CDDEP) in Washington, DC, and a senior research scholar and lecturer at the Princeton Environmental Institute at Princeton University. He is an affiliate professor at the University of Washington and a visiting professor at the University of Kwazulu Natal and the University of Strathclyde. Dr. Laxminarayan is founder of HealthCube, which works to improve access to health care and diagnostics worldwide. Since 1995, Dr. Laxminarayan has worked to improve the understanding of antibiotic resistance as a problem of managing a shared global resource. His work encompasses extensive peer-reviewed research, public outreach, and direct engagement in 11 countries in Asia and Africa through the Global Antibiotic Resistance Partnership. Through his prolific research, active public outreach (including a TED talk that has been widely viewed), and sustained policy engagement, he has played a central role in bringing the issue of drug resistance to the attention of leaders and policy makers worldwide and to the United Nations General Assembly in September 2016. Dr. Laxminarayan has served on the U.S. President's Council of Advisors on Science and Technology's antimicrobial resistance working group and is currently a voting member of the U.S. Presidential Advisory Council on Combating Antimicrobial Resistance. He is a series editor of the *Disease Control Priorities for Developing Countries*, 3rd edition.

Katherine D. Lee, Ph.D., is an applied environmental and natural resource economist. Her research primarily explores feedback between humans and natural systems and implications for resource managers and policy makers. Applications of her work include managing environmental uncertainty, biological invasions, conservation, and sustainable agriculture. Dr. Lee received her Ph.D. in economics from the University of Wyoming and a B.S. in economics and biology from the University of Wisconsin–Madison. She worked as a biological research technician in the Belovsky Lab at the University of Notre Dame from 2008 to 2011. Her work experience highlighted the importance of communicating ideas and results between

researchers, resource managers, and the public, and is the basis for her multidisciplinary approach to research.

Martin I. Meltzer, Ph.D., is lead of the Health Economics and Modeling Unit (HEMU), and a distinguished consultant in the Division of Preparedness and Emerging Infections, U.S. Centers for Disease Control (CDC) in Atlanta, Georgia. He received his undergraduate degree from the University of Zimbabwe in 1982, and master's and doctorate in applied economics degrees from Cornell University, in 1987 and 1990, respectively. From 1990 to mid-1995, he was on the faculty at the College of Veterinary Medicine at the University of Florida. In 1995, he moved to CDC, where he was in the first class of Prevention Effectiveness Fellows (health economist). He led the modeling teams supporting CDC's response to the 2009 H1N1 influenza pandemic, including producing monthly estimates of cases, hospitalizations, and deaths, as well as estimating effect of the vaccination program and use of influenza antiviral drugs. Other responses in which he led the modeling activities include estimating the residual risk associated with the 2012 contaminated steroid injectable products that caused fungal meningitis among patients, the 2014–2015 Ebola epidemic in West Africa, and the Zika epidemic. Examples of his research include estimating the effect of the 2009 influenza pandemic, the modeling of potential responses to smallpox as a bioterrorist weapon, and assessing the economics of controlling diseases such as rabies, dengue, hepatitis A, meningitis, Lyme, and malaria. Dr. Meltzer has published approximately 300 publications, including more than 140 papers in peer-reviewed scientific journals and more than 50 software tools. These tools include FluAid, FluSurge, and FluWorkLoss, designed to help state and local public health officials plan and prepare for catastrophic infectious disease events. They have been downloaded more than 130,000 times and have been used by local, state, national and international public health agencies with jurisdictions exceeding a total of 1 billion people. He is an associate editor for *Emerging Infectious Diseases*. He also supervises a number of postdoctoral health economists at CDC.

Suerie Moon, Ph.D., M.P.A., is director of research at the Global Health Centre, Graduate Institute of International and Development Studies, Geneva, and adjunct lecturer on global health at the Harvard T.H. Chan School of Public Health. She has served on a number of advisory bodies, including most recently the World Health Organization Fair Pricing Forum Advisory Group, Expert Advisory Group to the United Nations Secretary-General's High-Level Panel on Access to Medicines, and Proposal Review Committee of UNITAID. Prior to joining the Graduate Institute, she was study director of the Harvard-London School of Hygiene & Tropical Medicine Independent Panel on the Global Response to Ebola, and cofounded

and led the Forum on Global Governance for Health, a focal point at Harvard University for research, debate, and strategic convening on issues at the intersection of global governance and health. Her research and teaching focus on global governance, the political economy of global health (focusing on innovation and access to medicines; outbreak preparedness and response; trade, investment, and intellectual property rules; and development assistance for health), the evolution of international regimes, and innovative policies for addressing global problems. She received a B.A. from Yale, an M.P.A. from Princeton, and a Ph.D. from the Harvard Kennedy School of Government.

Tolbert G. Nyenswah, L.L.B., M.P.H., currently serves as the first director general of the National Public Health Institute of Liberia, an entity that was officially established on January 26, 2017, to prevent and control public health threats, post the 2014–2016 Ebola epidemic, that devastated Liberia's public health system and resulted in more than 11,000 cases with close to 5,000 deaths in Liberia alone. Prior to his appointment as director general, Mr. Nyenswah became Liberia's first deputy minister of health for disease surveillance and epidemic control, in the Department of Public Health, which was created within the Ministry of Health, after the World Health Organization's (WHO's) first declaration that Liberia was free of Ebola in the human population. He had been appointed incident manager of the Incident Management System, responsible for leading Liberia's national Ebola response activities. Mr. Nyenswah has worked in the public health sector in Liberia for the past 18 years in the Ministry of Health and Social Welfare, now Ministry of Health, in several capacities, beginning as an office assistant in 1999. Since then, he rose to the position of assistant minister of health and deputy chief medical officer for Preventive Services (2012–2015), responsible for the prevention and control of communicable and noncommunicable diseases, as well as mental health. Before assuming this position, he was the deputy program manager of the National Malaria Control Program (2007–2011), overseeing the coordination of malaria control and prevention activities, and formulating policies and implementation strategies. He also served concurrently as the acting program manager for 2 years (2009–2011). As acting and deputy program manager, he was a senior malaria specialist, overseeing the nationwide distribution of millions of bed nets and the effective treatment of millions of malaria cases in Liberia. Under his leadership, malaria prevalence was substantially reduced from 66 percent in 2005 to 28 percent by 2011. Mr. Nyenswah was instrumental in the development of the first National Health Policy and National Health Plan for Liberia in 2007. Mr. Nyenswah has received several distinguished service awards. In March 2017, the U.S. Centers for Disease Control and Prevention presented him with an honor and award certificate from the

National Center for Emerging and Zoonotic Infectious Diseases. He was honored with the first Bloomberg Hopkins Emerging Leader Award, on September 19, 2016. This award was established by Bloomberg Philanthropies, in honor of the Johns Hopkins Bloomberg School of Public Health's centennial celebration, to recognize a student or alumni with the potential to affect public health on a large scale for years to come. He also received the Outstanding Recent Graduate Award from the Johns Hopkins University Alumni Association in 2015, a distinction among more than 20,000 alumni globally. Additionally, the Johns Hopkins University Master of Public Health program graced him with a Certificate of Recognition in 2011. In 2015, Mr. Nyenswah was awarded one of the Liberia's highest honors, the Grand Commander, Order of the Star of Africa, by President Ellen Johnson Sirleaf, during Liberia's 168th Independence Day anniversary, for his service as the incident manager who coordinated the Incident Management System that brought the Ebola crisis under control in Liberia. Also in 2015, he received the Golden Image Award from Crusaders for Peace, a nongovernmental organization in Liberia. Mr. Nyenswah obtained the following degrees and certificates: Master of Public Health, Johns Hopkins Bloomberg School of Public Health (2012); Bachelor of Law, Louis Arthur Grimes School of Law, University of Liberia (2009); and Bachelor of Science (biology and chemistry), University of Liberia (2006). He has certificates and postgraduate diplomas in public health surveillance and population disease control, health and human rights, public health law, malaria in pregnancy, and global mental health, among others. Mr. Nyenswah is also a Doctor of Public Health candidate at the Johns Hopkins Bloomberg School of Public Health.

Mark Pearson, M.Sc., is deputy director for employment, labor, and social affairs (ELS) at the Organisation for Economic Co-operation and Development (OECD). Mr. Pearson works with the director to provide leadership in the coordination and management of the activities of ELS and ensure that it is at the forefront of the international social and employment agenda. Mr. Pearson joined OECD in 1992, initially working on tax issues. He then moved to ELS, becoming the head of the Social Policy Division from 2000 to 2008. During this time he initiated work on "Babies and Bosses," "Pensions at a Glance," and led the first cross-directorate work on gender and work on income inequality. In 2009 he became head of the Health Division where the central focus of work was on how to deliver health care with greater efficiency, including putting much more effort into prevention of obesity and harmful use of alcohol. Mr. Pearson has a degree in politics, philosophy, and economics from Oxford University and an M.Sc. in economics and econometrics from Birkbeck, University of London.

Paul Schaper, M.B.A., M.P.H., leads global policy efforts at Merck & Co., Inc., on infectious disease, including antibiotics and antifungals, HIV, and hepatitis, as well as on neuroscience. He represents Merck on the board of the AMR Industry Alliance, a coalition of biotechnology, diagnostics, generics, and research-based pharmaceutical companies and associations set up to work toward sustainable solutions to curb antimicrobial resistance. From 2013 to 2017, Mr. Schaper served as the board member for the Private Sector Constituency on the board of The Global Fund to Fight AIDS, Tuberculosis and Malaria. He currently serves as the Private Sector Alternate Board Member. Mr. Schaper earned his B.A. and master's degrees in public health policy and business administration from Emory University and a master's degree in clinical psychology from Georgia State University.

Lawrence H. Summers, Ph.D., is the Charles W. Eliot University Professor and president emeritus of Harvard University. During the past two decades, he has served in a series of senior policy positions in Washington, DC, including the 71st Secretary of the Treasury for President Clinton, director of the National Economic Council for President Obama, and vice president of development economics and chief economist of the World Bank. He received a bachelor of science degree from the Massachusetts Institute of Technology in 1975 and was awarded a Ph.D. from Harvard University in 1982. In 1983, he became one of the youngest individuals in recent history to be named as a tenured member of the Harvard faculty. In 1987, Dr. Summers became the first social scientist ever to receive the annual Alan T. Waterman Award of the National Science Foundation, and in 1993 he was awarded the John Bates Clark Medal, given every 2 years to an outstanding American economist under the age of 40. He is currently the Charles W. Eliot University Professor at Harvard University and the Weil Director of the Mossavar-Rahmani Center for Business and Government at Harvard's Kennedy School.

Jami Taylor is a board advisor at Stanton Park Advisors, a Boston-based investment bank, where she oversees the firm's capital raising and investor relations practices. Previously, Ms. Taylor was senior director of policy and partnerships within the Global Public Health division of Johnson & Johnson (J&J). In this role, she served as the designated J&J representative at major forums with international reach, including the Private Sector Delegation to The Global Fund to Fight AIDS, Tuberculosis and Malaria; the Partners Council at the Center for Global Development; and the Health Systems Leapfrogging Project of the World Economic Forum. A recognized expert in innovative financing for global health and development, Ms. Taylor secured a signature Blended Finance collaboration for J&J with Canada's Department of Foreign Affairs, Trade, and Development in 2015,

which was highlighted at the Global Financing for Development conference in Addis Ababa. In 2016, she co-founded Financing & Innovation in Global Health, a platform to drive more efficient resource mobilization in global health research and development and delivery. She is also the founder of WinnDev, a network of women advancing innovative approaches to the poverty reduction. In 2014, Ms. Taylor was named a Cross-Sector Leadership Fellow at the Presidio Institute, a program created by the White House Office of Social Innovation and Civic Participation to advance the work of leaders addressing society's most complex challenges. Prior to joining J&J, she spent more than 10 years in alliance development, policy communications, and grassroots mobilization. Her experience beyond industry includes work with the White House Office of Public Liaison, members of the U.S. Congress, and the U.S. Departments of Treasury, Commerce, and Health and Human Services to advance legislative and policy priorities on a nationwide scale. She is a published author and editor, and an alumna of the University of Virginia, Cornell University, Northwestern University, and Harvard University.

Kimberly Thompson, Sc.D., focuses her research and teaching on improving children's lives and global health by integrating the best available evidence into health risk and policy models that inform decisions and improve management. She focuses on the issues related to developing and applying quantitative methods for risk assessment and risk management, and consideration of the public policy implications associated with including uncertainty, variability, and complex dynamics in risk characterization. Drawing on a diverse background, Dr. Thompson seeks to effectively integrate economic, social, political, legal, and technological issues into analyses that inform public policy and improve decision making in what she calls the "Age of Risk Management." While on the faculty at the Harvard T.H. Chan School of Public Health, Dr. Thompson created and directed the Kids Risk Project. In January 2009, she incorporated Kid Risk, Inc. (www.kidrisk.org) as a self-standing, nonprofit organization that focuses on improving children's lives by understanding, characterizing, and communicating about the real risks that children face around the world and on empowering policy makers, parents, kids, and others to use the best available information to make better decisions. Dr. Thompson joined the faculty of the College of Medicine at the University of Central Florida in September 2012 and served as professor of preventive medicine and global health. She maintains long-standing interests in pediatric risk analysis and the potential trade-offs associated with policies designed to protect children and adolescents. Dr. Thompson received her B.S. and M.S. in chemical engineering from the Massachusetts Institute of Technology and her doctor of science (Sc.D.) degree from the Harvard T.H. Chan School of Public Health.

She is a past president and fellow of the Society for Risk Analysis, which recognized her with its 2004 Chauncey Starr Distinguished Young Risk Analyst Award. In 2008, she received the Jay Wright Forrester Award from the System Dynamics Society for some of the Kids Risk Project's research on polio. In 2014, Dr. Thompson led the U.S. Centers for Disease Control and Prevention/Kid Risk, Inc., team that won the Institute for Operations Research and the Management Sciences Edelman Award, the leading global prize in analytics and operations research for its collaborative work on global polio eradication. Dr. Thompson currently serves as the chair of the U.S. National Vaccine Advisory Committee.

Anna Vassall, Ph.D., is a professor in health economics at the London School of Hygiene & Tropical Medicine (LSHTM) and holds the Joep Lange Chair at the University of Amsterdam. She leads the economic evaluation and priority-setting group in global health at LSHTM. She is widely published and has led numerous large-scale economic analyses of tuberculosis (TB), HIV, and sexual and reproductive health interventions. She has substantial program experience directing health-sector development projects in several countries and supporting national strategic planning processes. She is a founding member of the TB Modelling Analysis Consortium and sits on the Strategic and Technical Advisory Group for the World Health Organization's (WHO's) Global TB Program (STAG-TB) and the Task Force on Catastrophic Cost Measurement for TB. She is a lead investigator of the Global Health Costing Consortium, a Bill & Melinda Gates Foundation–funded project to estimate HIV, TB, and other health service costs globally.

Ed Whiting, M.A., is responsible for Wellcome Trust's work to influence policy makers around the world in support of their objectives, for example, that Brexit enables excellent international science to flourish, that they are improving the global capacity to respond to epidemics and antimicrobial resistance, and that Wellcome is supporting scientists and researchers to enable rapid take-up of their work where there is potential for a significant positive impact on health. As chief of staff, he is responsible for supporting the development of Wellcome's new priority areas and how to deliver their existing priorities. He works closely with the chair and director to make sure they have identified and are delivering on top priorities and promises, and with other members of the executive leadership team to coordinate their big decisions. Before joining Wellcome in September 2016, Mr. Whiting worked in a number of Whitehall social and financial policy departments, including HM Treasury's financial stability team during the 2008–2009 financial crisis. He was most recently at 10 Downing Street as deputy Principal Private Secretary to the Prime Minister, leading on public

services. Mr. Whiting was awarded the OBE for public service and services to 10 Downing Street in the June 2016 Queen's Birthday Honours list.

Joanna Wolkowski, M.B.A., M.S., is vice president at Pfizer Inc. and lead of Portfolio & Decision Analysis (PDA). Her group is responsible for driving portfolio strategy and insight generation, enabled by innovative portfolio systems and robust reporting, to inform research and development investment decision making for Pfizer's senior-most leaders. She was elevated to her current role after having led strategic and portfolio oversight within PDA for the Vaccines, Oncology, and Consumer business segments. Formerly, Ms. Wolkowski was a principal at the Boston Consulting Group in the Health Care Practice Area. Her experience focused on corporate and commercial strategy within the pharmaceutical industry, driving strategic recommendations across therapeutic areas at the highest levels of client organizations. Earlier in her career, Ms. Wolkowski worked for 6 years with Pfizer as a discovery chemist, pharmaceutical sales representative, and strategic management group consultant. While a discovery chemist, she was part of a team that discovered azetidinyl ketolides for the treatment of respiratory tract infections caused by susceptible and multidrug-resistant bacteria. She also previously worked with Sierra Nevada Brewing Company in their Sales and Marketing division. Ms. Wolkowski earned a B.A. in chemistry from Middlebury College, an M.S. in chemistry from Yale University, and an M.B.A. in health care management and strategic management from the Wharton School of the University of Pennsylvania.