Rapid Medical Countermeasure Response to Infectious Diseases

Enabling Sustainable Capabilities Through Ongoing Public- and Private-Sector Partnerships

Workshop Summary

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Rapporteurs

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Although the reviewers listed above have provided many constructive comments and suggestions, they did not see the final draft of the workshop summary before its release. The review of this workshop summary was overseen by **LESLIE Z. BENET,** University of California, San Francisco. She was responsible for making certain that an independent examination of this workshop summary was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this workshop summary rests entirely with the rapporteurs and the institution.

Contents

APPENDIXES

1

Introduction[1]

"As the movement of people, goods, and services across borders increases, our national health security is increasingly dependent on global health security," states the Office of the Assistant Secretary for Preparedness and Response's (ASPR's) National Health Security Strategy,[2] describing the link between emerging infectious disease threats that may not have available treatments or vaccines, and the security of the world's health since these diseases also know no boundaries and will easily cross borders. The real and present danger of these emerging infectious diseases is illustrated in the 2013 emergence and persistence of H7N9 as a virus with pandemic potential; the 2014 Ebola virus disease (EVD) outbreak originating in West Africa and leading to isolated cases in several countries around the globe; and the recent surge in cases of Middle East respiratory syndrome coronavirus (MERS-CoV), originating in the Arabian Peninsula with recorded cases now in Asia, Europe, and the United States.

Yet, sustaining public and private investment in the development of medical countermeasures (MCMs) before an emerging infectious disease becomes a public health emergency in the United States has been extremely challenging. Interest and momentum peak during a crisis and wane between events, and there is little interest in disease threats outside the United States until they impact people stateside. In one example, an August 2014 analysis by EcoHealth Alliance, predicted the United States as one of the top three countries that would receive a patient with EVD

[1]The planning committee's role was limited to planning the workshop. This workshop summary has been prepared by the 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 Institute of Medicine, and should not be construed as reflecting any group consensus.

[2]For more on the updated National Health Security Strategy, see http://www.phe.gov/Preparedness/planning/authority/nhss/Pages/global.aspx (accessed July 29, 2015).

as a result of global air travel by an infected individual from West Africa.[3] The press release identified five U.S. airports at highest risk based on flight data, but the warning was essentially ignored by the media and decision makers, even though the World Health Organization (WHO) had already declared the outbreak an international public health emergency. Only a few months later would the first Ebola patient in the United States be diagnosed, causing national media coverage and widespread fear among the public and health care workers at all levels. Furthermore, an August 2015 *Nature* article noted that, while many are hopeful the EVD epidemic in West Africa will usher in a new era of how the world prepares for emerging infectious diseases, many public health officials are afraid that the impetus will fade, as after previous events, once Ebola fades from the limelight (Butler, 2015).

Current operational and business models involving government, the private sector, and academia to build and sustain MCM development capability are limited. Recent decreases in federal funding toward these efforts as well as the shifts from multiyear budgets to annual appropriations from Congress further hamper the ability to sustain capacity between outbreaks. Additionally, many regulations and policies that were developed in response to past events (e.g., severe acute respiratory syndrome, or SARS, in 2003, H1N1 in 2009) do not address potential future needs, or create capabilities and partnerships in a systematic manner. Instead they reactively address past gaps, making it difficult for partners to create broad capabilities able to address unknown future emerging infectious diseases. Although these challenges and others continue to present themselves, successes in MCM development for emerging infectious diseases over the past decade provide important opportunities from which to learn (e.g., the number of products approved and the manufacturing capability needed to support pandemic influenza response). In addition to learning opportunities, these successes in the past decade also provide existing systems that can be leveraged to build better capacity to predict, prepare for, and respond rapidly to emerging infectious disease threats in the future—if maintained at a functioning, operational level.

[3]See http://www.ecohealthalliance.org/press/101-ecohealth_alliance_identifies_ebolas_flight_path_to_the_u_s (accessed September 30, 2015).

ACHIEVING RAPID AND NIMBLE MCM CAPABILITY

On March 26 and 27, 2015, the National Academies of Sciences, Engineering, and Medicine, Forum on Medical and Public Health Preparedness for Catastrophic Events; Forum on Drug Discovery, Development, and Translation; and Forum on Microbial Threats co-convened a workshop in Washington, DC, to discuss how to achieve rapid and nimble MCM capability for new and emerging threats. Public- and private-sector stakeholders examined recent efforts to prepare for and respond to outbreaks of EVD, pandemic influenza, and coronaviruses from policy, budget, and operational standpoints. Participants discussed the need for rapid access to MCM to ensure national security and considered strategies and business models that could enhance stakeholder interest and investment in sustainable response capabilities. The objectives for the workshop,[4] as outlined by the workshop planning committee, are presented in Box 1-1.

BOX 1-1
Workshop Objectives

- Discuss the nation's capacity to provide rapid access to medical countermeasures (MCMs) for emerging infectious diseases, delineate preparedness gaps, and identify activities required by all stakeholders to improve capabilities.
  - Consider the impact of the current fiscal environment and reasonable expectations.
  - Examine the sustainability of public–private partnerships.
- Examine the role of MCMs for emerging infectious disease threats as a national security issue.
  - Discuss the ethical, economic, and global dimensions of these threats and the public–private partnerships required to establish robust capabilities.
- Discuss case studies of past incidents of emerging infectious disease threats to understand government and private-sector decisions and lessons learned.
  - Evaluate potential strategies for rapid availability of needed MCMs; and examine the operational and business models required to enable post-event rapid development, translation, and response in terms of regulatory pathways, financing and market

[4]For the full statement of task, see Appendix C.

opportunities, and the value proposition to private-sector partners.
    - Discuss the integration of the One Health efforts into ongoing threat assessments prior to a declared emergency.
- Consider how to operationalize next steps for the public and private sectors to coordinate a more rapid and nimble response to global emerging infectious disease threats.
    - Discuss common elements across a range of threats.
    - Consider the sustainability of business models to keep stakeholders invested.

ORGANIZATION OF THE REPORT

The following report summarizes the presentations from expert speakers and discussions among workshop participants. Chapter 2 highlights some of the persistent, critical gaps in international response capacity, in the context of the 2014 EVD outbreak. Chapter 3 considers preparedness from a national security perspective. Chapters 4, 5, and 6 discuss the challenges of rapid and sustainable development of MCMs in the context of three current threats: EVD, pandemic influenza, and coronaviruses, respectively. Chapter 7 explores business models and strategies for sustainable MCM development, and finally, in Chapter 8, panelists and attendees reflect broadly on the needs and opportunities discussed throughout the workshop.

OVERVIEW OF TOPICS HIGHLIGHTED DURING PRESENTATIONS AND DISCUSSION[5]

A number of themes emerged across multiple workshop presentations and discussions as participants considered current efforts and future strategies to ensure ready access to MCM for emerging infectious disease threats. The themes and opportunities highlighted below, drawn from the individual presentations and open discussions, are also discussed further in the succeeding chapters.

[5]Rapporteurs' summary of main topics and recurring themes from the presentations, discussions, and summary remarks by the meeting and session chairs. Items on this list should not be construed as reflecting any consensus of the workshop participants or any endorsement by the Institute of Medicine or the Forums.

- **Emerging infectious disease preparedness viewed as an issue of U.S. national security.** There was broad sentiment that emerging infectious diseases are a national security concern. A few participants raised concerns that the current focus on "all hazards preparedness" has diluted attention to infectious disease control, and that the national security implications of infectious disease threats are not given appropriate recognition beyond the public health sector.
- **Broader, earlier engagement of stakeholders.** Given the far-reaching consequences that can be associated with an outbreak of an emerging infectious disease, many participants highlighted the need to expand the discussion beyond the traditional MCM enterprise stakeholders.
    - John Rex, senior vice president and head of Infection Global Medicines Development, AstraZeneca, called for the involvement of economists, representatives from the Department of the Treasury, and global risk analysts to better understand and convey the potential collateral damage and economic impacts of inaction.
    - Because many, if not most, emerging infectious diseases are zoonotic, many participants noted the value in engaging animal disease surveillance and animal vaccine experts.
    - Although the private sector is clearly a key stakeholder and partner in the MCM enterprise, various participants stressed that the innovative pharmaceutical, biotechnology, and diagnostics industries need to be involved from the start, rather than brought in at some later time after a response strategy has been drafted.
- **Practical challenges to ensuring active cooperation.** Developing MCMs requires access, cooperation, and accountability. Virus sample sharing is encouraged, but Jeremy Farrar, director of the Wellcome Trust, pointed out that many countries are actually disincentivized to sharing virus samples because they will not be sold back MCMs at an affordable price. A partnership means that both parties will benefit, he said. Nicole Lurie, Assistant Secretary for Preparedness and Response at the Department of Health and Human Services (HHS), also pointed out that few people are publishing their protocols for treatment of EVD, so there has not been nearly enough analysis necessary

to understand life-saving treatments, let alone information for MCM development. Adding information sharing components as incentives for MCM development can bring more cooperation to the varying sectors involved.

- **Transparent prioritization followed by action.** Given the vast number of potential infectious disease threats and limited government, industry, and philanthropic budgets, it is clearly not possible to prepare for all eventualities. One participant summarized that "we are either paralyzed to inaction because there are too many threats and we don't know where to start, or we are too busy dealing with the threat of the moment to address anything else." Discussion supported the need for holistic threat assessment, considering not only the biological properties of viruses and hosts but also the social or behavioral contexts within which a disease could emerge to become a crisis. Transparency of the process and a clear signal of what is a priority would help partners (i.e., industry) to have some level of confidence in taking action and investing in development.
- **The role of industry as a commercial enterprise.** Approaches for effectively engaging industry need to be flexible while still company and countermeasure specific. A diverse array of approaches were discussed that could be used to incentivize and de-risk participation in the MCM enterprise (e.g., classic and novel push and pull mechanisms,[6] a portfolio partnership approach, product development partnerships). To entice and secure company investment, approaches could provide a return on investment or at least be cost neutral, several participants noted. Traditional government contracting mechanisms were described as cumbersome and laborious, and often not suitable for MCM development programs.
- **Sustaining interest and investment in MCM development.** The market for products and the investment in research and development fluctuate widely with the emerging and waning of an outbreak. Responses to emerging infectious disease threats

[6]Incentives for the development of MCMs that typically have no guaranteed market are categorized into "push" and "pull" categories. Push incentives lower the costs and risks of development, and pull incentives yield a reward if the product target is met. See more at http://www.nap.edu/catalog/12856/the-public-health-emergency-medical-countermeasures-enterprise-innovative-strategies-to (accessed August 28, 2015).

will continue to be reactionary unless better efforts are made during interepidemic periods to advance preparedness, noted Gerald Parker, vice president for public health preparedness and response at Texas A&M Health Science Center. Sustaining key capabilities for MCM development over time was a common theme, including maintaining scientific expertise, manufacturing pipelines, and having the networks, partnerships, and relationships for such development. Sustainability challenges and successes can be different for small and large companies.

  - **More effective risk communication.** Many participants noted the need for better risk communication so the media, policy makers, and the public can understand and relate to the potential implications of outbreaks and interventions, as well as the costs of inaction. A few speakers suggested using the current crisis, while it temporarily has the world's attention, to make the threats concrete and the planned actions clear.

- **The promise of platform technologies.** The ability to leverage a licensed manufacturing platform, in a facility approved by the Food and Drug Administration (FDA), has the potential to significantly reduce the time needed for MCM development in response to an emerging infectious disease threat. However, it will take some time for these platform technologies to mature and have the full buy-in of key regulatory agencies. Until then, as Monique Mansoura, Head, Medical Countermeasures & Government Affairs, Americas, at Novartis Influenza Vaccines highlighted, current assumptions and existing capabilities must be tested and exercised in order to provide verifiable assessments of preparedness before an event occurs (e.g., making and testing a vaccine, determining the dose, stockpiling, understanding the stability profile in the stockpile over time).
- **A framework to guide decisions on what level of "preparedness" is sufficient.** Lurie discussed the need for a better prioritized framework to determine when an MCM is needed versus a more traditional public health measure (e.g., handwashing, masks, vector control). The framework would also help to understand what type of MCMs would be required (e.g., vaccine, therapeutic), and to what stage of development a product should be taken (e.g., seed stocks, pilot lots, stockpiles). Such a decision framework needs to be transparent and easily

understandable to all partners across sectors. Other considerations for decision guidance include what basic science, platform-based technologies, and regulatory reforms are needed to enhance rapid MCM development for a given threat.

2

A Wake-Up Call: The 2014 Ebola Outbreak Response

By the time Victor Dzau, president of the National Academy of Medicine, welcomed participants to the first day of the workshop on March 26, 2015, there were more than 24,000 reported cases of Ebola, and more than 10,000 reported deaths. While Liberia had only one new case the prior week and no new cases for 3 consecutive weeks before that, Sierra Leone and Guinea continued to face many new cases and challenges in controlling the outbreak. Following this workshop, Liberia had a reemergence of cases in July 2015, showing the world that help was still needed, and illustrating the lack of a vaccine or treatment, more than 1 year after the outbreak had begun.

IDENTIFYING THE GAPS

Some experts believe the international response to EVD has failed miserably, Dzau stated. This chapter highlights what speakers described as critical gaps in preparedness and response across sectors. The multidisciplinary gaps include appreciating the threat level, achieving science preparedness, conducting disease surveillance, MCM development, relationship building, and accountability.

Gaps in Appreciation of the Threat and Consequences

According to Jeremy Farrar, director of the Wellcome Trust, the sense that the Ebola outbreak is coming to an end is misguided, and the "road to zero (cases)" is going to be bumpy and extraordinarily difficult. There was optimism in Guinea in August and September 2014, he said,

when the epidemic curve seemed to have peaked and the case count was decreasing. However, from August 2014 until March 2015, the curve has plateaued, and cases continue to be geographically dispersed, he explained. In contrast to epidemics like influenza, where population-level immunity develops, Ebola carries with it a difficult set of circumstances because the vast majority of people in the area remain susceptible to the virus.

Farrar expressed optimism about how the world is coming to regard emerging infectious diseases as priority areas with far-reaching consequences. As he stated, the Ebola outbreak not only has serious primary effects due to the direct outbreak itself, but also devastating secondary effects on health systems and society. In Guinea, Liberia, and Sierra Leone, he said, maternal and child health care, mental health care, diabetes management, and HIV care have all suffered during the EVD outbreak. As noted by Dzau, the three countries where Ebola has emerged already had preexisting fragile health systems, were emerging from a civil war, and/or lacked a sense of trust between the government and the governed. Still, the challenges of responding to epidemics are not limited to the developing world, nor are they limited to one nation or region, Farrar said. The United Kingdom, for example, had an intensive care occupancy rate of about 115 percent during the second wave of the H1N1 influenza epidemic in the winter of 2010. However, no intensive care units in the United Kingdom had spare ventilators. Additionally, urbanization is changing the nature of transmission of infections. Ebola is no longer a rural disease, and transmission occurs differently from previous outbreaks. In 1976, the average number of individuals in the Democratic Republic of the Congo associated with a single Ebola case was between 9 and 10. In 2014, the average number was 120 in Monrovia, Liberia. Individuals in urban centers travel more, have more contacts, and are often less willing to follow governing structures, he said. Most developing countries have fragile or fragmented health care systems, and there is not an appreciation of the benefits of public health, Farrar said. Health ministers in many countries are in relatively weak positions within executive body cabinets and are not empowered to be advocates for change within governments. In addition to strengthening the role of the health minister, it is also important to look beyond the health ministry

> If our efforts wane, if our interest dissipates, or we think it is done, … that will come back to haunt us.
>
> *— Jeremy Farrar, Director, Wellcome Trust*

to the finance and other ministries to strengthen the focus on health, Farrar noted.

Gaps in Science Preparedness

In Western countries, clinicians now consider Ebola to be a survivable disease, but according to Assistant Secretary Lurie, this did not translate very well to the events in West Africa. In a step toward global science preparedness, new vaccines and therapies in development are being tested in both established research networks and new research networks in West Africa, many of which are being led locally by African partners. Despite these efforts to become more scientifically prepared, she lamented, there was no standardized case report form either for patients in West Africa or for medically evacuated patients. Currently, there are no published guidelines for treatment of Ebola patients in West Africa. Some treatment units, have published their protocols, but results vary across units, and there has not been sufficient analysis of what is successful. Similarly, for MERS-CoV, there is a case definition but no uniform case report form, and limited analysis of what treatment protocols are effective. This will be the case for the next infectious disease and the one after that, Lurie cautioned, unless a change is made now.

Sustainable Commitment

Development of MCM for Ebola has moved forward as the need is clearly understood, but this has not been the case for MERS-CoV, Chikungunya, or other emerging infectious diseases for which the need and commercial market is currently not well defined. The two prevalent MCM strategies for Ebola during this outbreak were new product development and repurposing of existing pharmaceuticals, Lurie explained. The repurposing of current drugs (e.g., favipiravir, brincidofovir, amidarone) has not been particularly successful, and she noted a lack of transparency existing around data and clinical trials. Intellectual property disputes, issues with technology transfer, and challenges with data and specimen sharing have also slowed down development. Lurie applauded companies around the world that committed their own funding to MCM development without any guarantee of financial return on that investment. Some vaccine and therapeutic candidate development has been done in other countries (e.g., Canada, China), but the level of

country investment around the world has not been comparable to that of the United States. This, she said, raises concerns about the ability to sustain such efforts. She also commended the speed and flexibility of the FDA with regard to MCM development and clinical trials, but noted concerns about the lack of global coordination of the trials being done in West Africa. Investigators and companies complicate coordination by seeking prestige and advantage in countries that are in a desperate situation, with inadequate infrastructure to sort out the overwhelming requests while trying to manage the epidemic response. Officials in one Ebola-stricken country told Lurie that they had been approached by 35 different companies and investigators wanting to set up clinical trials in their country. She suggested that opportunism has trumped scientific rationality in too many cases, making progress even more challenging.

Gaps in Data Collection and Surveillance

In West Africa, efforts to collect and transmit data were very limited until late in the epidemic because of the challenges of working in the "hot zone" itself, and because the humanitarian workers in those countries believe their primary mission to be caring for the very sick, not to perform scientific data collection and analysis, Assistant Secretary Lurie commented. Science preparedness[1] was also hampered, she said, by global disagreements about study design, ethical standards, insufficient infrastructure to conduct clinical trials of any kind, and a perceived lack of urgency regarding how to move forward with experimental treatment therapies or potential vaccines.

Farrar stressed the importance of looking forward, adding that we tend to prepare for the previous epidemic when we need to prepare for the unknown disease in the next unexpected place. A greater understanding of the biology of epidemics is needed. For example, what drives the transmission route of a disease migrating from animal to human? What drives virulence in human-to-human transmission? Contemporary disease surveillance technology has uncovered an unprecedented number of circulating influenza viruses, but no one can predict which present the most risk in terms of developing into a global

[1]ASPR defines "Science Preparedness" as a collaborative effort to establish and sustain a scientific research framework that can enable emergency planners, responders, and the whole community to better prepare for, respond to, and recover from major public health emergencies and disasters. For more information, see http://www.phe.gov/Preparedness/planning/science/Pages/overview.aspx (accessed August 11, 2015).

pandemic. Better and smarter global disease surveillance and the sharing of real-time data to inform decisions are critical, he added, and the capacity to respond should be associated with such surveillance efforts. He noted that there are also competing disincentives to sharing data and samples (e.g., some countries have said that if they share samples of pathogens from outbreaks, they will then be sold interventions at prices they cannot afford). He suggested the need for a dedicated epidemic surveillance and response unit within a global organization that is semi-autonomous from the WHO member states, and also has the mandate and the leadership to bring about the coordination that is needed.

Gaps in Sustainable MCM Development

Elements of sustainable MCM development include partner commitment, financial models to ensure long-term resources, infrastructure, trust, advocacy by and for the beneficiaries of MCM development, and building on existing strengths and progress. Scientifically, Lurie said, there has been tremendous progress, not just with new vaccines and therapies but also platforms for rapid development of diagnostics and for product manufacturing. However, we need better, more effective products, and we need them faster, she said. Also needed are better approaches to life cycle management for both targeted and broad-spectrum products. This includes longer-life-cycle products that can be stockpiled as well as dual-use products that have day-to-day applications and are readily accessible to health care delivery systems around the world.

Farrar expressed concern about partnerships not including industry at the table from the start. Industry wants to help, but it must be understood that it is there as a commercial enterprise. "We do not ask for a cheap battleship when working with defense budgets," he said. "We ask for the best battleship and technology, and then we work out how we are going to afford it. Whereas with public health they ask for whatever can be bought with the least amount of money." The dynamic of always asking for a cheap drug or affordable intervention for public health emergencies needs to change. "We will not have what we need unless we are willing to pay for it," Farrar said. While some funding comes from philanthropy, governments often provide the majority of funding in a response. To make sure amounts are adequate, improved communication and true understanding of threats are needed.

Gaps in Relationship Building

A 21st-century public health response involves more than just public health measures (e.g., masks, isolation); it involves diagnostics, drugs, vaccines, information technology, logistics, and, where necessary, a military presence. The response needs to happen over days to weeks, not weeks to months or longer, Farrar emphasized. Getting there requires manufacturing capacity, regulations, ethics, design of studies, and other capacities that need to be developed in the interepidemic period. Farrar added that any activity not built on a trusting relationship between public health and communities will have limited success. Trust and mutual respect are built up over many years and involve local capacity building. They do not come from flying in with resources during a crisis and flying out when the event is over, he said.

Gaps in Accountability

The health infrastructure in developing countries, particularly where Ebola has recently emerged, is almost nonexistent despite decades of investment in health system strengthening by bilateral donors and national governments, said Rajeev Venkayya, president of the Global Vaccine Business Unit at Takeda Pharmaceuticals. This represents a colossal failure on the part of the global community, he said. Although substantial improvements have been made in maternal and child health, as well as immunization, there is not much more than well-functioning immunization programs in these countries. Venkayya considered improving the health infrastructure as a collective responsibility.

Many of these countries have resources, but they choose not to allocate sufficient resources to health, he said, illustrating Farrar's previous statement about looking past the ministries of health to include other sectors and decision makers. Venkayya called for a need for accountability that ensures that donor funds complement government funding for health. In many cases, governments use donor funds to replace the funding that the national government had been investing in health (i.e., government money for health is reallocated elsewhere). Global response to a crisis needs to be overseen by an organization that has command and control over assets that are precommitted to the response. There need to be preidentified, appropriately trained personnel from multiple countries who are ready to step up and equipped to respond, he noted.

Venkayya said the White House can play an important role in bringing together federal agencies whose day-to-day activities may not be aligned—as the agencies and people in them are doing phenomenal work—but the overall response could be improved by coordination. Venkayya observed that, during some of the recent health crises, there was not an office inside the White House that had technical health experts who also understood policy and could bring the agencies together and hold them accountable for delivering results. This coordinating, overarching role, allowing the departments and agencies to focus on and execute their roles and responsibilities without overlap or duplication, could be very helpful.

3

Preparedness as an Issue of National Security

In October 2014, President Obama stated that he considered the Ebola outbreak and response "a top national security priority."[1] The Global Health Security Agenda and the 2015 National Security Strategy include preparedness and response to infectious disease outbreaks.[2] Although several presidents have recognized that epidemics of infectious disease are a national security concern, multiple pieces of legislation have been drafted and passed, and new organizations created to address epidemics, we continue to lament the lack of capacities for timely and adequate responses. As illustrated in Chapter 2, gaps in international response capability persist, and according to Parker at Texas A&M Health Science Center, reports suggest that the global community is ill prepared for the next epidemic or pandemic. In this chapter, experts representing a variety of sectors (e.g., national security, biosecurity, defense, economics, risk, industry, and ethics) discuss their perspectives, focusing on what can be done during interepidemic periods to envision MCM availability through a lens of national security, fill the gaps in preparedness, and enhance MCM capabilities.

ECONOMIC IMPACTS

The emergence of a new and more dangerous infectious disease is what economists such as Robert Shapiro, co-founder and chair of

[1]See https://www.whitehouse.gov/the-press-office/2014/10/06/remarks-president-after-meeting-ebola (accessed June 30, 2015).

[2]See http://www.cdc.gov/globalhealth/security/and https://www.whitehouse.gov/sites/default/files/docs/2015_national_security_strategy.pdf (accessed June 30, 2015).

Sonecon, LLC, refer to as an exogenous event—one that comes from outside the economy, so it is unpredictable. A strong economy may mitigate the impacts of exogenous shocks, while a weaker economy can suffer lasting negative effects. Shapiro likened a strong economy to a society that is prepared for the outbreak of a dangerous disease. In predicting the potential impact that a shock (i.e., outbreak) will have on the society, one needs to consider all of the following: who is in charge, how vital data and information are obtained, how reliable those data are, whether the dissemination of key information is well managed and controlled, whether concrete measures are in place with resources to isolate and control the spread of the disease, and whether there are facilities ready to develop new treatments to rapidly produce them and efficiently distribute them.

The effects of an exogenous shock on the overall economy depend on two dimensions: how widespread the effect of the shock is and how long the effects are sustained. A shock that is fairly localized and does not last long (e.g., a hurricane or the 9/11 terror attacks) has little macroeconomic effect. This kind of event, however, has distributional effects. Following the events of September 11, 2001, for example, Lower Manhattan real estate values fell, but those in Midtown rose; hotels and airlines suffered temporarily, but consumers instead spent their money on televisions and recreational vehicles; the federal government cut interest rates, boosting interest rate-sensitive industries. These dimensions also apply directly to the economic effects of an unanticipated natural disease outbreak or intentionally released infectious agent (e.g., whether it has the potential to become a pandemic, spread over a wide area for a protracted time).

Much of the economic cost of disease outbreaks arises, not from direct effects but from public anxieties because of misinformation about the spread of disease and lack of clear or appropriate leadership response at the outset. Economic effects of an event become nonlocalized as a result of large-scale quarantines, disruption of business, calls to close schools and cancel large public gatherings, and demands to suspend air flights and close borders between states. Public panic, either financial or otherwise, is the absence of reliable information. Shapiro indicated that information must be followed with concrete measures that effectively contain and treat the infection. These conditions emphasize the critical need for advanced investment and planning, including the designation of a credible agency or person in charge who can allay fears and disseminate credible information.

In a world of limited resources, the public resources to plan and prepare for a pandemic almost certainly must come from spending for another public purpose or from additional taxes, he said. However, people are generally unwilling to bear short-term costs in order to avoid a larger unknown long-term cost. Given this political reality, Shapiro suggested the idea of a philanthropic-financed entity, perhaps working with the Centers for Disease Control and Prevention (CDC), that would examine the level of state and federal preparedness and recommend steps to better plan and prepare. This could be accompanied by a new tax incentive for pharmaceutical firms to establish facilities that could quickly produce vaccines and treatments for emerging infectious disease outbreaks.

GLOBAL RISK ANALYSIS

What is needed now, according to Suresh Kumar, senior partner at Oliver Wyman Public Sector and Health and Life Sciences Practice, Marsh & McLennan Companies, is an objective, outside-in global health security strategy for the future. This strategy would consist of enabling frameworks for raising money; conveying resources and services to affected populations; establishing policies and protocols that enable the development of innovative products, programs, and pathways; and understanding and sharing risks, liabilities, and responsibilities to preempt, combat, and contain infections. He agreed with others that industry is going to be part of the solution and needs to be involved at the start.

World Economic Forum: 2015 Global Risk Report

Marsh & McLennan produces an annual global risk report for the World Economic Forum. The report is based on an annual Global Risk Perception Survey of more than 900 leaders and decision makers from business, the public sector, and academia to identify risks, their potential impact, and the likelihood of occurrence. Of concern, Kumar said, is that rapid and massive spread of infectious disease made the list for 2015 after a hiatus of 6 years, and was ranked second for risk in terms of potential impact.[3]

[3]See http://www3.weforum.org/docs/WEF_Global_Risks_2015_Report15.pdf (accessed June 30, 2015).

The 2015 report delineates risks from trends and the interrelationships between them that could be a cause for further concern. A global risk is an uncertain event or condition that, if it occurs, can cause significant negative impacts for several countries or industries within the next 10 years, he explained. By definition, it is not always predictable, but one can prepare for it. A trend, he said, is a long-term pattern that is currently taking place and that could contribute to amplifying the global risk and/or the relationship between them. Unlike risk, trends occur with certainty and can have positive or negative consequences. Global health security concerns will be exacerbated by trends toward rapid and unplanned urbanization, particularly in developing countries; inadequate infrastructure associated with water, electricity, and sanitation; increasing resistance to antibiotics and antiviral drugs; and growing human mobility, which compounds the risk of transmission.

> An epidemic like Ebola is not an African problem. It is a global problem, a human problem, the solution for which lies in building local, regional, and global collaborations and shared responsibility.
>
> *— Suresh Kumar, senior partner at Oliver Wyman Public Sector and Health and Life Sciences Practice, Marsh & McLennan Companies*

Kumar stressed the need for agreement on what constitutes global health security and alignment on risk mitigation pathways (e.g., building resilience, resource mobilization, treatment of infected patients/health care workers, identifying and isolating infected people versus quarantines and embargos). The response to the EVD outbreak has exposed a globally broken, antiquated system where efforts are likely duplicated, technology is inadequately leveraged, and resources are not optimally deployed. Mistrust between donors and recipients persists, donors demand accountability, and recipient countries are uninspired to work with external experts who come and go with each crisis, failing to build sustainable institutions or capabilities.

Facilitating pathways need to address issues such as ownership of intellectual property, liability, regulatory pathways, technology, new hospitals/prefab modular hospitals, telemedicine, and training of health workers. Kumar stressed that each person needs to move the conversation in his or her area of expertise. Furthermore, this is a global problem that calls for a confederation, not multiple localities addressing their unique needs. A participant noted that outbreaks are going to start and spread from countries where the United States and other major powers do not have access, such as those in the Middle East or northern

Africa. Venkayya said that, if a health agency is in charge, it must be complemented by the diplomatic and security apparatus necessary to execute a response. The United Nations and influential governments must use their diplomatic, financial, and other levers to encourage governments of impacted countries to do the right thing, he advocated.

LEVERAGING THE DEPARTMENT OF DEFENSE MISSION

Infectious diseases, whether naturally occurring, accidentally released, or intentionally caused, continue to threaten U.S. military personnel and their beneficiaries, both at home and abroad, said Commander Franca Jones, medical director of the Office of the Deputy Assistant Secretary of Defense for Chemical and Biological Defense Programs. Therefore, the Department of Defense (DoD) plays a critical role in global health security through ongoing threat reduction and MCM development programs for their personnel, as well as through enforced health protection efforts.

Within DoD, the Chemical and Biological Defense Program is charged with developing capabilities to enable the warfighter[4] to deter, prevent, protect against, mitigate, respond to, and recover from chemical and biological threats and their effects. Specifically, the program's efforts to develop MCM, which include prophylaxis, therapeutics, diagnostics, and biosurveillance information systems, all support this mission as well as the U.S. Global Health Security Agenda.

Applications to the Civilian Sector

Because biological threats range from common infectious diseases to the potential for complex engineered organisms, the DoD program uses an integrated layered approach, seeking holistic solutions, not just for individual agents, but potentially for classes of agents, that protect the warfighter both from the inside and the outside (e.g., personal protective equipment, decontamination, MCM). The program relies on requirements provided by the warfighter, and programmatic efforts focus on solutions for the warfighter. However, much of DoD's research and development efforts can be leveraged for the broader civilian population, both domestically and internationally. For example, DoD's Ebola

[4]The term "warfighter" is used to describe a soldier in combat.

diagnostic test was the first to receive emergency use authorization (EUA) for use in U.S. citizens. As of March 2015, it is the only test used throughout the U.S. Laboratory Response Network and in U.S. laboratories in West Africa. DoD's early investment in the Ebola therapy, ZMapp, led to that drug's use in Phase II and III clinical trials. It is important to note that these products were in development years before the current Ebola outbreak due to a warfighter requirement for diagnostic, preventive, and therapeutic capabilities against filoviruses. Ultimately, according to Jones, had it not been for these ongoing efforts, it is less likely that products would have been at a stage to move forward into the field as quickly as they were. As Tara O'Toole, senior fellow and vice president of In-Q-Tel, Inc., pointed out, the DoD Ebola diagnostic test was able to quickly be applied for field use, while vaccines and other countermeasures being developed still take many months of trials and analysis before use in the field, highlighting the importance of supporting point of care diagnostics to assist in rapidly halting epidemics.

Prioritization of Threats for the Warfighter

> It is impossible to stay ahead of every threat that may present itself. Within the DoD, our strategy is to develop broad solutions that may have application to multiple threats.
>
> *— CDR Franca Jones, medical director of the Office of the Deputy Assistant Secretary of Defense for Chemical and Biological Defense Programs*

DoD must balance its work against a broad range of threats, including nuclear, chemical, biological, radiological, explosive, cyber, and others. Even within the biological threat, there are multiple viruses, bacteria, and toxins. To prioritize, DoD thinks about how best to reduce risk to the warfighter. The strategy for MCM development focuses first on those agents that have a high mortality rate, are rapidly lethal, spread rapidly from person to person, or put a warfighter out of the fight for a prolonged period of time. Second, DoD works toward being able to rapidly field certain countermeasures through "interim field capabilities," such as pre-EUA packages submitted to the FDA, or through contingency investigational new drug applications (INDs). DoD also encourages the development of broad-spectrum MCMs that address both current clinical needs and emerging infectious diseases. Finally, DoD coordinates efforts domestically

through the ASPR Public Health Emergency Medical Countermeasures Enterprise (PHEMCE), as well as with international partners, to provide synergistic value.

Jones said that, during the recent Ebola outbreak, although DoD did have products available, initiating clinical trials was very difficult. Therefore, she recommended the development of protocols for randomized controlled clinical trials through WHO and other organizations, with buy-in from countries that have the minimum essential elements to be prestaged as clinical protocols. Many trials that are ongoing in these countries are not well designed, will not lead to licensed products, and will not help develop products for the next outbreak, she claimed.

Staying ahead of every threat that may present itself is impossible, Jones acknowledged, and this has been one of the biggest roadblocks. Within DoD, the strategy is to develop broad solutions that may have application to multiple threats. Moving forward, she said, DoD's international and interagency partnerships will be critical to ensuring that multiple potential threats are addressed by the defense and health sectors with countermeasures to ensure a world safe and secure from infectious disease threats.

BIOSECURITY STRATEGY

O'Toole of In-Q-Tel concurred with others that the public health sector must ask for what it needs, noting that, within public health alone, there is not nearly enough money to construct a sound, strategic biodefense strategy. The nation's public health sector has been decimated since 2008 by the economic recession, especially at the level of the state health department, which is often where the local response capacity lies. She added that, while those within government are focused on how to sustain their programs and survive, external stakeholders are needed to advocate for what must be built. In the United States, the private sector has always been the prime source of innovation. However, it has become increasingly difficult for private organizations to harmoniously work with government due to a variety of challenges (e.g., cumbersome acquisition systems, risk-averse contract officers, insufficiently funded projects). Therefore, O'Toole advocated, it is necessary to create novel ways in which the government and private sector can work together. One option she suggested is that MCM design and production be moved out

of government and assigned to a new type of organization that is not hampered by government acquisition rules.

Raising the Profile of Public Health

Biosecurity is not a top priority of any agency, O'Toole said. Public health needs a higher profile, including a seat at the National Security Council table, and an agency dedicated to public health, with cabinet-level power that can command the attention and the resources of government committees. Such an agency could begin to illuminate the true costs of what is needed and define how to achieve it, educating policy makers and the American public on why we can expect these epidemics to continue (e.g., human activity in once-remote ecosystems, antibiotics in poultry feed).

ENGAGING INDUSTRY

Daniel Abdun-Nabi, president and chief executive officer of Emergent BioSolutions, shared his perspective based on more than 15 years of acquiring and developing MCMs for biological and chemical threats for governments across the globe. In 1998, Emergent Biosolutions acquired the anthrax vaccine for development, working in close collaboration with DoD, which was the principal government agency responsible for MCM to protect the warfighter. The 2001 anthrax letter attacks made it clear that anthrax was no longer only a military problem, but also a civilian one. Infectious threats could be natural or human-made, emerging at any time or from any source.

In 2004, Project Bioshield was signed into law, allocating $5.6 billion for the research, development, acquisition, and stockpiling of MCMs for civilian use, through programmatic initiatives that included public–private partnerships. Abdun-Nabi said that the management of Project Bioshield by ASPR's Biomedical Advanced Research and Development Authority (BARDA) has led to 12 MCMs now in the Strategic National Stockpile (SNS) to address bioterror threats—10 of which are licensed and 2 of which are available under EUAs. He noted that Emergent BioSolutions provided several of those products to the U.S. government under long-term contracts. While this shows some successes and end-stage products, others criticize Project Bioshield because, with $5.6 billion spread across 14 different threats, their awards

are too small to motivate large pharmaceutical companies, and so it has only attracted smaller biotech and pharmaceutical companies (Matheny et al., 2007) illustrating the difficulty in finding a "one-size-fits-all" solution.

The key to the BARDA strategy is collaboration among government agencies and partnerships with industry early in development. Resources from these partnerships are ready to be tapped, Abdun-Nabi said. For example, Emergent BioSolutions has a number of technologies that are relevant to Ebola, but it had not fully developed any of them because they were low in priority as established by the company's resources and capabilities. However, during the outbreak, the company made a candidate vaccine at risk and subsequently partnered with the National Institutes of Health (NIH), GlaxoSmithKline (GSK), Oxford University, and the Wellcome Trust for further development. Within 90 days that product went from candidate identification to clinical trials. The company has additional assets that could be applied to treating Ebola, including a portfolio of monoclonal antibodies, a polyclonal technology, and a flexible manufacturing facility if opportunities become available.

Abdun-Nabi emphasized that, to attract industry to MCM development, there needs to be a vibrant and sustained market opportunity, including long-term contracts from government for product development, manufacturing, and procurement, and an increase in the integration of financing so there is equity on both sides of the agreement. Long-term agreements with large-scale deliverables can help to establish pricing that is fair and reasonable to the government, while providing reasonable return on investment to pharmaceutical companies. He agreed with others that a more streamlined and simplified contracting process would help to enable pharmaceutical companies and others to enter the MCM space.

A few participants noted that it has been very challenging to induce credible leaders in industry to speak openly to Congress about what they would need to invest in the MCM enterprise. Venkayya at Takeda agreed that it is risky for companies to advocate for government research and development investment in products that will benefit the industry somehow, as it almost always appears self-serving. Sophisticated stakeholders inside and outside of government, including academics and patient groups, also need to validate industry needs and concerns in front of Congress, a participant added. John Rex of AstraZeneca concurred that industry cannot advocate for itself in this area.

ETHICAL CONSIDERATIONS

Lisa Lee, executive director of the Presidential Commission for the Study of Bioethical Issues, referred participants to the Commission's recent report, *Ethics and Ebola: Public Health Planning and Response*.[5] The report highlights important ethical dimensions of the predominantly national security rationale for public health action and preparedness. Garnering the political will and the resources necessary for public health action can be extremely difficult, she said. National and/or health security arguments during and immediately following a high profile public health emergency can be quite compelling, both to the policy makers and to the public, who otherwise might be either skeptical or have limited knowledge of public health infrastructure. However, as noted by others, interest and momentum wane between events. Invoking a predominantly national security rationale to address public health problems can be very effective in contributing to policy and programs that strengthen the public health infrastructure, but there are unintended consequences with ethical dimensions and direct practical implications for preparedness.

The Ebola epidemic and other recent disease outbreaks have demonstrated that prevention continues to be undervalued and underfunded, Lee said. It is hard to measure or capture the value of something not happening. Public health emergencies most often arise from long-standing conditions of social injustice and inequity, and the global attention to public health emergencies is often reactive and fear based. Trust in government and meaningful involvement of affected communities are essential to prevent and to respond to emergencies, according to Lee. While pharmaceutical MCMs have had dramatic impacts on public health emergencies involving novel threats, the traditional low-technology, public health practice approaches have been proven to be the most useful in those countries that have successfully averted disaster (e.g., public health surveillance, community engagement, quarantine and isolation, contact tracing).

While deliberate development of ethical, evidence-based public health policies is essential in a society committed to global public health, public health experts and policy makers would be remiss if they did not also attend to the health security implications. As outlined by the Commission in its Ebola report, there are both ethical and prudent

[5]See https://bioethics.gov/node/4637 (accessed June 30, 2015).

reasons for U.S. engagement in response to public health emergencies. Ethical reasons are both humanitarian and justice based. Health is a global public good, and from a humanitarian perspective, the suffering of others demands action. Social justice, which Lee said is a central ethical foundation of public health, involves a commitment to sufficient levels of health and well-being, regardless of location or national affiliation. Beyond ethics, prudence acknowledges that our national interests are clearly tied to the interests of others.

Unintended Consequences of a National Security Lens

Lee highlighted some of the possible unintended consequences of a predominantly national security or health security orientation to response. All parties are best served by a broad approach to what constitutes both health and national security. When public health policy and action are grounded in a narrow definition of national or health security, there can be numerous unintended, often interrelated, consequences that can negatively impact public health efforts. For example, public health programs might be perceived as intended to protect high-income countries against the diseases of the lower-income, afflicted country. This perception can result in stigma, discrimination, and inattention to health problems that are unlikely to affect high-income countries. There is often an emphasis on short-term solutions to control acute infectious diseases when they emerge, rather than long-term efforts to build health infrastructure and address the underlying issues that contribute to the likelihood of such outbreaks (e.g., war, poverty). Other concerns include the increased politicization of health problems, the association of public health programs with misuse of authority, including governmental or military power, and decreased cooperation and sharing in the goals of public health efforts.

Moving forward, it is important to recognize that there are both ethical and prudent interests in working to improve global health, and that the rhetoric surrounding an emergency response can have both clear and unintended consequences.

CAPITALIZING ON THE CURRENT MOMENTUM

Andrew Weber, deputy coordinator for Ebola response at the Department of State, stressed the importance of capitalizing on the

momentum from the Ebola response, and referred participants to a recent commentary by Bill Gates on lessons to be learned from the Ebola epidemic (Gates, 2015). Incremental progress has been made over the years, Weber said, but Ebola has once again demonstrated our collective vulnerability. The global population is only as safe and healthy as the weakest links around the world. The response to the EVD outbreak quickly outstripped the capacities of the health agencies of Guinea, Liberia, and Sierra Leone. Despite the largest field deployment by CDC in its history (more than 200 persons), there are still acute shortages of key personnel (e.g., French-speaking senior field epidemiologists for Guinea) to dedicate to this response.

He also noted the long lead time for product development. One year has passed since WHO confirmed the Ebola epidemic in West Africa, and vaccines are still undergoing trials. O'Toole of In-Q-Tel emphasized the need for diagnostics, both laboratory and point-of-care, and said the lack of better diagnostics is a market failure. Weber agreed whole-heartedly, saying that diagnostics are key to global capacity building, and we have been underinvesting in their development and underestimating their value and return on investment. For example, the Naval Medical Research Center Laboratory in Bong County, Liberia, was able to reduce the time to Ebola diagnosis from 5 to 7 days, to 3 to 5 hours. This allowed for the ability to triage cases, rather than sending all those waiting for test results to already overwhelmed Ebola treatment units. He also highlighted the importance of information technology and bio-surveillance (including a global, real-time early warning system).

The response needs to be multisectoral and multinational, Weber said. More than 70 countries, and numerous private and philanthropic organizations, have contributed resources, technical expertise, personnel, and money to the response in West Africa. He highlighted the agility and capability of the philanthropic sector in contributing to the response effort and in coordinating different sectors to innovate solutions. Efforts are under way in the private sector to develop three promising vaccine candidates that are currently in Phase II and Phase III clinical trials in West Africa. Preparing the world to prevent and respond to future epidemics requires capitalizing on this extraordinary global effort and international goodwill.

During discussions, Venkayya and Rex raised the issue of sustainability of prevention efforts centered around a vague threat with significant consequences. "We need to use the current crisis, while we temporarily have the world's attention, to make the threats concrete and

the planned actions clear," Venkayya said. This entails communicating how government and industry partners are going to share risk and cost in addressing defined targets. There is also a need for leadership in the executive branch to buy into this concept and propose the necessary investments.

Shapiro of Sonecon again highlighted the importance of being very precise and clear about what is actually needed and being requested when advocating for public resources with Congress and the administration. Numerous needs and wants were mentioned in the discussions (e.g., funding for an agency that evaluates preparation and facilities to develop vaccines). The system is very resistant to taking money away from one entity in order to give it to a new entity, and is even more resistant to raising additional revenues. In some cases, mobilizing the public interest can create leverage within the government (e.g., by explaining to the public, as well as the business sector, what would be lost in the absence of securing funding). Kumar of Marsh & McLennan added that budgets are generally set based on the prior year's budget, plus or minus some amount. In addition to being clear about what is needed, it is important to be very specific about what will no longer be done and what duplications will be eliminated.

4

Rapid Development of Ebola Vaccines

Perspectives on the MCM response to the 2014 Ebola outbreak were provided by panelists from government and the private sector. (Detailed technical accounts of the MCM development process are included at the end of this chapter in the Chapter 4 Annex.) Michael Osterholm, director of the Center for Infectious Disease Research and Policy (CIDRAP) at the University of Minnesota, referred participants to the *Recommendations for Accelerating the Development of Ebola Vaccines: Report & Analysis*.[1] The report, released in February 2015, was authored by the Ebola Vaccine Team B, a joint project of CIDRAP and the Wellcome Trust. The Team B panel was co-chaired by Osterholm and Farrar of the Wellcome Trust and consisted of 26 international vaccine experts, including 8 senior scientists from Africa. Over the course of about 3 months, the team reviewed the issues surrounding the development of Ebola vaccines and made 48 recommendations in 7 focus areas: manufacturing, safety and efficacy/effectiveness determination of Ebola vaccines, regulatory pathways, ethics, community engagement, vaccination strategies, and funding. This followed an interim Team B report, released in January 2015, on the minimal criteria for Ebola vaccines for use in epidemic settings, recognizing that there may be multiple vaccines developed for use in different strategies, and multiple regulatory pathways and governance authorities involved.[2]

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[1]See http://www.cidrap.umn.edu/recommendations-accelerating-development-ebola-vaccines-0 (accessed June 30, 2015).

[2]Fast-Track Development of Ebola Vaccines: Principles and Target Product Criteria, available at http://www.cidrap.umn.edu/fast-track-development-ebola-vaccines-principles-and-target-product-criteria-0 (accessed June 30, 2015).

Norman Baylor, president and CEO of Biologics Consulting Group, and a member of Team B, reiterated that the Team B approach was a very rapid process in identifying issues and challenges and developing a roadmap with recommendations and a target product profile. During the Team B meetings, information was received from individuals on the ground in real time, and recommendations were modified accordingly. In outlining its recommendations, Team B considered both what a given group could do with what was in their "toolbox," as well as what type of recommendations could be made if there were no restrictions on a group's activity.

The Team B approach is a very effective process, Baylor said, but it needs to occur before the incident. The challenge is deciding when a particular risk needs to be taken up, as most often stakeholders find themselves trying to catch up with the crisis propelling ahead. Osterholm agreed that the Team B process could easily be applied in anticipation of an event, not just in response to an event. Important public health interventions can be brought to bear relatively quickly, but MCMs cannot be deployed if they do not exist.

PUBLIC HEALTH PERSPECTIVE

Since August 3, 2014, BARDA has been in response mode to the Ebola epidemic, said Robin Robinson, director of BARDA. He noted that Ebola is both a bioterrorism threat and an emergent infectious disease, and he briefly discussed BARDA's role and activities in response to the most recent outbreak. BARDA has been involved in the procurement and development of a number of therapeutic candidates for Ebola (e.g., monoclonal antibodies such as ZMapp). BARDA has also been supporting the advanced development, manufacturing, and testing of three Ebola vaccine candidates, and is in negotiations regarding the development of two other earlier-phase candidate vaccines. Current and planned Ebola vaccine clinical trials include both randomized controlled trials and open-label trials.

BARDA also provides funding to support manufacturing and analytical testing (e.g., scale-up from pilot to commercial scale, thermostability of vaccines). Robinson emphasized the value of thermo-stable vaccines in regions where cold storage can be a problem. He added that BARDA is working with pharmaceutical colleagues on new formulations, including lyophilized vaccines. Of concern, Robinson

noted, was one or more of the vaccines that may provide waning immunity and require administration of a booster dose. BARDA is working with the Global Alliance for Vaccines and Immunization (GAVI) and the United Nations International Children's Emergency Fund (UNICEF) to understand what would be needed to manufacture vaccines, ensure supply, and establish appropriate pricing.

Robinson emphasized the value of BARDA's numerous partnerships with industry, federal partners, WHO, and, more recently, non-governmental organizations, such as the Wellcome Trust and the Bill & Melinda Gates Foundation. Over the past 4 years, BARDA has developed a package of core service assistance programs to help MCM developers with preclinical animal studies, advanced development and manufacturing, fill finish manufacturing, and clinical studies. To build the U.S. infra-structure for these core activities, BARDA has established Centers for Innovation in Advanced Development and Manufacturing through public–private partnerships and a Clinical Studies Network. BARDA is also discussing with partners the need for a coordinated global infrastructure for response to emergent infectious disease.

REGULATORY PERSPECTIVE

To help facilitate timely Ebola vaccine development, the FDA has engaged in numerous meetings with IND sponsors to discuss product information (chemistry, manufacturing, and controls, or CMC), clinical development programs, and different pathways to licensure for Ebola virus vaccines, said Marion Gruber, director of the Office of Vaccines Research and Review in the Center for Biologics Evaluation and Research at the FDA. A dedicated team is committed to expedited review of CMC product information, preclinical and clinical protocols, and clinical trials data (where available) for Ebola vaccine candidates. For example, review of an IND is normally completed within 30 days as required by law; however, the FDA has been reviewing INDs for Ebola vaccine studies within days or weeks. The FDA has also approved several emergency-use INDs for postexposure prophylaxis products. For example, select vaccine candidates that have shown at least some protection in animal models were made available through emergency-use INDs to health care workers who have suffered needle stick injuries when taking care of Ebola patients.

This is a global effort, Gruber said, and the FDA is engaging in international consultation and collaboration with its sister national regulatory agencies (European Medicines Agency, or EMA; Health Canada; and others) to discuss the review of Phase I, II, and III clinical protocols and to try to reach regulatory convergence where possible. The FDA has also been assisting African regulators with reviewing Phase II and III clinical trial applications taking place in their countries. Through joint reviews convened under the auspices of WHO, the FDA has reviewed protocols, provided comments, and responded to questions from their African regulatory counterparts.

Because science informs regulatory decision making, the FDA co-convened a workshop in December with NIH on Ebola vaccine immunology. Understanding randomized clinical trials are not the only method to demonstrate vaccine efficacy, Gruber noted, the FDA was also planning a Vaccines and Related Biological Products Advisory Committee meeting that took place on May 12, 2015. While safety and effectiveness in trial design are still paramount, they will be discussing options for regulatory approval of Ebola vaccines to be based on outcome measures other than clinical disease endpoints.

Pathways to Licensure

Approval of a new vaccine by the FDA typically requires specific evidence and is based on a clinical disease endpoint trial that shows protection against the disease, or immunologic response as a marker of protection from disease. However, such clinical trials are not always possible or may not be successful because decreasing disease incidence impedes endpoints from being met. In these cases, alternative pathways to licensure are available, Gruber explained. Accelerated approval can be given to products for serious and life-threatening illnesses that provide meaningful benefit over existing treatment (21 CFR 601.40/41). Ebola vaccines would clearly fall into this category, she said, and the sponsor can perform adequate and well-controlled clinical trials demonstrating an effect on a surrogate endpoint, such as an immune response marker that is reasonably likely to predict benefit. When the product is licensed, the sponsor must conduct confirmatory studies to verify the clinical benefit.

Another alternative pathway to licensure is the animal rule (21 CFR 601.90/91). The rule allows for approval of products for serious or life-threatening conditions when human efficacy studies are not ethical or feasible and approval based on other efficacy standards is not possible. If

a well-characterized animal model for predicting response in humans is available, adequate and well-controlled studies can be conducted in animals to provide evidence of effectiveness. Postmarketing studies are then required to verify the product's clinical benefit and to further assess safety, at a time when such studies are feasible and ethical.

Gruber noted the importance of immunological assessments for Ebola vaccines. A clinical study or using a combination of human and animal data could potentially identify an immune marker that is reasonably likely to predict protection in vaccines. These could then be used to support accelerated approval, and the markers could be used to bridge doses between animals and humans for approval under the animal rule.

Scientific and Regulatory Issues

Gruber highlighted a variety of scientific and regulatory issues related to the approval of vaccines for Ebola. Nonclinical studies are very important. Nonhuman primates mimic human infections in many important aspects, and they are also important for understanding the mechanisms of protection. However, the vaccine doses required to induce comparable immune responses may differ between humans and nonhuman primates with other concerns to consider, including stability, manufacturing consistency, and product testing.

A compressed clinical development timeline means that the FDA is relying on interim data decide whether to allow a sponsor to proceed to the next phase of the study. The FDA is often conducting parallel reviews of multiple candidate vaccines from different sponsors and must take care to preserve confidentiality in communications. Some of these studies are not conducted under a U.S. IND, but the results need to be considered in regulatory decision making. As discussed above, there are different pathways to licensure, so a challenge for alternatives is how to design and conduct postmarketing studies to verify the clinical benefit. For example, when the meningitis B outbreak began at several U.S. colleges and without any licensed vaccine in the United States, the FDA engaged with the manufacturers and made use of accelerated approval pathways to expedite review and approval of a vaccine. Gruber noted that past public health emergencies like this present important opportunities from which to learn in preparation for the next emergency. In closing, Gruber stressed that continued engagement with all stakeholders, such as vaccine manufacturers, clinical trial sponsors, and

national and international partners, is critical for successful clinical development and licensure of Ebola vaccines.

VALUES OF MULTISTAKEHOLDER PARTNERSHIPS: LARGE COMPANY PERSPECTIVE

New partnership models can potentially deliver results in an area of great complexity and uncertainty where no one entity is well positioned or capable of doing it alone, said Mark Feinberg, vice president and chief public health and science officer at Merck Vaccines. Multinational pharmaceutical companies have a tremendous amount to offer, he added, and he shared his perspective on effectively engaging them as partners, based on Merck's recent experience in Ebola vaccine development.

Developing an Ebola Vaccine

Merck first heard about an opportunity to develop an Ebola vaccine on October 1, 2014, and it quickly became apparent that there was a public health imperative to advance a promising vaccine candidate. At that time, the epidemic was expanding and expected to get much worse. Merck wanted to contribute in a way that would be valuable and impactful, using the company's unique attributes to help fill a gap. According to Feinberg, the company recognized from the start that this was not a commercial opportunity and that vaccine development efforts would be best advanced in collaboration with public-sector partners to pool expertise, share costs and risks, and manage uncertainties. Merck was also encouraged by the commitment from donor organizations such as GAVI and UNICEF to support vaccine procurement.

> Our collective success will depend upon the extent to which we can develop effective new partnership models and networks to address these challenges.
>
> *— Mark Feinberg, vice president and chief public health and science officer at Merck Vaccines*

A successful vaccine program advances through a very coordinated, multidimensional, aligned process where the individual stages of development are closely integrated from discovery to delivery, known as an "end-to-end" process. Many mechanisms are in place to hold the people and the company accountable for delivering results in a timely way. This is challenging enough for a single company where accountability, tracking, and incentives are internally aligned, he said. When multiple stakeholders are involved, delivering timely results

becomes much more complex, given different levels of experience, different priorities, and different awareness of product development issues. Success is predicated entirely on the extent to which effective partnership models exist, he said, and developing them during a crisis adds to the task.

Successes and Challenges of Multistakeholder Partnerships

Multistakeholder international partnerships have enabled the rapid development thus far. Feinberg noted the vaccine candidate came through the Public Health Agency of Canada and NewLink Genetics. Clinical studies were done at multiple sites around the world, supported by WHO, NewLink, Merck, and the Public Health Agency of Canada, with funding from DoD, the National Institute of Allergy and Infectious Diseases (NIAID), The Bill & Melinda Gates Foundation, the Wellcome Trust, and the European Commission.

However, Feinberg highlighted several issues that still need to be clarified moving forward. The magnitude and timing of the vaccine need are not yet clear. As discussed by Gruber of the FDA, there are challenges in expediting and integrating regulatory and policy decisions, including the path to licensure if the Ebola epidemic wanes, thereby hindering a formal demonstration of efficacy. A need exists to generate data that inform next-generation products and delivery strategies (e.g., more thermostable formulations, multivalent vaccines). If the pace of the epidemic wanes, the maintenance of momentum and commitment to Ebola product development may be put into question, which may put the progress seen thus far in Ebola MCM development in question as well. Further questions transpire from this process regarding leadership, decision making, risk bearing, and responsibility and accountability for success.

Ultimately, the ability of a company to provide vaccines in desired scale, at the appropriate time, and at the most affordable price is primarily dependent on external factors, Feinberg commented. These include the feasibility and timing of formal demonstration of efficacy, the timing of regulatory approval, need for and timing of WHO prequalification,[3] and timing of the WHO Strategic Advisory Group of

[3]To ensure that medicines purchased and supplied by international procurement agencies for use in resource-limited countries meet acceptable standards of quality, safety, and efficacy. See http://www.who.int/mediacentre/factsheets/fs278/en (accessed June 30, 2015).

Experts on Immunization recommendation. Additionally, affordability is an important factor that Feinberg said is actually a community responsibility. If the manufacturer knows the magnitude and timing of vaccine demand, it can make a product affordably, but when there are many uncertainties up front, the initial supply is often less than the demand, and prices end up being higher, he said.

In closing, Feinberg said we need to consider how best to optimize these partnership models to accelerate vaccine development and delivery efforts in response to current and future public health needs. We should learn from the current outbreak to inform and enable the development of better products to prevent or contain future outbreaks. In addition, we should recognize that the precedent set by the nature and success (or failure) of the current response will inform and influence the global health community's response to future emerging infectious disease outbreaks.

ENGAGING THE INNOVATORS: SMALL BIOTECHNOLOGY COMPANY PERSPECTIVE

Small biotechnology companies are actively involved in innovation, said Wouter Latour, chief executive officer of Vaxart, and he urged their inclusion in public–private partnerships for MCM development. Latour described Vaxart's work on an oral vaccine administered by room temperature-stable tablets as an example of emerging technology.

Latour pointed out that, for a small company like Vaxart with no revenue, developing breakthrough technologies is dependent on capital. There is pressure to deliver on milestones that drive economic value and help to raise the next level of financing. It is very difficult to convince traditional investors to put their money in a company that is working on Ebola, he said. Vaxart is very interested in working on meaningful targets such as Ebola, but there is a real limit on how much a small company can do without a clear development path and government funding or public–private partnerships to help spread the risk and cost.

PRE-POSITIONED EUA FOR DIAGNOSTICS

DoD has been very interested in diagnostics for Ebola for some time, said Thomas Dunn, program manager for Next Generation Diagnostics

System (NGDS) Increment 1. NGDS is located in the Joint Project Management Office for Medical Countermeasures Systems, which develops medical devices for the warfighter and the deployed environment. Dunn explained that NGDS Increment 1 was developing about 70 different assays for various indications of interest to DoD, and the development of assays for Ebola and some of the other viral hemorrhagic fevers were among the indications that had been prioritized. In 2010, the capability to detect Ebola was developed (a high-complexity-nucleic-acid-test), and a pre-positioned Ebola EUA diagnostic package was submitted to the FDA. Dunn noted that, at the time, there was no expectation that this assay would ever be used in a real-world context. The Ebola diagnostic was intended for pre-positioning a capability to service the warfighter, simply as a precaution.

In August 2014, when the Ebola outbreak was emerging, NGDS Increment 1 was able to leverage this prior investment, and the program was the first to receive an EUA for an Ebola virus diagnostic. Dunn pointed out that, because of forward thinking, the assay had been developed not only for use with DoD deployed systems, but assay performance had also been evaluated on commercially available systems that are commonly used in the Laboratory Response Network across the United States and worldwide. Therefore, the EUA cleared the use of the assay on multiple assay devices, so it was not limited to DoD purposes, but was able to be deployed to support the Ebola response. Unlike other approaches to diagnosing Ebola that can take days, this test can be completed in about 2 to 3 hours.

This is one example of how DoD is able to meet DoD-specific requirements for servicing the needs of the warfighter and to find areas of synergy where a product also meets the needs of the civilian sector. As a government program manager, Dunn noted the challenges of finding industry partners willing to work with the government. He acknowledged that it can be cumbersome and laborious for industry partners to work with the government, and he expressed appreciation for those companies that have expressed their willingness to engage in public–private partnerships.

LESSONS LEARNED

Osterholm of CIDRAP asked panelists to consider whether, knowing what they know now, they would have made the same decisions at the

start of the outbreak and what they might have done differently. Latour responded that when making a decision to engage in a project like this, companies weigh the risks and look at the potential benefits from a financial point of view. In the case of Ebola, however, his company felt a definite calling to develop a potentially useful tool that they had in concept. Multiple outbreak scenarios were still possible when the decision to reactivate the Ebola program was made in the August–October 2014 timeframe, and there were several unknowns regarding the spread. In retrospect, he said, they learned a lot, and it was still the right decision to make an investment, even for a small company like Vaxart with numerous budget constraints.

Identifying models of collaboration between public and private partners, and potentially between private-sector partners, is critically important for success in the future, Feinberg of Merck said. Expecting that any individual entity could do this on its own is unreasonable. Particularly when there is no clarity around what the need is, it is unreasonable to expect even a large company like Merck to launch a project. To feel comfortable engaging in a high-risk area where there will likely be no return on investment, a framework is needed for partnership and collaboration where different stakeholders step up and contribute what they can uniquely provide. The Merck experience with the current response has been very positive, Feinberg said, but there is still room for improvement regarding how different partners work with each other. Models of collaboration need to envision what might happen and lay the groundwork to combat emerging infectious diseases that may not even have a name yet.

Regarding prioritization, Robinson said that BARDA conducts assessments of threats and the consequences of those threats, and then considers target products and specific needs. Questions include how and when the top threats should be prioritized, who is going to do the prioritization, and how the workload will be distributed. While Robinson reiterated Feinberg's point that no single institution or government should be responsible for addressing threats, he said it is necessary to determine where the resources and infrastructure will come from when unknown threats arise. Robinson called for a coordinated global group to conduct an assessment to identify the top 25 threats, and subsequently, to determine how to distribute the resources and labor to properly address those top threats. He suggested that the approach to influenza risk assessment and measured response could be a template for other types of

diseases.[4] Both Feinberg and Gruber agreed that, as we move forward, greater clarity about expectations and deliverables will be needed given the range of parties involved, including vaccine manufacturers, clinical trial sponsors, and others.

ENGAGING INDUSTRY

Participants discussed potential incentives or rewards to drive industry participation in the MCM enterprise. Feinberg said that for small companies dealing with tight budgets and questionable survival beyond the next quarter, commercial incentives are clearly important (e.g., creating a market, awarding priority review vouchers). Osterholm added that for a smaller start-up company, incentive funds may offer a lifeline for the business. Latour agreed, and said that, while obtaining a priority review voucher was not the deciding point for his company, it was there as "a potential carrot." The indirect economic benefit plays into the equation when making the decision to invest, he said, which can vary depending on the target disease and corresponding perceived market (e.g., pandemic influenza strain, where there is likely a global need to purchase any product, or dengue fever, which has limited geographic spread and therefore carries a limited marketplace).

For a larger company, Feinberg opined, although financial considerations are important, it is unlikely that enough commercial incentive could be created for that to be the primary driver behind involvement. Other reasons, he said, such as wanting to contribute their expertise and demonstrate social responsibility, play into this decision. Still, research budgets at large pharmaceutical companies are tight, and they need to maximize the productivity of their pipeline. Feinberg noted that every project a company takes on affects the pursuit of other endeavors. While companies do not necessarily want to make a lot of money in this space, they do not want to lose a lot of money either. Feinberg reiterated that a possible way to increase private-sector involvement in high-risk/low-reward endeavors is to have trusted partners come together in a collective effort through shared responsibility, financial support, and clarity about efforts to define the best path forward in circumstances of uncertainty.

[4]Influenza risk assessment is discussed further in Chapter 5.

Guiding Industry from the Federal Sector

Past emergencies illustrate the importance of formally mapping out a pathway to licensure for many products that could aid in a future public health emergency. In the case of meningitis, discussions and planning for how the FDA would license meningitis B vaccine products took place well ahead of the college outbreaks. Still, because limited resources have inhibited the FDA from doing this in other instances, Baylor inquired whether the FDA could go through an exercise of defining the regulatory pathway to licensure for early-phase products. While this pathway seems to be a necessary tool for mitigating future public health emergencies, Gruber noted that company commitment also plays a large role. In the event of the Ebola outbreak, the FDA received some applications for vaccines in Phase I that were ultimately either withdrawn or not actively pursued by the sponsor. Therefore, company commitment to pursue development is equally important, especially given the difficulty many products have in advancing beyond early clinical development. At the end of 2013, the FDA was thinking about H7N9 clinical trials and development when the EVD outbreak emerged in West Africa and the agency had to readjust and redirect resources because of the crisis at hand. Because there was no sustainable continuity mechanism in place, work on H7N9 will suffer, and in the event that virus emerges on a global scale, MCMs will again be inadequate.

Robinson stressed the need to identify, assess, and prioritize threats. BARDA can work with a prioritized list of the top 5 to 10 emergent infectious diseases and work with small companies, providing not only funding but also assistance with development. Without prioritization, though, this becomes very difficult and diffuse, to the point where nothing will get done. Feinberg suggested thinking not just about specific targets, as they will always be numerous and likely with specific needs, but also about platforms or mechanisms that could expedite development for multiple targets. For example, developing a platform that could be used for all coronaviruses, not just the current outbreak of Middle East respiratory syndrome (MERS), would be useful for the next unknown coronavirus that may emerge. Following a question from Mansoura at Novartis about dealing with public opinion when an investment has been made and the threat did not materialize, Osterholm replied that preparedness is never wasted. Any preparedness work done will not be wasted, because we do not know what will happen next year, or the year after, or in the future.

Chapter 4 Annex

This annex contains technical details from the speakers' presentations related to the development of products targeting the Ebola virus.

Mark Feinberg
Vice President and Chief Public Health and Science Officer, Merck Vaccines

The Merck Ebola vaccine candidate (rVSV-ZEBOV-GP) is a recombinant attenuated vesicular stomatitis virus (rVSV) vaccine vector that substitutes the Ebola glycoprotein for the VSV-G glycoprotein. It is replication competent, which means it has the promise of being a single-dose vaccine, and it provides 100 percent protection in nonhuman primates against a high-dose, lethal challenge. The manufacturing process is straightforward and scalable, and the vaccine could potentially be used for both general prophylaxis and postexposure prophylaxis, Feinberg explained.

The typical timeline for full vaccine development is 15 to 20 years, Feinberg said (see Box 4-1).

BOX 4-1
Typical Timeline for Vaccine Development: 15 to 20 Years

- Scientific opportunity
- Translation and feasibility
- Definition of desired target product profile
- Clarity on anticipated vaccine demand and economic/public health value
- Definition (and enforcement) of key milestones and "go/no go" criteria
- Process development
- Dose selection
- Establishment of proof of concept
- Additional Phase II evaluation
- Manufacturing/supply solution for affordable production
- Phase III demonstration of safety/efficacy
- Licensure (informed by broad and deep evidence base)
- Generation of evidence to guide policies and recommendations

- Demonstration of feasibility and impact of introduction
- Provision of affordable, appropriate, reliable, and sustainable supply

SOURCE: Feinberg presentation, March 26, 2015.

In describing the accelerated vaccine development timeline for rVSV-ZEBOV-GP, Feinberg said Phase I studies of the vaccine started on October 13, 2014, and Merck finalized a licensing deal with NewLink Genetics and the Public Health Agency of Canada on November 21. By January 25, 2015, enough clinical data had already been generated in collaboration with partners to make a dose selection decision for efficacy and effectiveness trials, and the NIH-Liberia Phase II/III study was initiated on February 2. A Phase III study was initiated by WHO in Guinea[5] on March 7, and Feinberg added that a CDC study in Sierra Leone was slated to start on March 30. Importantly, Merck committed on January 26 to providing this vaccine at no-profit prices to GAVI-eligible countries.[6] According to Feinberg, licensure of the vaccine and target procurement by GAVI is projected for the second half of 2015.

Wouter Latour
Chief Executive Officer, Vaxart

Similar to the rVSV vector vaccine described by Feinberg, Vaxart uses a viral vector platform. Latour described the many advantages of an oral vectored vaccine platform. First, there are advantages that are common across vectored vaccines, including versatility (suitable for delivery of virtually any protein antigen), speed and manufacturability (rapid construction, high yield, consistency), and safety (recombinant protein eliminates the need to work with pathogens). An advantage specific to Vaxart's platform is oral delivery via room-temperature-stable tablets that are especially relevant for locations with limited infrastructure. The ability to store, distribute, and administer is greatly simplified. There are no needles, which eliminates the risk of needle sticks and increases patient acceptance (especially where there may be

[5]As of this summary's release, in fall 2015, published interim results for the clinical trial in Guinea show the vaccine to be highly efficacious and safe in preventing EVD. See more at http://www.thelancet.com/pb/assets/raw/Lancet/pdfs/S0140673615611175.pdf (accessed August 5, 2015).

[6]Countries are eligible for GAVI support when their gross national income per capita is at or below 1,580USD. For more information see http://www.gavi.org/support/apply/countries-eligible-for-support (accessed August 5, 2015).

cultural resistance against injectable products, particularly if the products are coming from Western societies). There is also no need for a cold chain, allowing for shipment with far fewer controls and reduced cost.

In 2012, Vaxart began a collaboration with the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) to make an Ebola vaccine construct, which scientists at USAMRIID then tested and found to be protective in mice. Vaxart submitted a request for funding for non-human primate studies, but the program was ultimately shelved due to limited resources. In August 2014, because of the urgent need, USAMRIID and Vaxart reactivated the Ebola program. Latour noted that Vaxart committed some of its own very scarce resources to manufacture vaccine for nonhuman primate and Phase I studies, while resubmitting funding proposals. To date, Vaxart had received no concrete funding, but he was optimistic that it would be forthcoming.

Thomas Dunn
Program Manager, NGDS Increment 1, Department of Defense

In 2013, NGDS Increment 1 began developing the next-generation Ebola test, awarding contracts to multiple vendors from the diagnostics sector to competitively develop an assay, which would lead to selection of a single system that DoD would further develop. In a period of about 6 months, multiple vendors were able to develop an Ebola test using government-furnished information and materials, with access to government sites for testing. The goal, Dunn said, was to develop a lower-complexity test with integrated sample preparation, a "single sample to answer" procedure that would drastically reduce the number of steps a technician would need to do. Analytical time, from sample to answer as a single test, was reduced from 2 to 3 hours to about 70 minutes. The test was designed to be multicomplex; however, due to the Ebola outbreak, it was developed expeditiously to deliver Ebola testing capability.

5

Influenza Risk Assessment and Pandemic Preparedness

"Pandemic influenza is different from the other emergencies that we prepare for," said Andrew Pavia, chief of the Division of Pediatric Infectious Diseases at the University of Utah. It is the one biological emergency that is certain to happen. However, given the enormous geographic diversity, the number of influenza viruses, and the rate of mutations, it is unknown how, when, and where pandemic influenza will emerge. Predictions to date have not been very accurate, and pandemics such as the 2009 H1N1 influenza confounded all preparedness models. It is also different in that it is intensely studied, and there is a commercial market, albeit small, for influenza products, which separates it from other infectious disease threats in this report. For example, all of the profits from the antiviral medication, Tamiflu, came from selling it to the SNS.

Despite how much is known about influenza, challenges in developing MCM for pandemic influenza remain. A large number of new viruses are discovered every year and consequently generate many false alarms. The inconsistent presence of pandemic influenza also creates a fluctuating market for products and the corresponding investment in research and development. When it is the "disease of the month," Pavia said, money becomes available and efforts are made, but sustainable funding does not exist in the interepidemic periods. In this section, representatives from the government and the private sector discussed evaluating risk, developing tools and capacity, and partnering with influenza vaccine manufacturers to make a range of MCM available. (Detailed technical accounts of the MCM development process are included at the end of this chapter in the Chapter 5 Annex.)

INFLUENZA RISK ASSESSMENT TOOL

Jacqueline Katz, deputy director (acting) of the Influenza Division at CDC, gave a brief overview of the CDC Influenza Risk Assessment Tool (IRAT). IRAT is a simple, additive, multiattribute assessment tool to prioritize pandemic preparedness activities.[1] Specifically, it evaluates the risk from novel influenza viruses that are circulating in animals. Using the tool, subject-matter experts from different disciplines evaluate available data and provide a quantitative risk assessment regarding the likelihood that a novel virus will emerge in humans and the likely public health impact if that does occur. Katz clarified that IRAT cannot predict the next pandemic; it is designed to compare the risk from circulating viruses. She emphasized that it will continually be updated as new information, technologies, and methods to assess data and risk become available. With new influenza A viruses constantly emerging from animal reservoirs, and the tenfold increase in the number of human infections with different novel influenza A viruses since the 1990s, Katz said, risk assessments are needed to guide decision making with respect to vaccine development, testing, and manufacturing, as well as the procurement of MCMs and other preparedness needs (e.g., diagnostics).

Putting IRAT into Action

IRAT is an objective, transparent approach that measures risk consistently with minimal bias and provides documentation to support government decisions, Katz said. The same standardized approach can be used year to year to assess influenza virus variants. The tool builds on a strong global influenza network for virus and genetic sequence sharing (WHO Global Influenza Surveillance and Response System).[2] IRAT can also help to identify gaps in knowledge and data and encourages data sharing and input from both public health and animal health sectors. As noted, the tool is evaluated and reviewed regularly in an iterative process and can be rapidly updated. By evaluating many viruses including H7N9, H5N1, H9N2, and H3N2v, IRAT has informed vaccine development and procurement decisions by the government.

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[1]See http://www.cdc.gov/flu/pandemic-resources/tools/risk-assessment.htm (accessed June 30, 2015).

[2]See http://www.influenzacentre.org/centre_GISRS.htm (accessed August 14, 2015).

Guiding Decision Making

Katz noted that IRAT scores are provided regularly to agencies within HHS to guide pre-pandemic risk management decisions, including which additional vaccine antigens should be produced, stockpiled, or selected for clinical trials to mitigate the potential public health impact of an emerging virus. IRAT is one component of a multifaceted decision-making process, she said. In assessing pandemic vaccine priorities, key elements are human infection, antigenic relationship, global distribution, infection in animals, and genomic variation. When considering which virus poses the greatest impact to public health, CDC considers the antigenic relatedness relative to a vaccine already available in the SNS and the antigenic relatedness to a candidate vaccine virus that may already exist but has not progressed to pilot lot production.

Risk Management

Information from IRAT is used at the HHS Pandemic and Seasonal Influenza Risk Management Meeting (also known as the Flu Risk Management Meeting, or FRMM)[3] to make decisions about influenza strains for inclusion in the pre-pandemic vaccine stockpile, explained Rick Bright, acting director of the Influenza Division at BARDA. FRMM is a senior-level forum for decision makers from stakeholder agencies to identify and address risk management issues related to the development, acquisition, deployment, and use of medical and public health countermeasures for influenza. Decisions are evidence based, using a measured approach to response that ranges from monitoring novel strain emergence to a full pandemic vaccine production response, Bright said. As mentioned by Katz, IRAT is one piece of information considered in the risk management process.

Over the past 10 years, BARDA has made decisions early on to buy bulk lots of vaccine candidates for H5N1 influenza and store those bulk lots in long-term storage. Although BARDA has gained valuable knowledge in doing this, it is an expensive approach, Bright noted. Producing and storing a full-sized bulk lot of vaccine for each threat that might emerge is not economically feasible. Recalling Robinson's previous comments on the need for prioritization and assessment, Bright said BARDA works with CDC to implement IRAT and other factors that

[3]See http://report.nih.gov/crs/View.aspx?Id=2641 (accessed August 14, 2015).

inform decisions on how, where, and to what level a response is initiated. This facilitates better preparedness for a wider variety of threats instead of investing all or a significant portion of funds into only one or two threats. Importantly, everything along this continuum involves the manufacturer, he added. BARDA has a flexible contracting mechanism so it can respond in a variety of ways, to a variety of threats, with different manufacturers who may or may not be able to respond at the time needed.

BARDA Decision Making for Pandemics

Bright described several examples where the risk-based, measured approach was used. The 2005 H5N1 influenza outbreak in Southeast Asia, for example, was determined to be a significant threat. In response, BARDA established a stockpile, met stockpiling goals, and implemented an innovative mix-and-match program with NIH to begin evaluating different antigen-adjuvant combinations that might be needed in a pandemic response. In 2009, the H1N1 influenza pandemic "took us by surprise," Bright said, and BARDA went into full response mode. A total of 186 million doses of H1N1 vaccine were produced and filled by the manufacturers, along with production of 120 million doses of bulk adjuvants as a contingency. One of the first times IRAT was used was for the H3N2v influenza outbreak in 2012. In this case, clinical lots of candidate vaccines were made, and clinical trials were conducted to determine the dosage needed, but no further development was done. Currently, the 2013 emergence of H7N9 influenza is the highest threat, according to the IRAT, and the decision was made to produce clinical lots, to conduct clinical studies, and to stockpile bulk antigen. Bright emphasized that the stockpile program and measured response approach have enabled BARDA to gain valuable knowledge about the physical properties of antigens and adjuvants, storage conditions, potency over time, and other information that is needed to manage risk and inform development of the next generation of influenza vaccines.

INDUSTRY PARTNERS IN PANDEMIC PREPAREDNESS AND RAPID RESPONSE

The national vaccine goals for pandemic influenza preparedness call for pre-pandemic vaccine stockpiles to protect 20 million people as well

as for manufacturing infrastructure to support rapid production of 600 million doses, said Monique Mansoura of Novartis. She emphasized the dynamic nature of the influenza threat and questioned the match of vaccine stockpiles that were purchased 10 years ago against today's circulating strains. The H5N1 influenza emerging in Egypt in 2015 is not necessarily the H5N1 strain that emerged in Vietnam in 2004. She concurred with O'Toole of In-Q-Tel and others that the public health sector is largely underestimating and under-requesting what is needed to protect Americans from pandemic influenza and other threats. Although focus has been largely on the cost of purchasing pharmaceuticals for the nation's SNS, she highlighted that little attention is given to the cost of inaction. There are countless other dynamic pandemic threats, and Mansoura noted that creating a dynamic and strategic stockpile strategy should be considered.

> We are focused on the cost of buying a stockpile, but we are not necessarily focused on the cost of inaction.
>
> — *Monique Mansoura, Head, Medical Countermeasures & Government Affairs, Americas, Novartis Influenza Vaccines*

Following the 2009 H1N1 influenza outbreak, during which the vaccine supply lagged behind the demand, the President's Council of Advisors on Science and Technology (PCAST) released a report on reengineering the nation's influenza vaccine enterprise to enable a more rapid vaccine response to pandemic influenza (PCAST, 2010). The recommendations from the White House focused on new or enhanced science and technological advances, including investment in new vaccine manufacturing platforms. The PCAST report also called for studies of the use of adjuvants and development of the FDA guidance on the use of adjuvants with seasonal influenza vaccines to improve vaccine efficacy.

Needs for Future Stockpiles and Capabilities

Mansoura called for a "rebranding" of how stockpiles and response in the pre-pandemic phase are typically conceived. The H7N9 influenza response was an unprecedented response to a pre-pandemic threat, she said. Within 8 months of identifying the first case, HHS had a vaccine stockpile. Much was learned along the way about integrating new technologies, synthetic seeds, adjuvants, clinical trials, antigens, measured response, and stockpiling. Mansoura raised a concern that it took five separate contracting actions to secure an HHS decision to

purchase the stockpile once created, and there seemed to be an expectation that manufacturers would do this type of work when needed at their own risk. This, she said, is a very challenging way to do business. While the development of innovative platforms may someday enable a sufficiently rapid response after a new threat emerges, Mansoura contended that current assumptions and existing capabilities must be tested to provide verifiable assessments of the nation's state of preparedness before an event occurs (e.g., developing and testing a vaccine, determining the dose, stockpiling, understanding the stability profile of the pharmaceutical over time).

Mansoura went on to note that the vaccine industry is among the first responders to pandemic influenza threats, and as a result, manufacturers need to have reliable pandemic plans that need to be exercised to ensure effective performance under pandemic conditions. Vaccine development is challenging, and the ability to produce seasonal influenza vaccine is not the only preparedness activity for a pandemic response. Mansoura highlighted the importance of testing and evaluating innovative technologies, strategies, and policies (e.g., biosafety assessment, permitting, contracting) for continued improvement. With each practice round, she said, we understand more about the nature of this dynamic threat. She advocated for the need to expand the strain-specific knowledge base and develop regulatory science to integrate new technologies.

Pre-Pandemic Versus Pandemic Development

David Vaughn, head of External Research and Development at GSK Vaccines described his company's experience with the H5N1 and H1N1 influenza outbreaks. The GSK AS03 adjuvanted H5N1 vaccine was licensed in the United States in November 2013, but the usual economic incentives that typically encourage companies to develop influenza vaccines did not apply for a vaccine to address the virulent strain of H5N1, Vaughn said. In this case, GSK received most of its external funding from BARDA, with additional funding from the Canadian and Japanese governments. Due to concerns about an impending H5N1 pandemic, GSK got off to a very fast start. The contract with BARDA was signed in January 2007, and the pre-biologics license application (pre-BLA) meeting with the FDA took place in September 2008. However, when H1N1 influenza emerged in 2009, focusing on an H5N1 vaccine became difficult because all attention had shifted to the crisis at hand. Instead of submitting the BLA in 2009 as planned, it was not

submitted until 2012. Because of the pre-pandemic development of the H5N1 vaccine, Vaughn noted there was "the luxury" of extending the timelines, as there was no current pandemic demanding the final product. In this case the BLA was ultimately submitted, but he cautioned that, in some cases, a project is never seen to completion without the immediate demand. Vaughn also stressed the importance of considering pediatric development from the onset.

Increasing Capabilities Between Pandemics

Looking beyond H5N1 and H1N1 influenza, Vaughn said there is a need to improve the overall response to pandemics and ways to address interpandemic drift. In this regard, GSK is striving to increase its capabilities in research, development, and manufacturing in order to respond to a number of biosecurity threats. GSK has entered into unique public–private partnerships with the Defense Threat Reduction Agency and BARDA for antibacterial product development. Through recent acquisitions, GSK has also gained new platform technologies that may facilitate a faster response, both in terms of development and production. Vaughn noted that any plug-and-play rapid technology needs to be repeatedly successful with a variety of disease threats so that regulatory authorities and governments can make decisions in urgent situations to deploy vaccines under an EUA with little or no clinical data.

To enhance national preparedness, GSK proposes to embed MCM activities within the pharmaceutical industry's research and development capabilities, Vaughn said. One of the best ways to ensure that technologies are scalable is to start the development process within the final manufacturer from beginning to end. Funding rapid response technologies will depend on multiyear federal appropriations to allow for continued pharmaceutical development and prevent the delay or termination of viable projects once they have been started. Vaughn concurred with others that current contracting approaches can be complex and time consuming, especially when programmatic responsibilities fall within one company and financial responsibilities another. Contracting hurdles have been overcome quickly in exceptional circumstances, he acknowledged, but for these efforts to be sustainable, streamlined contracting and integrating MCM activities into a company's portfolio should be the norm, not an exception.

DEVELOPING AND SUSTAINING NEW VACCINE PLATFORMS

The market for seasonal influenza vaccine is a large-volume, low-margin market, Pavia of the University of Utah said, which does not particularly encourage innovation. Larger companies that already have a substantial share of the seasonal influenza vaccine market face challenges in moving to new platforms. Mansoura said the ability to leverage a licensed manufacturing platform in a licensed facility provides an enormous enhancement to current capabilities in responding to threats. For example, synthetic vaccine seed technology allows for rapid progress from viral sequence to vaccine manufacturing within days. While the science and technology have advanced, key rate-limiting steps in the process include permitting, funding, and intellectual property issues. The application and review process for the funding of new programs can take 1 year. In addition, program focus and availability of government funding can shift from year to year. If establishing rapid response capabilities to make vaccines quickly is a government priority, then it should be stated and funded as such, Mansoura argued. But there are no signals from government to industry leadership of such a commitment. The opportunity costs for large companies are significant, and for smaller companies, the investor community will not be supportive of these endeavors if government is the only partner, making any sustained progress difficult to achieve.

Manon Cox of Protein Sciences Corporation said that BARDA invested significantly in her company's recombinant influenza vaccine platform because it could potentially shave 6 to 12 weeks off the delivery timeline for an influenza vaccine. However, she noted that one of the challenges after achieving product licensure is successful commercialization. Existing players aggressively defend the sizable seasonal influenza market, creating a barrier for smaller newcomers to establish themselves in the market—even with innovative platforms. Cox encouraged government funders, such as BARDA, to consider how they can then help sustain the technology over time. Mansoura agreed that the seasonal influenza vaccine market is oversupplied and hypercompetitive compared with the pandemic influenza vaccine market that comes and goes. A combined market between seasonal and pandemic influenza vaccine is needed, she said. Government officials are limited in what they can do to incentivize industry without a market. At current funding

levels, BARDA cannot mount rapid, nimble responses for new pandemic threats under existing contracts, she said.

BARDA's Platform Investments

Bright noted his encouragement by the amount of progress that has been made by BARDA's partnerships with industry. BARDA had set out to implement the national pandemic influenza strategy in a stage-wise approach to build better vaccines that are available sooner. This was achieved by investing heavily in public–private partnerships to build the domestic manufacturing infrastructure and increase the capacity for egg-based vaccine production, which was the routine process at the time. BARDA then invested heavily in cell-based manufacturing, which does not rely on the availability of eggs and the idiosyncrasies of egg-based vaccine production. Next, BARDA invested in three different recombinant-based technologies, which are even faster because they do not rely on growing the virus itself. This process further clarified that the use of adjuvants offered an antigen-sparing approach to make more doses of vaccine available sooner. All of these platform technologies can be incorporated to enable a more rapid and effective response. A side benefit of the increased pandemic capacity has been the application of the new technologies to the seasonal influenza vaccine. Domestic manufacturers have been able to provide quadrivalent flu vaccines, high-dose vaccines, intradermal vaccines, and egg-free vaccines.

Although vaccine capacity has increased, there is still room for improvement in vaccine efficacy, which remains at about 50 percent. Bright explained that a new BARDA initiative will invest in the development of more effective influenza vaccines, with a goal of greater than 50 percent efficacy in all populations and broader immunity to overcome vaccine strain mismatch challenges. This process also has the potential to create a baseline readiness level for response to pandemic strains. It may also be possible to develop vaccines that afford longer duration of immunity. BARDA has demonstrated that capacity can be built, next-generation technologies developed and implemented, and end-to-end time reduced through interagency and industry partnerships. Bright hoped this would serve as a strong signal to industry and academic stakeholders to engage in another public–private partnership approach to improving PHEMCE.

FUNDING A BETTER INFLUENZA VACCINE

Bright pointed out that 2015 was the first year that BARDA received appropriated dollars from Congress. BARDA did receive significant supplemental funding in 2006 and 2009 to respond to the influenza pandemics, which has been supporting all of its programs until this year. He added, though, that the 2015 appropriation was much lower than what BARDA considers to be necessary to accomplish all of its goals. Developing a more effective influenza vaccine is going to cost nearly $1 billion, Bright said, and will likely entail having four to six different technologies in the portfolio. As previously discussed, a product typically takes 10 to 20 years to move from discovery to reaching FDA approval. This will require a very prudent, prioritized approach in partnership with industry. Cost-sharing approaches will be critical, and government agencies will need long-term support from Congress and others, he added. Mansoura said that because BARDA has shifted from multibillion dollar, multiyear supplemental budgets to an annual appropriation, it looks like an increase (i.e., the annual budget has gone from nothing to something). However, there is a lack of transparency regarding the financing needs, and it is not clear if the pandemic preparedness plan from a decade ago is the basis for the current appropriation. What is needed, Mansoura said, is a dialogue about what pandemic preparedness should look like in 2015. She added that there has to be an aggressive research and development program that will improve vaccines, but not at the expense of testing and sustaining the systems and infrastructure that need to be in place to produce these vaccines. BARDA budgets over the past 3 years have been 90 percent dedicated to a research and development program, and lack a lifecycle management plan.

Challenges in Government Funding

Phyllis Arthur, senior director for BIO, pointed out that funding for BARDA and preparedness has bipartisan support and has been a priority for the president. Yet, Pavia said that even with a highly effective economic analysis of the net present value of investment in new influenza vaccines, creating the political will to spend the tax dollars could be difficult. With a multilayered budgeting process, agencies can ask for money in the departmental budget, but that budget is edited by the Office of Management and Budget, and then by Congress. Those

who are best positioned by their subject-matter expertise to estimate need are not in control of the financial decision making to impact the final product. Pavia said the alternative is to use government as the facilitator or the convener of the process. Osterholm of CIDRAP noted that now is the time to enlist the support of the business community in pandemic preparedness, and not just government and pharmaceutical industry partners, as the private sector understands how pandemics can impact both their supply chains and the company's workforce.

In the push to increase flu vaccination among the general public, public health and the media have created an environment where everyone thinks the current influenza vaccine sufficiently protects the public and does not need improvement, according to Osterholm. He shared that he received significant negative feedback on a published meta-analysis showing that current influenza vaccines were only moderately protective (Osterholm et al., 2012). He also suggested that there was systematic bias in the 2010 and 2011 Advisory Committee on Immunization Practices statements that favored the current influenza vaccines. He emphasized the need to take a step back and assess what is known about the current vaccine and explain why a better vaccine is needed—because with the current mindset that it is very effective and does not need improvement, investors and companies will not step forward to develop a new season flu vaccine. However, he did stress that the current vaccine method and annual international decision process are the best available, and even 10 percent protection is better than zero. Though, understanding the limitations and assessing what is truly needed will be an important step in moving forward.

A Manhattan-Like Project for a Better Influenza Vaccine

Osterholm referred to an increasing number of studies showing that annual influenza vaccination is leading to waning immunity. Those who are protected could have about 90 to 100 days of protection, and vaccination is now commonly started as early as August or September, meaning that during the winter months—peak times for flu season in many parts of the country—even those who are vaccinated will have limited levels of immunity. Participants discussed the progress on development of a universal influenza vaccine. One participant suggested that the knowledge has sufficiently advanced and the technology exists, but there has not been investment in taking a product through to clinical development. An additional advantage to a universal flu vaccine, as Cox

pointed out, would be an opportunity to evaluate the platform's use for a range of other diseases instead of creating new and untested additional platforms. No resources have been allocated yet to evaluate the usefulness of platform technologies for other emerging viruses. Several participants likened the level of organization and commitment (including funding) needed for such an endeavor to that of the Manhattan Project.[4] Katz of CDC said the key is to bring together different manufacturers, different intellectual property, and different platforms. The task is two-fold: develop a broader-immunity vaccine for the long term that will provide longer-lasting, broader protection (perhaps also against a potentially pandemic subtype) and simultaneously address the limitations of current vaccines for the short term by developing new platforms for seasonal vaccines. These new platforms could then be sustained for broader MCM applications if they are sufficiently resourced.

Chapter 5 Annex

This annex contains technical details from the speakers' presentations related to the development of products targeting pandemic influenza.

Jacqueline Katz
Deputy Director (acting) of the Influenza Division at CDC

To implement the tool, she explained, subject-matter experts score influenza viruses on 10 elements (Trock et al., 2012). The elements are grouped into properties of the virus, attributes of the population, and the ecology and epidemiology of the virus (see Figure 5-1). The scores for each of the 10 criteria are then weighted by the significance of each to virus emergence and public health impact. Each reviewer also provides a confidence score to address uncertainty. Composite scores are then used to rank and compare viruses in terms of potential pandemic risk.

[4]The Manhattan Project is the unofficial designation for the former U.S. War Department's secret program, organized in 1942, to explore the isolation of radioactive isotopes and the production of an atomic bomb. Initial research was conducted at Columbia University in New York City, New York.

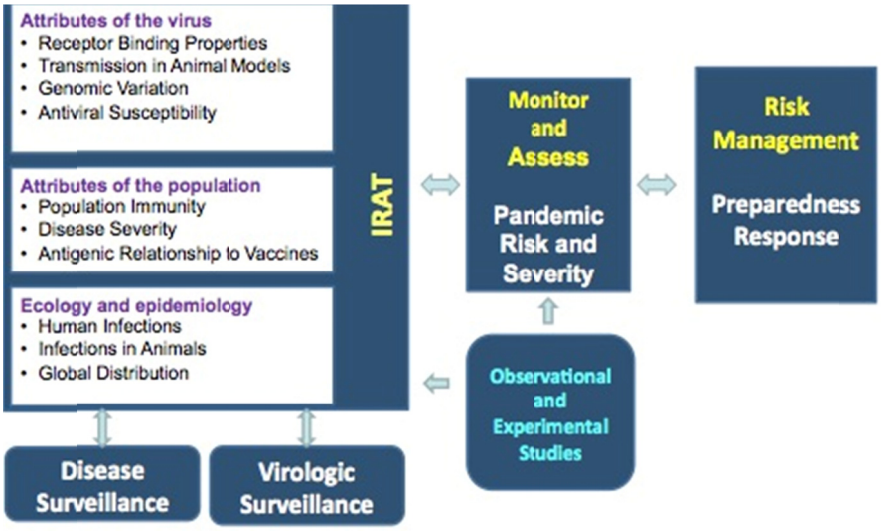

FIGURE 5-1 Influenza risk assessment and management using the CDC Influenza Risk Assessment Tool (IRAT).
SOURCE: Katz presentation, March 26, 2015.

Rick Bright
Acting Director of the Influenza Division at BARDA

Applying IRAT to Pandemic Scenarios

To illustrate a measured response, Bright described two pandemic scenarios involving a high pathogenicity avian influenza and a high pathogenicity influenza in special populations. The former would have a rapid, high peak and then ebb, and the latter would have a slower, gradual, lower peak, and then ebb (see Figure 5-2). It takes 24 to 26 weeks to make and release vaccines using current influenza vaccine manufacturing technologies and production processes. With no preparedness, therefore, the vaccine would become available only as the pandemic ebbs in both scenarios. If, by using IRAT and other available tools, an emerging virus is perceived to pose some risk, a decision could be made to have CDC or manufacturers produce a seed lot of vaccine, thereby shaving 2 to 3 weeks off of a response time. If the risk assessment deems the threat to be higher, a decision could be made to

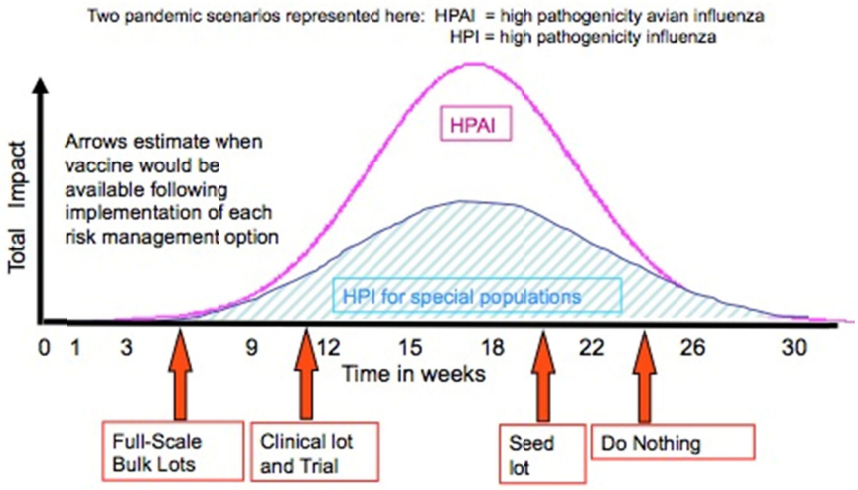

FIGURE 5-2 Pre-pandemic influenza vaccine availability by risk management option.
SOURCE: Bright presentation, March 26, 2015.

produce a clinical lot of vaccine and conduct a clinical study, collecting valuable data (e.g., dosage, adjuvant) that could shave 12 to 14 weeks off the time to respond to a pandemic. If the virus is assessed to be very high risk, a full-scale bulk lot could be manufactured and stored just short of finishing and filling the vaccine, and available vaccine would be ready in several weeks.

David Vaughn
Head of External Research and Development at GSK Vaccines

Vaughn explained that the H1N1 vaccine development experience was very different from the H5N1 experience, due to the extent of the outbreak and immediate need for MCMs. While the H5N1 development process had the "luxury" of extending timelines, H1N1 vaccine development needed to be done in a timely manner. Importantly though, there was a global market for an H1N1 vaccine, giving some prediction of a positive return on investment. In the summer and fall of 2009, GSK initiated 28 clinical trials with funding from BARDA for the H1N1 vaccine. Three of those trials evaluated the use of an adjuvant in case it was needed in the United States to respond to that pandemic. The GSK

H5N1 vaccine requires an adjuvant, but for the H1N1 vaccine, the use of an adjuvant is optional. GSK took a global approach, by prioritizing the importance of vaccine coverage, and the use of adjuvants such as ASO3 or MF59 with the H1N1 vaccine allowed for the vaccination of more people in less time. Vaughn noted that GSK conducted an efficacy trial of AS03 in 6,000 children, and the data showed that the use of an adjuvant paired with the antigen increased the protective efficacy of the vaccine by 77 percent over two doses of antigen alone (Nolan et al., 2014). Because of some adverse events reported following the H1N1 adjuvant vaccination of Pandemrix in Europe in 2009, and a link to increased incidence of narcolepsy in children, public concern surrounding the use of adjuvants in flu vaccines also exists.[5] Largely because of this, it would not have been possible to license an adjuvanted H1N1 vaccine in the United States in fall 2009, Vaughn said, as no approved flu vaccines in the United States then or now contain an adjuvant. However, as of November 2013, an H5N1 vaccine has been licensed for use in the SNS, and he suggested that, in the future, there may be greater public acceptance of adjuvants if they are needed for an influenza pandemic—recognizing their advantages in treating more people in a shorter time.

[5]For more on the adverse events linked to the Pandemrix vaccination, see http://www.cdc.gov/vaccinesafety/Concerns/h1n1_narcolepsy_pandemrix.html (accessed August 14, 2015).

6

Developing MCMs for Coronaviruses

When the SARS coronavirus spread around the world in 2003, it resulted in more than 8,000 cases, nearly 800 deaths, and $50 billion in economic damage. During this time, understandably, there was short-term momentum for developing pharmaceuticals to combat SARS, said Tom Inglesby, director of the UPMC Center for Health Security. However, that momentum has long since waned, and there are still no products available to treat or prevent SARS. This poses a serious threat because the potential for SARS to reemerge persists, whether naturally or as a result of a research accident in a laboratory. In addition, there is no complete inventory of where the SARS virus is worked on around the world. More recently, another globally threatening coronavirus known as MERS emerged in 2012, leading to about 1,000 cases thus far and more than 400 deaths (Maurice, 2015). Similar to the SARS experience, 3 years after the first case, MCMs for MERS still do not exist.

In this chapter, panelists discussed the important period of opportunity for development and action prior to a virus reaching an emergency-level epidemic threshold. (Detailed technical accounts of the MCM development process are included at the end of this chapter in the Chapter 6 Annex.) Using coronaviruses as an example, speakers and participants introduced important concepts like One Health and the need for ongoing risk assessments and alternative product options to contain the spread of disease.

CORONAVIRUSES

A brief background on coronaviruses and an update on the status of the MERS coronavirus outbreak was provided by David Swerdlow, associate director for science at the National Center for Immunization and Respiratory Diseases at CDC (see Box 6-1).

BOX 6-1
Coronaviruses

- First identified in the 1960s
- Named for the crown-like spike proteins (S proteins) on the surface, which are the target of current vaccination efforts
- Found in many animals, including bats
- Six human coronaviruses have been identified: four cause mild, seasonal disease ("common cold"), two cause severe disease (severe acute respiratory syndrome, or SARS, and Middle East respiratory syndrome, or MERS)

SARS Epidemic (2002-2003)

- 8,098 probable cases and 774 deaths (10 percent fatality rate)
- Estimated economic losses of more than $30 billion
- Association of cases with "superspreading events" (e.g., from one hotel guest to many others and their contacts)
- Experts concerned that transmissibility increased over the course of the epidemic, associated with changes to the S protein
- Control strategies: surveillance to identify cases, isolation of ill persons, quarantine of exposed persons, good infection control to prevent onward transmission

MERS Outbreak (2012-present)

- 1,075 total cases confirmed by World Health Organization, 404 deaths (38 percent fatality rate)
  - Most cases in Saudi Arabia (951 cases, 372 deaths), cases exported to 19 countries
  - 221 cases since August 2014, primarily Middle East, with some recent cases in Europe, Asia
  - Two U.S. cases (Florida, Indiana) were health care workers who worked in Saudi Arabia and traveled home; no secondary cases among contacts

- Demographics: 66 percent male, median age 50, most with underlying health conditions
- Transmission likely respiratory: human to human (not sustained), health care associated outbreaks, animal sources (bats, camels)
- No established treatment or vaccines (investigational products in development)
- Epidemiological and laboratory activities in the United States included developing and broadly disseminating case definitions, infection control guidance, travelers health recommendations, epidemiology toolkits, serology, and polymerase chain reaction diagnostics.

SOURCE: Swerdlow presentation, March 27, 2015.

Adapting Tools: Creating a Coronavirus Risk Assessment Tool from IRAT

IRAT is a very useful tool because there are so many influenza viruses, Swerdlow pointed out, so a key challenge in creating a useful coronavirus risk assessment tool is the low number of identified coronaviruses in comparison. In addition, there were not enough data to grade the risk elements and not enough coronavirus experts to do the grading. The final conclusion of the exercise was that MERS was like SARS (especially before the transmissibility of SARS increased in later phases). Unfortunately, he said, the coronavirus risk assessment tool did not add much to the overall assessment of risk. Risk assessment is critically important, he stressed, but they found that IRAT could not be adapted for use with coronaviruses.

Assessing Coronavirus Threats at the Source

To stop the next SARS outbreak at its source, we need to know where it is coming from, said Peter Daszak, president of EcoHealth Alliance. With funding from Fogarty International Center at NIH, the EcoHealth Alliance sought to identify the wildlife origin of SARS. While crossover from civets into humans was of particular interest, the data suggested that civets are not the wild reservoir but instead are infected in the live animal markets of Southern China. Serology and phylogenetic analysis show that bats harbor a SARS-like coronavirus that is phylogenetically closely related to the human and civet SARS viruses (Li et al., 2005). The bat virus is a precursor, but is not the SARS that

infected humans. With funding from the U.S. Agency for International Development (USAID), Daszak and colleagues found there is a huge diversity of bat SARS-like coronaviruses. Researchers in China have identified novel bat coronaviruses that are more closely related to the SARS coronavirus. The S proteins of these bat viruses are able to bind to the human and civet angiotensin converting enzyme II, which is the receptor for the SARS virus (Ge et al., 2013). With funding from NIAID, EcoHealth Alliance continues to look across Southern China for these bat viruses, interviewing and taking samples from people potentially at risk (e.g., those trading bats in the markets, hunting bats, living in caves) to look for cases of spillover from the wildlife reservoir.

MERS-CoV Outbreak

Although MERS continues to be the clear and present danger of the coronavirus group, Daszak concurred with others that the general public in the United States is not aware of or concerned with an outbreak until it arrives on the continent (at which point there is typically significant media attention). Although there have been two MERS cases in the United States, there has been no secondary spread. Daszak cautioned, however, that this virus still poses a significant risk to the public's health.

The wild reservoir of MERS is still unknown, he continued, although as discussed, there is good evidence that it is common in camels across Saudi Arabia and the whole of North Africa. However, even this is a spillover from the true wildlife reservoir, which some evidence shows to include bats as well (Memish et al., 2013). Juvenile camels are most likely to have MERS infection, and important cultural and virus transmissibility questions exist when considering the role of slaughter-houses, camel milk production, pet camels, racing, and camel beauty pageants. Daszak pointed out that it is extremely difficult to work in Saudi Arabia because of cultural differences and government restrictions, and in many other places where MERS has emerged or could do so. Although EcoHealth Alliance was invited in by the Saudi government, Daszak said that these connections are not secure, and long-term, sustainable methods are needed to work in unstable countries on important and potentially threatening viruses.

Daszak described ecological niche modeling, which can be used to deduce the MERS "epizone," from data on all known bat reservoirs and camel breeding data. A predictive computer model shows the risk of MERS being transmitted into humans to be highest not in Saudi Arabia,

but in the horn of Africa, where most camels are produced. Therefore, this is where EcoHealth Alliance is now going to shift its focus, and again emphasized the inherent challenges of working within some countries in that region. Those places where the infrastructure and stability are gone, Daszak noted, and where animal migration is uncontrolled, are where we should be most concerned about a virus like MERS. It may be quietly spilling into the human population, becoming more prevalent in camels, and materializing to a real pandemic concern before we can become aware of it.

Assessing Viral Diversity

Many groups are doing viral discovery in wildlife, Daszak said. The challenge is to rank the viruses for follow-up genetic and experimental studies to assess further potential for spillover to humans. Ranking the risk for zoonotic potential of novel viruses is done based on virus-independent and virus-specific traits (see Figure 6-1). Even with these studies and the availability of modeling technology, Daszak cautioned that there is a tendency in the interepidemic period to reduce resources and allocate them elsewhere, showing a lack of priority and a long-term vision.

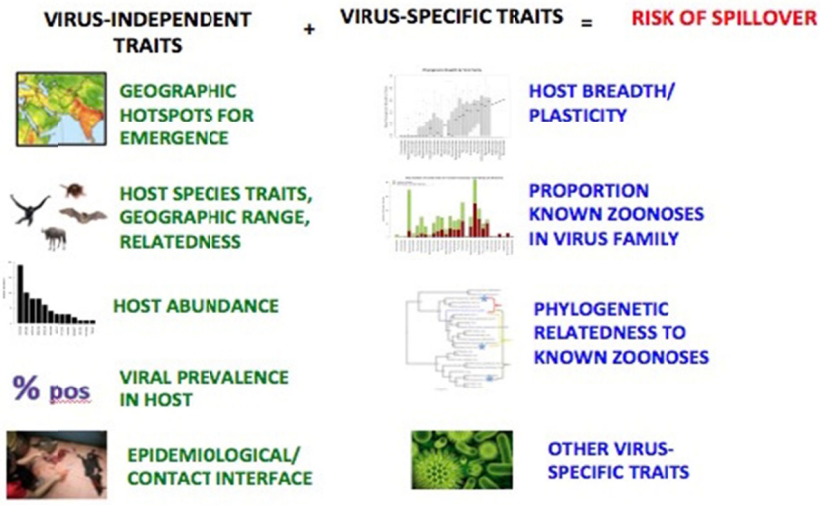

FIGURE 6-1 Ranking risk for zoonotic potential of novel viruses.
SOURCE: Daszak presentation, March 27, 2015.

RESPONSE TO THE 2003 SARS OUTBREAK

In November 2002, SARS emerged in Southeast Asia and quickly spread, aided by superspreader events, to become a global pandemic. Most of the cases were household contacts of those infected and health care workers. Frederick Cassels, chief of the Enteric and Hepatic Disease Branch of the Division of Microbiology and Infectious Diseases (DMID) at NIAID, noted that onset of fever was a very important symptom in the pretransmission phase, and isolating people with fever was a key intervention to control the spread, curbing the epidemic by April 2004.

NIAID/DMID Response: Contracts, Research, and Grants

Cassels explained that NIAID has a dual mandate on both the basic and applied research side and on the rapid response side of the spectrum. In addition to a host of different grant mechanisms, NIAID provides support across the product development pipeline through resource facilities, partnerships, contract resources, and clinical trial support (generally through Phase II). The NIAID response to SARS included contracts, intramural research, and grants. The initial mechanism in 2003 was to rapidly supplement existing coronavirus grants. In 2004, approximately $100 million in SARS-specific grant funding was awarded. Contracts were established quickly, including three vaccine development contracts and a monoclonal antibody contract; however, funding was provided for only 4 years. Cassels added that the risk–benefit ratio changes over the course of an outbreak. When there are many cases, the risk is much higher. As the number of cases decreases, interest in finding a vaccine starts to wane, as others have highlighted, and the risk/benefit ratio changes, making a vaccine a "harder sell" from a regulatory perspective—among others.

Commercial SARS Vaccine Development

An important consideration is not only the dynamic nature of infectious disease threats but also the dynamic nature of the industry on which we depend to develop these vaccines, said Mansoura of Novartis. She briefly described a SARS vaccine development program on behalf of Jeffrey Ulmer, global head of External Research at GSK Vaccines, who worked on the SARS vaccine while at Chiron in 2003. The scientific

assumption being tested was that neutralization antibodies against SARS coronavirus would mediate protection, Mansoura explained.

An important note is that Chiron initiated and funded this program at their own financial risk when they saw the emergence of the outbreak in Hong Kong and Southeast Asia in 2002–2003, Mansoura said. Also important was the fact that researchers at Chiron had an ongoing collaboration with the University of Marburg Biohazard Level-4 facility, which enabled them to begin work immediately. Unfortunately, Mansoura said, the program ended in August 2009 due to expiration of the NIH grant and disappearance of the threat. In a large company like Novartis or GSK, opportunity costs drive decisions. If GSK is developing a SARS vaccine, they are taking resources away from developing the next-generation influenza vaccine. Therefore, if external funding disappears, it is unlikely the company will continue a program using only internal funds.

Mansoura summarized several of the success factors of the Chiron program:

1. Established access to containment facilities enabled the rapid sequencing and identification of the pathogen.
2. Preexisting insight into pathogen biology guided rational approaches to vaccine discovery and development.
3. External funding facilitated vaccine development.

A key limitation was the disappearance of the threat, which resulted in the lack of will to pursue this vaccine development program further. Another limitation was that traditional vaccine technologies are not amenable to rapid response, stressing the need for platform technologies. Arguably, she concluded, a decade of coronavirus vaccine development has been lost, and said it is time to ask the hard questions about what the cost of that inaction could be, before the consequences are seen.

Small Biotechnology Company Platforms Targeting Emerging Infectious Diseases

Michael Wong, senior medical director for Infectious Diseases at Sarepta Therapeutics[1] shared his perspective on some of the challenges

[1]The statements made are Wong's personal observations and are not made on behalf of Sarepta Therapeutics.

for a small-scale biotechnology company participating in the MCM enterprise.

Early work on SARS coronavirus identified several potential targets, Wong noted, and a lead-candidate therapeutic agent moved rapidly through animal studies to IND submission. Unfortunately, at that point, the epidemic had waned and the funding disappeared. Much was learned in the process, but none of that knowledge or data has been applied to looking into MERS or other emerging viruses because of limitations in the ability to be flexible within the context of a small biotechnology company.

Challenges for Small Companies

Wong described some of the issues from a commercial standpoint for a small company, including scale-up, funding, regulatory harmonization, and timelines. The economics of scaling up from synthesis and research, or small clinical study to production, is unfortunately not commercially feasible for MCMs that do not have some commercial output, he said. Smaller companies just do not have the resources to do this unless they are collaborating with federal agencies or co-marketing with other companies in the private sector. Downstream organizations, such as commercial manufacturing organizations that smaller companies contract with, also need to scale up. If they cannot, then the innovator is not capable of scaling up. Similarly, if downstream companies cannot meet timelines, this impacts the innovator's timelines.

Another challenge for small companies is that bridge funding stops at certain points, leaving gaps in funding that impede progress in development. Regulatory and trade issues of bringing investigational agents into other countries continue to exist as well. Wong also mentioned the difficulty in articulating to countries and populations the need to ensure the safety and efficacy of a product, and a real-life, on-the-ground need to respond in an emergency—previously alluded to regarding clinical trials during the EVD outbreak. "We need to keep the dialogue going about how this is done within developmental, legal, and ethical frameworks so that we are ready to respond correctly," he said. Finally, he concurred with others that the appropriate infrastructure needs to be in place for countries or organizations to be ready to accept the type of support or aid that industry is attempting to contribute.

SUSTAINING PRODUCT DEVELOPMENT

Themes throughout the presentations included the missed opportunities for coronavirus research after both the threats and funding decreased, and the potential urgent need to reinstate vaccine candidate development programs within a short timeline, Inglesby of the Center for Health Security said. Panelists discussed what would be needed to sustain a viable coronavirus vaccine development program in the absence of an outbreak. The focus would need to be defined, said Cassels of NIAID. Would such a program be SARS-specific, MERS-specific, or pan-coronavirus? Universal influenza vaccine efforts have arisen from decades of research to identify potentially universal strategies, yet there is still a long way to go and the coronavirus field is not yet ready for that, Cassels stated. Daszak agreed that developing pan-coronavirus platforms will be very difficult. However, viral discovery suggests that there will be many other coronaviruses that are close to MERS or SARS that may use the same receptor, or a different receptor that could be covered by a MERS or SARS vaccine. Wong also called for the need for dedicating resources toward coronavirus therapeutics discovery and development in addition to vaccines.

Sustainability depends on the mission and the direction of the company, Wong continued, saying the will and vision of a strong leader can move a company, but it also requires the company to have the resources to sustain the process. A company must consider the value or return on investment of the program. For smaller companies, value plays a much larger role in making strategic decisions to move forward or to suspend a program. Wong also reiterated that his company has done many proof-of-concept studies with Sarepta's phosphorodiamidate morpholino oligomer (PMO) platform, but only the filovirus program is progressing because it is the current hot topic and some limited funding is available. Waiting for a virus to emerge to move platforms forward in development will not be a sustainable way to achieve progress.

Mansoura reiterated the point made by Venkayya of Takeda and others that corporate social responsibility alone will not drive a company to develop a product. Partnerships and the approaches to reduce the risk for companies are needed. One of the challenges for government funders is allocating the right amount of money to draw in the types of partners needed. Government partners also face challenges in ensuring the size of the market. The days of multibillion dollar, multiyear budgets are gone, she said, and agencies are limited to working with annual appropriations

that are subject to change each year. Inglesby added that it would be useful to have a sense of the funding needed to develop a final licensed product targeting a coronavirus. Additionally, a separate, lower number, that shows the amount of funding needed to develop a product to a certain endpoint is needed, for example, a Phase III–ready asset. Pavia of the University of Utah stressed the need to engage more experts in business, economics, and even behavior to understand how to sustain momentum in funding and support when the need is not clearly present. Participants also highlighted an opportunity for more innovative ways to secure funding. We should not always be looking to the government, Cox said. Compelling stories are needed to interest investors, and we need to learn how to better engage potential stakeholders that have an interest in finding a solution.

Lack of Public Understanding of Threats

Investors are interested at the height of a crisis, Daszak said. He pointed out that the share value for Roche Holding, a Swiss global health care company, increased during the H1N1 influenza pandemic. Unfortunately, as discussed, the interest and hype are short lived and focused around the outbreak. Daszak shared a story of a publication in *Nature* describing SARS in China and work done with colleagues from China's government-funded laboratory. The publication garnered no interest from the Chinese government, he said, and no one they talked with from the live animal markets seemed concerned about the findings. What was surprising for Daszak was how little interest was shown in the article from outside governments and the general public. Based on his experience and understanding, significant attention and interest should have come out of that article, but instead only a few virologists were interested in the paper for academic purposes—again showing the strong influence the media can have on public perception of threats.

Daszak also shared that during the recent Ebola outbreak, EcoHealth Alliance issued a press release and an analysis predicting which countries would be the first to be infected as a result of global air travel.[2] The United States was predicted to be one of the top three countries that would receive infected individuals from countries with EVD, and it was predicted the patient would arrive into Dulles, Boston Logan, Newark, and/or JFK airport. They anticipated a lot of attention and coverage, but

[2]See http://www.ecohealthalliance.org/press/101-ecohealthallianceidentifiesebolas flightpathtotheus (accessed September 30, 2015).

instead, again, there was very minimal pickup by the media. Daszak reiterated that, until an infectious disease crisis is very real, present, and at an emergency threshold, it is often largely ignored. To sustain the funding base beyond the crisis, he said, we need to increase public understanding of the need for MCMs such as a pan-influenza or pan-coronavirus vaccine. A key driver is the media, and the economics follow the hype. We need to use that hype to our advantage to get to the real issues. Investors will respond if they see profit at the end of process, Daszak stated.

Prioritizing Investment

At the workshop there was broad recognition that many threats exist, with only limited financial resources to address these threats. Hundreds of thousands of viruses exist, and it is impossible to prepare for all of them, Swerdlow of CDC said. A participant summarized that "we are either paralyzed to inaction because there are too many threats and we don't know where to start, or we are busy dealing with the threat of the moment." Pavia added that we need to consider how prepared is prepared enough: What basic science is needed; what regulatory reforms are required; what stage of development should products be taken to; and what platform-based technologies are needed to fulfill an even cost–benefit ratio? However, he acknowledged that if the funding to answer these questions is not available, if the FDA does not work on regulatory pathways, if partnerships cannot be established in the interepidemic period, none of these things will happen at the rate that a response demands.

Incorporating Holistic Assessments and Transparent Needs

Prioritization and transparency are pragmatic keys to moving forward. Participants discussed the feasibility of an IRAT-like tool that could prioritize across threats that are not yet at crisis level. Richard Hatchett, chief medical officer and deputy director at BARDA, noted that BARDA is working on this type of assessment tool. He also emphasized the importance of a holistic assessment, considering not only the biological properties of viruses and hosts but also the social and behavioral contexts in which a disease could emerge to become a crisis. Certain categories of threat would be clearly prioritized (e.g., organisms capable of respiratory transmission; highly lethal viruses, such as hemor-

rhagic fevers, that will be disruptive with just a few cases). Daszak concurred about the importance of considering the social context. He noted that EcoHealth Alliance does behavioral risk characterization in all of the countries in which it works, interviewing people most at risk to get a sense of how they are connected to the wildlife and where potential spillover incidents could occur. He suggested that the percentage of the gross domestic product spent on health care is also a predictive factor to consider (impacting the ability to report and to manage a disease), as are issues of governance and political corruption (impacting the willingness to report and respond to international authorities).

Mansoura of Novartis said it is informative to look at previous prioritization efforts and their outcomes. For example, there have been six agents on NIAID's Category A priority pathogens list, including Ebola, since it was created in 2002. Yet, nearly 15 years later, there was not an Ebola vaccine available during the outbreak. The 2012 PHEMCE strategy document gave very ambiguous signals about whether or not an Ebola vaccine was a priority. Conversely though, the private sector looks at those reports very closely to guide their work, she said. Transparency and a clear signal are important. Courage and political will are needed to sustain these investments, she argued, and we are not even asking for a fraction of what we need.

Daszak of EcoHealth Alliance said it is important to be working for the long term on products such as a pan-coronavirus vaccine platform and working on an animal vaccine, but near-term public health control measures, such as changing behavioral risks, increasing infection control in hospitals, are just as critical. Despite the analysis of travel patterns showing a clear risk that people with EVD would arrive in the United States, airports were very slow to enact the simple measure of screening the temperature of arriving passengers, Daszak said. While MCM development is a key piece of the response puzzle, Osterholm of CIDRAP highlighted the need for stronger human and animal surveillance to help guide industry actions and public health interventions together.

ANIMAL VACCINES

Several participants discussed options of potentially preventing outbreaks through vaccination of animal sources, specifically, developing a MERS vaccine for camels. Osterholm suggested that a camel vaccine

could be developed and approved much more quickly than a human vaccine, and could help to lower the risk of further spread.

Daszak concurred that the current human exposure to MERS is clearly through camels. He added that Australia also has a large population of camels, but MERS has not been identified in that population. Although there is a market for a camel vaccine, he believed the potential for funding such a vaccine was limited because the immediate focus is on addressing human disease. He suggested that perhaps the Saudi government and others could be persuaded to commit resources to a camel vaccine, but recalling Kumar's statements from Chapter 3, these issues should not be left for individual governments to solve alone. Swerdlow mentioned that there has been discussion about camel vaccines during reviews of the PHEMCE portfolio, and it was also his understanding that the Saudi government was working with some companies on this issue. With the One Health concept encouraging more and more interaction between human and animal health experts, continued discussion could promote multidisciplinary approaches to solving the same problem—in this case, eradicating a human disease transmitted by animal populations.

Chapter 6 Annex

This annex contains technical details from the speakers' presentations related to the development of products targeting coronaviruses.

David Swerdlow
Associate Director for Science, National Center for Immunization and Respiratory Diseases, CDC

In 2012–2013, ASPR, BARDA, and CDC collaborated to create a coronavirus risk assessment tool based on IRAT, Swerdlow said. As discussed by Katz in Chapter 5, IRAT uses information about novel influenza virus isolates (virus properties, population properties, viral ecology) to assess the risk of emergence and the potential public health impact if the virus does emerge. Risk elements from IRAT were reviewed for relevance to MERS-CoV and categorized as most important for coronaviruses (disease severity), very important (human infections,

global distribution, infection in animals, antiviral treatment options), or important (antigenic relationship, genomic variation). Several IRAT elements were not at all relevant to coronaviruses or could not be assessed with available data (population immunity, receptor binding, transmission in animal models), which made it difficult to gain a true assessment of MERS-CoV.

Peter Daszak
President, Ecohealth Alliance

Daszak and colleagues also sought to understand the extent of viral diversity in mammals. A fruit bat species was repeatedly sampled for the occurrence of 55 viruses from 9 viral families. Using statistical methods to estimate the total unknown diversity of viruses from that species, they estimate 58 unknown viruses in that bat species, and extrapolate about 320,000 unknown viruses in all mammals, including about 72,000 in known bat species (Anthony et al., 2013). The cost to identify 100 percent of these unknown viruses is estimated to be $6.8 billion. Because it is an exponential curve, cost to identify 85 percent is estimated to be $1.4 billion. While that seems like a large amount, for comparison, Daszak stated that the cost of responding to SARS was $10–$50 billion for a single outbreak. The cost of the current EVD outbreak response is estimated to be $32 billion. However, as noted throughout this report, funding is difficult to procure until the country is in "response mode."

Put simply, emerging infectious diseases are increasing over time and there is an unknown diversity of potential pathogens. He noted that the rate of discovery of bat viruses has increased significantly in the past 5 years, but only 7 percent of the total estimated viruses are known. Modeling hot spots for emerging diseases, though, can be used to target surveillance and resources more effectively (Jones et al., 2008). Daszak pointed out that West Africa was identified as a hot spot in 2008, and, although they approached USAID to fund the study of wildlife reservoirs in the area, no resources were available at the time.

Michael Wong
Senior Medical Director in Infectious Disease, Sarepta Therapeutics

The company has about 300 employees across three campuses, and although the company's primary vision is addressing a neuromuscular disease (Duchenne muscular dystrophy), Sarepta is now assessing the use

of this technology in the anti-infective arena. The proof of concept for infectious diseases had been performed in vitro in more than 21 viral families, including filoviruses (Ebola, Marburg), coronaviruses (SARS), and pandemic influenza. Wong noted that therapeutic candidates for Ebola, Marburg, and pandemic influenza have gone through animal efficacy and Phase I human safety and pharmacokinetic studies. He added that much of the work is being done with company funding that is from investors/stockholders, at their own risk.

Michael Osterholm

Director, Center for Infectious Disease Research and Policy (CIDRAP)

Osterholm noted that, while culling civets in the markets in Southern China helped to control the SARS outbreak, there has been no similar success in controlling human exposure to animal carriers of MERS mainly because of the social implications of camels. The camel population is huge, he said, and they are integral to the life and culture of people in the Middle East. He said there are 1.5 million dromedary camels in the Arabian peninsula, and 10.5 million in the horn of Africa through Northern Africa, and there is increasing trade of camels between the Arabian peninsula and Africa. MERS in camels will likely spread throughout the region, including to terrorist-controlled areas where there is limited infrastructure, increasing potential for human exposure.

7

Sustainable Business Models to Ensure Rapid and Nimble Responses

Panelists from diverse sectors discussed the business aspects of developing MCMs. The discussion delved further into topics raised during the discussions of Ebola, influenza, and coronaviruses, including collaboration, public–private partnerships, value, and building sustainable, resilient, business models despite the uncertainties. There are challenges not only in sustaining product development and production, but also in sustaining partnerships, networks, people, and expertise.

ADDRESSING "MARKET FAILURES" IN GLOBAL HEALTH AND BIODEFENSE

Venkayya of Takeda Pharmaceuticals shared his personal perspective on lessons from global health, government, and industry that may apply to the biodefense and MCM enterprise for emerging infectious diseases.[1] Prior to 2000, research on agents of bioterrorism and neglected diseases in global health was limited to small groups of passionate, poorly funded researchers. In 2000, Bill & Melinda Gates launched their foundation and made a critical initial investment in GAVI, the vaccine alliance, which seeks to provide children in the poorest countries of the world with access to the same life-saving interventions that are available to children in rich countries. In 2001, there was significant investment in biodefense and the launch of many new activities following the 9/11 and anthrax terror attacks. As a result of

[1]The statements made are Venkayya's personal views and are not made on behalf of Takeda Pharmaceuticals.

these events, there has been a revolution in global health and in biodefense, Venkayya said.

The Gates Foundation continues to invest about $4 billion in its programs each year. A number of new actors have also entered the space to address "market failures" in global health and biodefense. This includes the spectrum of companies developing products, from those focused primarily on profit, to those passionately committed to improving the lives of others. All companies, though, are accountable to either shareholders or boards of directors and must demonstrate rational allocation of capital. Venkayya observed a pervasive ideology in the global health community and in governments that companies should not be allowed to make undue profits. This impedes fully tapping into the innovation that exists in the world, he claimed.

> Any rational actor will allocate capital to the programs that provide the best return on investment.
>
> *— Rajeev Venkayya, President, Global Vaccine Business Unit, Takeda Pharmaceuticals*

A large amount of innovation is happening in small start-up companies. Venkayya used Apple's "app store" platform as an example of one of the most distributed forms of innovation possible, which is fully open to developers. Anyone can innovate and immediately have access to a market of billions of people. Apple is now coming out with a platform that will allow researchers to create apps to conduct clinical research and gather data from laboratories around the world. Exciting innovation is also happening in academic institutions, but most cannot advance on their own from innovation to commercialization and impact. "How can we, as a community, tap into this innovation and address some of the market failures?" he asked.

As a company, Takeda is passionate about making an impact in infectious diseases where there are unmet needs, including norovirus and dengue. The company deliberately chose to develop vaccines that would have a market in both developed and developing countries, to touch as many lives as possible and have the maximum impact possible in a sustainable way.

Venkayya explained that pitching a vaccine business to company leadership as corporate social responsibility is not a successful approach. Any rational actor will allocate capital to the programs that provide the best return on investment (e.g., oncology, diabetes, hypertension, Alzheimer's disease). Prevention, especially in the form of vaccines, does not generally provide a good return on investment. The investment

bodies in a company need to see a business model that works and a commercial potential that contributes to the company's future. One such approach in vaccines is tiered pricing, which allows a company to charge more for a vaccine in a wealthy country, and just a few dollars for the same vaccine in the poorest countries. This tiered-pricing model is currently supporting access in some of the poorest countries of the world and needs to be preserved, Venkayya said. He acknowledged that some people are uncomfortable that wealthy countries are subsidizing the health of children in poor countries; however, we live in a world of tremendous inequity. There is a fundamental responsibility to address these market failures, he said.

Product Development Partnerships

Financing this innovation is essential, Venkayya stated, and there are a variety of approaches to innovate, including incentives for companies. Push incentives help to provide a clear, de-risked pathway to the market through investment and by providing key capabilities. Pull investments essentially guarantee a market, which is especially important in places where the commercial potential is not apparent.

Another approach to financing is product development partnerships, Venkayya offered, such as the Malaria Vaccine Initiative, Rotavirus Vaccine Program, Aeras (a tuberculosis, or TB, vaccine initiative), International AIDS Vaccine Initiative, and others. A product development partnership is essentially a program manager, securing funding from bilateral donors (e.g., donor governments who provide aid to a recipient country or organization), pushing that funding out to the innovators with the most promising drug, diagnostic candidates, or platforms, and providing some level of project management support. A product development partnership can also provide downstream certainty, helping the technical partner to address issues such as market potential, regulatory pathways, pre-qualification, or stratification of subjects who would receive the MCM. This type of partnership is attractive for companies that may not have the bandwidth to address market and regulatory issues.

Targeted Limited Investments by Government

According to Venkayya, the real promise is novel vaccine platform technologies (e.g., the Vaxart platform described by Latour in Chapter 4)

that move development away from the "one bug, one drug" approach. However, it will take some time for these platform technologies to mature, and to have the full buy-in of the key regulatory agencies, Venkayya noted. Until then, one proposal is to work closely with industry to expand the investment in a suite of vaccine and drug candidates that have potential—NIH and BARDA are already doing this, he noted. The best case would be to have a Phase–III ready compound (i.e., all potency and serologic assays developed, final manufacturing process at final scale developed). Phase III–ready assets are very expensive to acquire, he said, as they have largely been de-risked. The U.S. government could make investments to get products as close as possible to Phase III–ready, and then make the product available to companies to acquire for Phase III development. There would need to be some incentive for companies, he noted, and a stockpile purchase by the government is not likely to be sufficient incentive to justify the large investment a company is going to make to lead the product through to Phase III—especially for larger companies. Incentives might include, for example, the freedom to sell the product in any market in the world, and at any margin, or licensing the technologies or intellectual property that was created in the development of that product at a discount.

The U.S. government needs to become more sophisticated about how companies do business, Venkayya pointed out, and it has to be very flexible in crafting deals with companies that de-risk their investment in these programs. Government also has a role in streamlining the regulatory pathway, including defining clear and transparent alternative approaches to licensure, because regulatory un-certainty represents risk for a company. Government does not have to do everything, though. One existing operating model described by Venkayya is the approach used by the biotechnology company Celgene. The Celgene business model makes targeted limited investments in acquiring promising technologies and candidates. Importantly, he said, it allows the acquired companies to continue to operate and make decisions as usual (no new management team installed by Celgene, no governance committees that review product development and make stage gate decisions). This is one type of approach that we need to bring into government, he said.

Effective approaches to engaging industry need to be very flexible, and company and countermeasure specific. Venkayya suggested the need for a toolbox of different approaches that could be used in agreements with companies to ensure that the return on investment for the company is compelling enough to make it worth their while, or is at least cost-

neutral. Companies want to do the right thing, he said, but they cannot make business decisions that will put them at a loss.

WHAT MOTIVATES COMPANIES?: LESSONS FROM ANTIBACTERIAL DRUG DEVELOPMENT

The efficacy of antibacterial drugs is currently threatened by increasing antimicrobial resistance, said John Rex of AstraZeneca.[2] CDC estimates that 23,000 deaths per year in the United States are attributable to antimicrobial resistance. The pipeline of new products to address this and other such challenges is essentially empty, he said, and the number of active companies in 2013 was estimated to be the same as the number of active companies in 1960. Rex offered three reasons why this is the case: it is difficult to discover new antibacterial products; it is hard to develop them; and the return on investment is poor, despite the fact that a new antibacterial agent could have a dual use as an MCM (Kinch et al., 2014). There are also several basic tensions in anti-bacterial development, including the need to minimize the use of all antibiotics, the desire to have new antibiotics available on demand, and the need for those antibiotics to be developed before an epidemic. In some ways these tensions are irreconcilable, he said. Continuing, he described lessons from the work surrounding antimicrobial resistance and translations of that work that could address the MCM-specific challenges and barriers.

Net Present Value

One European Union (EU)-based model examining the cost of creating a hypothetical antibiotic estimates that approximately $600 million is spent on discovery and development (including failures) for the first 13 years of the product lifecycle, Rex explained. Approximately $2.5 billion[3] is earned in the market during the next 20 years, which includes about 10 years of some market exclusivity, followed by about 10 years of declining sales (Sharma and Towse, 2011; Spellberg et al., 2012). Although this might sound like a good return on investment, it

[2]The opinions expressed by Rex are his own and are not made on behalf of AstraZeneca.

[3]For reference, the top 100 prescribed drugs by U.S. retail sales in 2013 ranged between $725 million and $6.2 billion annually. See more at http://www.drugs.com/stats/top100/2013/sales (accessed August 4, 2015).

does not compare to high-selling "blockbuster" drugs, and Rex pointed out that the model does not take into account net present value (NPV). NPV is an important measure of how much an investment is actually worth in today's terms, based on the cost of capital, risk, and other parameters, resulting in a per-year discount. Ten percent is a commonly used discount in industry, he stated. For example, at a 10 percent per-year discount, $100 in 10 years' time is worth only $39 today. A project NPV takes into account all future monies, both receipts and expenditures, and discounts them back to a selected starting year so clear cost/benefit amounts are better understood. Any NPV of more than zero means that at least some value has been created.

Rex reconsidered the EU cost model in terms of NPV, starting at year 0 (the day discovery starts), and taking into account expense and revenue projections discounted at 10 percent per year over the lifecycle. At the end of 33 years, he calculated that NPV adds up to a loss of about $50 million. A recent U.S.-based analysis shows similar results, with a comprehensive model considering drug development for six different key indications (Sertkaya et al., 2014). They found that the NPV of the new drug was always less than $40 million. However, the study also estimated the value to the patient based on the value of days of work and life restored, and found that to be much higher than just the monetary NPV, ranging from $500 million to $12 billion per drug. Together, Rex suggested, these models show that, while starting antibacterial research and development is financially irrational, we as a society under-value these drugs. Incorporating the societal value of these investments into drug development adds a critical angle to understanding and communicating different types of incentives to the public, investors, and other stakeholders.

Restoring Vitality to the Pipeline

To ensure that life-saving drugs needed in the future will be available, this problem of low or negative NPV must be addressed and resolved. The global antibacterial community has been working to move the economic models back into consistently positive territory through a range of initiatives, incentives, and new regulatory guidance. As an example, Rex described the New Drugs for Bad Bugs initiative that was created under the auspices of the EU Innovative Medicines Initiative, a public–private partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations

(EFPIA)[4] member companies. Seven topic-specific collaboration areas exist, with topic 4 as the Drive-AB project that is centered on driving reinvestment in research and development and the responsible use of antibiotics. Drive-AB was launched in the fall of 2014 and is focused on addressing the tension between economics and stewardship, Rex explained. A multidisciplinary, multistakeholder community will develop evidence-based measures for responsible antibiotic use and create actionable options for new commercial models that address the needs of multiple stakeholders.

Incentive Approaches from Antibiotic Efforts

A range of approaches are being explored, and Rex noted there is a particular interest in de-linking usage from reward to the innovator (i.e., reward should not be based on sales). One suggestion identified during the workshop is a push incentive in the form of a refundable tax credit. This approach has an immediate impact on NPV. Another is a pull incentive that is an insurance-based approach. There would be national acquisition of a new antibiotic at a fixed, predictable rate over a period of time. This annual fee approach would guarantee availability of the drug, whether used or not. Rex suggested that this approach is akin to life insurance in the sense that we pay the insurance premium, and we are happy when the insurance does not need to pay out.

U.S. GOVERNMENT MODELS FOR INCENTIVIZING DEVELOPMENT

Different models will be needed to incentivize the development of MCMs for identified threats before they emerge, and for the rapid and more expensive development of MCMs in response to a disease after it emerges, said Joe Larsen, acting deputy director of the CBRN (chemical, biological, radiological, and nuclear) Division at BARDA. From BARDA's perspective, business models in general need to have transparency of requirements, goals, and objectives, and a clearly defined marketplace. Flexibility in the approach of incentive programs is essential, including flexible partnering mechanisms. Because of this,

[4]The EFPIA is the trade organization representing EU-based pharmaceutical companies.

Larsen said, traditional government contracting mechanisms will not be suitable for some MCM development programs.

BARDA's incentive programs to date have focused largely on push incentives for advanced research and development (e.g., subsidizing development costs) and pull incentives in the form of procurements (stockpiling or vendor-managed inventory of pharmaceuticals and supplies). Larsen acknowledged that, in order to respond to an emerging infectious disease, alternative business models will likely be required to incentivize industry, and a mix of push and pull mechanisms need to be considered and implemented, especially when considering how to appeal to both small, nimble companies and larger companies with more resources and capabilities. Larsen elaborated on a novel portfolio partnering approach to overcome some of the challenges of government contracting, and briefly reviewed several alternative pull mechanisms (see Box 7-1). For products targeting emerging infectious disease threats, partial or full de-linkage pull models will likely be necessary to reward innovation in the face of market uncertainty, he said.

BOX 7-1
Pull Incentives

Procurement-Focused

- Conventional stockpiling: U.S. government places order, contractor fills. May include advanced and milestone payments for initial development. (Although effective for influenza, not likely to be a cost-effective medical countermeasure model for other emerging infectious disease threats.)
- Vendor-managed inventory: U.S. government states inventory requirement, industry guarantees that quantity in their inventory at all times, and government rights to use it.

Partial De-Linkage Model

- Company develops product up to end of Phase II and then enters into contract/agreement with government
- Agreement includes $300–$500 million payment to reward innovation upon Food and Drug Administration approval (level of payment determined by novelty of technology, differentiation in market place, addressing unmet medical need, the need for support of Phase III and Phase IV postmarket commitments)
- Industry can sell product commercially (condition for antibiotics is implementation of a stewardship plan)

Full De-linkage Model

- Company develops product up to end of Phase II (antibiotics) or end of Phase I (emerging infectious diseases) and then enters into contract/agreement with government
- U.S. government or other entity buys intellectual property from industry and assumes control, manages further development
- If disease emerges, terms could be negotiated to return or sell license back to industry

Fee for Service

- Establishes a consortium of companies through an Other Transactions Authority–like mechanism to rapidly identify, screen, and characterize products for emerging infectious disease
- When not actively responding, pays consortium a fee to have them on retainer and assume a "ready" position

Prize Model

- U.S. government creates list of priority pathogens (20–40), with the ability to be modified at any time
- Establishes a monetary prize (value of at least 11 percent plus cost of capital) that a company would win upon getting the product to end of Phase I
- Would still require follow on infrastructure to respond to an emerging infectious disease event

SOURCE: Larsen presentation, March 27, 2015.

During the discussion, Venkayya observed that the incentive programs all had a reward (cash payment, investment by the government) for reaching a certain point. He raised a concern that cash payment by the government to a pharmaceutical company could be problematic in the eyes of policy makers or the public. Larsen suggested though, that public opinion on government reward of private research has shifted, at least with regard to antimicrobial resistance and antibiotic development. He reiterated that some of the pull mechanisms, such as the partial de-linkage model, include clear stipulations that are built in as a condition of the payment (e.g., programs for appropriate use of the product). Such stipulations that ensure limited and appropriate use might also engender a bit more public support. Meghan Majorowski, director of global health at FSG (formally the Foundation Strategy Group), agreed that there is a tension around payments to pharmaceutical firms for

development, although the palatability of the American public toward this approach is improving. She stressed the need for innovative funding strategies that are not cash payouts. Rex noted that the previously mentioned Drive-AB project is meant to precipitate a very public conversation about the true value of an antibiotic, both an antibiotic correctly used, and an antibiotic available but not used, which will be a long process working in many directions. One participant suggested that through future meetings, the Academies could consider a similar approach to increasing understanding of the true value of MCM development—separate from the typically understood "market value."

Venkayya also observed that, in addition to the palatability of cash rewards, there is a level of uncertainty in some of the pull incentives discussed. The potential to get a reward is very different from a guaranteed reward when putting a project forward internally, he said. Larsen replied that the de-linkage model is really meant to target additional incentive toward development of those antibiotics for which the government believes there is the greatest unmet medical need (including resistance). He recognized, however, that there is still risk as the government decides who will receive the funding/contract, but any developer that reached a defined point in developing an antibiotic would get the refundable tax credit. Venkayya suggested the possibility of a priority review voucher as an incentive for neglected product development because clear criteria are in place. If a company brings an MCM to the market, they will get a priority review voucher. Advancing the approval timeline on a potential blockbuster with the help of a voucher is potentially very lucrative.

Portfolio Partnership Approach to Antibacterial Drug Development

To highlight another potential MCM approach, Larsen described a model established in 2013 by BARDA and GSK as a 5-year, $200 million public–private partnership that supports the development of multiple antibiotic candidates. The agreement is flexible and allows for activities and resources to be adjusted fluidly to adapt to technical risk and programmatic priorities. The agreement comes under the HHS Other Transactions Authority (OTA), a mechanism that has been used widely by other agencies, but had not been used by HHS previously. Agreements under OTA are outside of the federal acquisition regulations that apply to other government contracts, allowing for a maximum

amount of flexibility and the design of mutually agreeable terms. The BARDA/GSK agreement allows GSK to have external collaborations for co-development, or through licensing. Governance is collaborative through a BARDA/GSK Joint Oversight Committee.

Larsen suggested that this model could be employed for emerging infectious diseases where there is a high degree of uncertainty in MCM development and in the commercial marketplace. Perhaps a consortium of companies could be formed through this type of flexible partnering mechanism, dedicated to development of products for emerging infectious diseases. More examples of these types of public–private partnerships and consortiums are described by additional speakers in the next sections.

VIRAL HEMORRHAGIC FEVER CONSORTIUM: A UNIVERSITY-BASED MODEL

Robert Garry, professor of microbiology and immunology at Tulane University School of Medicine, and program manager for the Viral Hemorrhagic Fever Consortium (VHFC), described how a modestly funded university-based consortium was able to quickly develop an Ebola rapid diagnostic test. Established in 2010, VHFC comprises universities (including, among others, Harvard University, Tulane University, the University of Texas Medical Branch at Galveston, and the Scripps Research Institute) and several small-to-medium biotechnology companies (including Zalgen Labs, Autoimmune Technologies, and Corgenix Diagnostics). There are also partners in West Africa, including the Kenema Government Hospital in Sierra Leone, where VHFC has a Lassa fever program.

The Kenema Government Hospital was a very important site for research on Lassa fever by CDC and others in the 1970s and 1980s, Garry explained. The facility was closed down by CDC in 1993 because of the civil war in Sierra Leone. In 2005, a group of investigators refurbished the laboratory and rebooted the program to focus on modern diagnostics for Lassa fever. In 2008, recombinant Lassa fever ELISA assays were established and are now in use across Sierra Leone, Nigeria, and other parts of West Africa. In 2010, a rapid diagnostic lateral flow immunoassay for Lassa was introduced (ReLASV®).

Switching Gears from Lassa Fever to Ebola

When EVD emerged, VHFC was already in West Africa and was in a unique position by having an existing research program on a viral hemorrhagic fever, Garry said. VHFC first worked to protect its collaborators and colleagues by establishing Ebola diagnostics at the Kenema Government Hospital. The consortium sequenced the first 99 Ebola genomes (Gire et al., 2014), and rapidly published clinical data (Schieffelin et al., 2014). VHFC developed the first rapid diagnostic immunoassay for Ebola (ReEBOV™), and received an EUA from FDA, and emergency use authorization and listing (EUAL) from WHO, in February 2015.

Garry explained that the previous method for diagnosing Ebola was quantitative reverse transcriptase polymerase chain reaction (qPCR). qPCR requires venipuncture by a skilled phlebotomist and takes 1 to 5 days to transfer the tube of blood to a central laboratory and get a result. The assay requires a skilled technician and laboratory with electrical power, PCR machines, and centrifuges. The lateral flow immunoassay rapid diagnostic test developed by VHFC requires only a finger stick, minimal training to collect the drop of blood, a 15-minute assay, and minimal training to perform the assay, which requires no power or laboratory equipment. Garry stressed that development of this point-of-care test could not have been done without the existing consortium, and their prior experience with Lassa fever, demonstrating the significance of having an ongoing program in place at the site of an outbreak.

Funding Challenges

Stepping back to explain initial stages of the Ebola diagnostic development, Garry said funding from NIH for initial development was received in May 2014, and field testing was initiated in July and August of that year. Additional funding was received in December 2014 from the Gates Foundation and the Paul Allen Foundation to push the product through to approval for emergency use. The question in March 2015 was how to get this test into broader use and to West Africa where it was really needed. Looking forward, the market for the product is the federal government (e.g., stockpiling by BARDA) or perhaps for sale to wealthier African nations with a need (e.g., Nigeria). Other options include subsidization or outright purchase of the tests by philanthropic

organizations or foundations (e.g., the Bill & Melinda Gates Foundation). However, depending on the status of the outbreak, the future challenge will be convincing the U.S. government of the need to stockpile this product for future outbreaks, or convincing wealthy countries or foundations to buy or subsidize the product when there is no immediate demand. Garry also suggested implementing orphan drug–type incentives[5] as a potential approach to encourage development of MCMs for emerging infectious diseases.

CRITICAL PATH TO TUBERCULOSIS DRUG REGIMENS: A PUBLIC–PRIVATE PARTNERSHIP MODEL

The Critical Path Institute is a nonprofit, neutral third party that drives a number of large public–private partnerships focused on various high-end medical need areas. One of those partnerships is the Critical Path to TB Drug Regimens (CPTR) Consortium, which was described by Debra Hanna, executive director of CPTR. She noted that their neutral role in the process becomes very important where there is multisector involvement, especially when for-profit industry and regulatory health authorities are involved.

CPTR was established in 2010 with the core mission of accelerating the development of an entirely novel four-drug regimen for the treatment of TB. The aspiration is to have a regimen that is safer, shorter in duration, and more efficacious than the current standard of care, which Hanna noted is more than four decades old, for TB. CPTR expanded its mission in 2013 to support the development of rapid drug susceptibility testings (DSTs) and diagnostics to ensure the effective deployment of new drugs and drug regimens if development is successful. This added mission will both improve outcome for patients and provide market durability for any new agent that is developed going forward.

[5]An orphan drug is defined in the 1984 amendments of the U.S. Orphan Drug Act as a drug intended to treat a condition affecting fewer than 200,000 persons in the United States, or which will not be profitable within 7 years following approval by the FDA. For more on the Orphan Drug Act see http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/UCM311928.pdf (accessed October 4, 2015).

Establishing the Consortium

TB is not an emerging infectious disease; in fact, one-third of the world has been infected with TB, and 1.5 million people die from TB each year. However, Hanna said TB is a case study for what happens when it is globally decided to declare an infectious disease problem as solved. Drug and diagnostics development programs are divested and pipelines go dry. Subsequently, drug development tools, biomarkers, methodologies, and regulatory strategies in the area go stagnant. This makes the assessment of new molecules and improvement on existing regimens that much harder.

The complacency toward TB began to shift in 2007–2008 when the number of multidrug-resistant and extensively drug-resistant cases of TB began to rise even as the global burden of the disease began to drop slightly. Around that same time, there was also a reemergence of TB drugs in the pipeline, largely because of the courage and goodwill within a few companies, Hanna said. Some were repurposed antibiotics, while others were intentionally designed to be effective against TB. The Bill & Melinda Gates Foundation looked for mechanisms to accelerate the development of these new drugs and an entirely new drug regimen. It was very clear to them at the time that no one sector could take on this problem by itself. Pharmaceutical companies cannot bear the cost of full research and development for each individual drug, and especially not for four new drugs to be put together in a new regimen. Academic laboratories had models to assess the feasibility of molecules but could not design and manufacture molecules. Resources would need to be combined to make true progress.

In 2009, the Gates Foundation partnered with the TB Alliance and the Critical Path Institute to operationalize this public–private partnership and create a neutral third party, with regulatory authorities participating actively from the start. There are now more than 40 different organizations that participate in this large public–private, cross-sector partnership, with 350 individual participants giving of their expertise and time, she said. Participants from all sectors helped build the strategy for the initiative and develop the initial roadmap for projects that CPTR would do. CPTR is fully funded by the Bill & Melinda Gates Foundation, with significant in-kind contributions, as well as data and intellectual property contributions from various partners.

The CPTR Model

The CPTR model was intentionally designed around key areas or gaps for accelerating the process (see Figure 7-1). One key area, The Regulatory Science Consortium is focused on improving and validating the available methods and drug development tools. This includes biomarkers needed to support effective decision making and de-risk this costly process, especially when transitioning from early- to late-stage clinical trials, and when relying on combination studies. CPTR worked through a formal drug development tool and biomarker qualification process that has been defined by both EMA and the FDA. All of this requires sharing of information and data. Another facet of the initiative, The Drug Development Coalition, has developed a legal framework that protects companies' intellectual property but allows CPTR to move forward with these projects. The Rapid Drug Susceptibility Testing consortium is focused on facilitating and informing the development of rapid DST that will be needed to effectively deploy these new drugs.

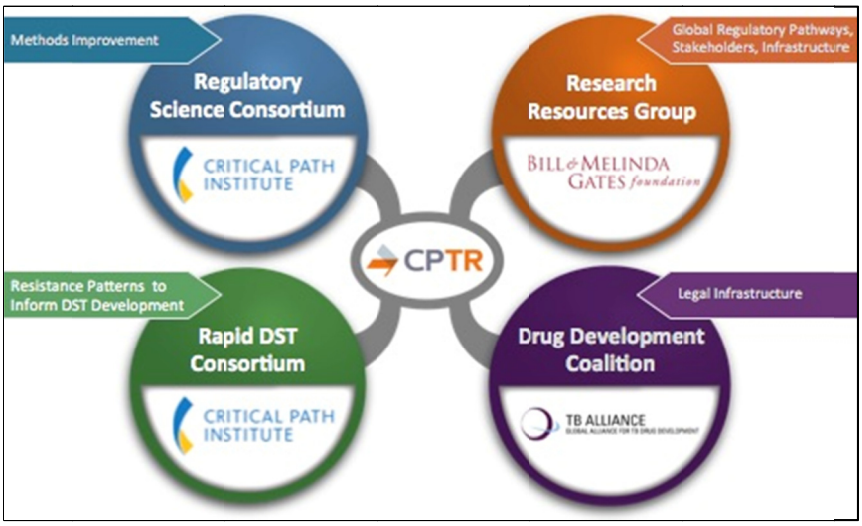

FIGURE 7-1 Critical Path to Tuberculosis Drug Regimens (CPTR): Holistic Approach.
NOTE: DST = drug susceptibility testing.
SOURCE: Hanna presentation, March 27, 2015.

The Research Resources Group is addressing issues such as infrastructure, access to populations, appropriate use, and ethics associated with running clinical trials in the countries where TB is endemic. Within this group, the Global Regulatory Pathways program focuses on harmonization and accelerating approval from national regulatory authorities where these drugs will be used in that space, after approval in major markets. Hanna noted that CPTR does not focus on new molecule discovery; rather, it works with several discovery engines to fill the pipeline.

One key gap in the consortium's approach is that all of the funding comes from the Bill & Melinda Gates Foundation. CPTR is working on a sustainability mechanism and seeking additional funders to continue work on diagnostics and data platform as well as the drug regimen. Another concern is relying on political goodwill to maintain these drugs moving through the development path. Hanna noted that several of the major pharmaceutical partners have completely divested their anti-infective research and development, which has had a very serious impact in the TB drug development space. Although not part of the original focus, advocacy and incentive development for pharmaceutical companies to stay in antibiotic drug development is becoming a priority for the consortium going forward.

CREATING SHARED VALUE FOR SOCIAL CHANGE

Meghan Majorowski of FSG described how the concept of shared value could apply to MCM development. FSG was started by Michael Porter in 1999 with the idea that foundations could be achieving more impact with their dollars. The organization now also works with companies on their philanthropic and corporate social responsibility activities, and with business units in particular to deliver social impact.

Shared value is the concept that the business value of a company and social value can overlap using the company's assets or skills (Porter and Kramer, 2011). Shared value should actually enhance the competitiveness of the company, Majorowski said, and shared-value activities can become the focus of a company in a for-profit sector. Majorowski described three ways to create shared value:

1. Reconceiving products or redefining marketplaces
2. Examining the supply chain for ways to reduce costs to the organization, reduce the raw materials needed, and increase job

skills, that together improve the company's bottom line with the company's existing resources
3. Increasing value through cluster development (e.g., putting the supply chain and the distribution chain closer together in markets)

To help in visualizing these concepts, Majorowski described an example of a shared value business model of the Novartis social venture, Arogya Parivar, in India. Novartis created a distribution network to bring 80 of their products from 11 therapeutic areas into rural India. Products were sold in smaller quantities, making it easier for people in rural areas to afford what they needed. Novartis also went into the villages and trained doctors. Within 30 months, the company was able to break even financially on the venture, she said, and the rural market in India is now a growing part of their portfolio. Another example is the Novo Nordisk efforts to address diabetes in China through provider training, patient education, public awareness, and health system strengthening. As a result, the company has seen a growing market share in insulin sales in China. What starts out as a social design can become a large economic part of the company over time, she said—they do not need to be mutually exclusive.

Translating Shared Value to MCMs

Reconceiving products and markets is especially applicable to MCM development, she thought. For shared value, there needs to be a defined social purpose or need that is shared both internally and externally. An important aspect of this, she explained, is shared-value measurement. This can be a challenge both externally and within companies. Another element is the co-creation aspect of shared value. The shared-value business model usually requires that the company partner with different types of organizations (e.g., nongovernmental organizations, government, foundations). For MCMs, establishing shared value is a bit more difficult, she said. FSG does work with companies in terms of strengthening health systems, which is applicable to the ability to respond to threats and deliver MCMs. Many companies are involved in strengthening the health system with the idea that, over time, it will allow them to enter those markets. There are also opportunities for shared value in terms of establishing partnerships to enhance discovery capabilities. Majorowski noted that the shared value model is easier to implement in

emerging markets where there is a very clear, unmet need, but is more difficult in the U.S. market.

SUSTAINING CAPABILITIES

Sustaining key capabilities for MCM development over time was a common theme of the discussion in this session. Majorowski emphasized the importance of commercial entities being able to sustain their internal capabilities, including scientific expertise and pipelines. She said that some pharmaceutical companies are having discussions to create venues where they can keep key capabilities alive, yet still deliver value to their stakeholders. It is important to describe the need and provide a forum for partners that allows them to contribute those assets.

In addition to creating venues to sustain capabilities, there is also an ongoing fundamental question of funding. The Lassa fever team in place in West Africa was almost entirely dependent on NIH grants, Garry of VHFC said, noting also that the environment for funding is extremely competitive right now with some NIH institutes funding only 1 in 10 grant applications. Leading research institutions are having to take cost-cutting measures, including layoffs, because of reduced NIH grant funding. Even with alternative sources of money (e.g., foundations, other funding agencies), it is challenging to keep a specialized team together under such circumstances. Garry estimated that the direct cost to keep operations going in Nigeria, Sierra Leone, and institutions in the area is between $4 and $5 million per year. Rex of AstraZeneca suggested that, overall, that amount is relatively inexpensive in terms of maintaining the infrastructure and ability to make an immunoassay lateral flow test for a new pathogen.

> VHFC could not have developed the Ebola rapid diagnostic test in about 7 months if they had not had that group of very skilled experts already assembled.
>
> —*Robert Garry, program manager for the Viral Hemorrhagic Fever Consortium (VHFC)*

Sustaining Clinical Trial Capabilities

Rex noted that CPTR now has clinical trials capabilities in place, which can be viewed as a tool for rapid MCM development, but ensuring those capabilities are maintained in different locations around the globe can be difficult as well. Hanna of CPTR pointed out that it took nearly 2

years to conduct an organized analysis of the clinical trial sites being used throughout the world for TB clinical trials, and to identify which of those trial sites were best trained and which needed more training. CPTR, as the neutral entity, brought together all the right partners in order to conduct the training, develop training manuals, and make sure the clinical trialists were well educated, she said. The actual trials are run either by the companies themselves or through the TB Alliance as the product development partner. The trials are funded in part through the companies, like Janssen, who have new TB medicines. However, many of the trials are also supported through NIH funding mechanisms and through the Bill & Melinda Gates Foundation and other funding sources. Even if a company is able to bring a product through early development, there are internal challenges in convincing leadership to commit resources through Phase III development, because those corresponding costs are so high. CPTR is bringing together different kinds of funding partners to help make sure those trials are seen through to completion. The group is also bringing forward validated models and clinical trial strategies, and modeling and simulation tools that can help to design better trials. The existence of the clinical trials network will not necessarily make product development less expensive, she said, but there is a potentially large cost advantage to having capabilities available to pull together, and to be able to start clinical trials more quickly. The key with product development partnerships, Hanna noted, is showing flexibility in how they partner with and reward pharmaceutical companies to bring in drugs from their pipeline.

A DISCUSSION OF PRIORITIES MOVING FORWARD

Following Rex's challenge to identify one area they would highlight for action in the near term, Hanna said there is a need to articulate and test a suite of funding options and incentive models with all the key stakeholders. This point was further emphasized by Arthur of BIO, who added that this suite of options and incentives may have to be different for small versus large companies, and also include different considerations for classic MCMs versus products for emerging infectious diseases.

Majorowski reiterated earlier statements from Farrar of the Wellcome Trust about clarity of language and requests, stressing the importance of clearly defining the unmet MCM needs and targets that

qualify as national or international security threats. A recommitment to basic science is also needed, Garry noted. For example, the NIH budget has been relatively flat for the past 10 years, which is an actual decrease in real funding of at least 25 percent over that time. Larsen of BARDA suggested that, from a policy standpoint, a framework of prioritization for emerging infectious diseases would be valuable, so that the list is manageable and tangible in terms of product development and all partners are clear on priorities. Developing some consensus on appropriate stopping points in development would also be helpful Larsen added. Given the limitations in capabilities to develop these products, aligning business models and incentives to reach reasonable points in development could improve understanding and decision making.

8

Supporting MCM Development Across Threats and Funding Cycles

This final chapter reflects on the discussions of preparedness of the nation as a national security concern; commonalities across three case examples, EVD, pandemic influenza, and coronaviruses; and sustainable strategies and business models for MCM development. Session chairs provided brief highlights from the panel discussions.

PREPAREDNESS AS A NATIONAL SECURITY IMPERATIVE

The sentiment of the first panel session, and of much of the discussion, was that emerging infectious diseases are a national security concern, Parker of Texas A&M summarized. He expressed concern, however, that national security implications of infectious threats are not being recognized appropriately beyond the public health sector. He commented that infectious disease control has become diluted in the "all hazards preparedness" environment. Responses to emerging infectious disease threats will continue to be reactionary unless better efforts are made during interepidemic periods to advance preparedness. This requires a strong leadership function, Parker stressed. One participant suggested the possibility of having a public health agency, separate from HHS. Emphasizing the need for this, Venkayya of Takeda had noted the current lack of an overarching health security office inside the White House, and called for one with technical experts who also understand policy that could align the efforts of departments and agencies and hold them accountable for delivering results. Parker also noted that there has to be a link to the federal budget. Because diseases readily cross borders,

there is an international dimension that is also critical to national security. Global leadership is needed, both during the interepidemic period and during a crisis, Parker said. Participants discussed the dynamic roles of the United States. and other developed world countries, WHO, and other organizations in public health emergencies of international concern.

RESPONDING TO EMERGING INFECTIOUS DISEASE THREATS

Osterholm of CIDRAP called attention to the need for a real-world understanding of risk, saying there is significant focus on biological assessment of risk, with less attention to social, political, and economic factors. For example, the fastest-growing areas of the world are the developing cities of the developing world, he said. How does transportation out of the Middle East impact the potential movement of the MERS virus? The extent of the 2014 Ebola outbreak was likely less due to changes to the virus, and more a result of changes in Africa and the world, he commented, again reiterating the importance of considering behavioral risks. Another challenge is that the world has become dependent on "just-in-time" delivery systems. Infectious diseases can disrupt supply chains and international trade. Any break in the supply chain can then disrupt access to critical medicines, and there are few stockpiles or reserves that can be deployed to backfill the gaps. In assessing risk and responses, Osterholm noted that there is a need for candor in discussing the data and defining what is really needed. The intent is not to lay blame for what may or may not have happened in past responses, but to develop a path forward to a safer world.

There was much discussion across all panels about prioritizing and funding. Inglesby of the Center for Health Security suggested the need for a dedicated, high-priority emerging infectious disease threats development program in the U.S. government, which would work closely with industry. Currently, he stated, everything is partitioned. There is a biodefense program, a pandemic influenza program, but there is nothing to address emerging infectious disease threats that have not yet reached the emergency threshold status. A dedicated program would mean that new programs do not have to be created when a threat emerges, or that one program does not have to steal staff and resources from another

when a crisis reaches the emergency stage. Such a program could be overseen by BARDA, or BARDA and NIH together, he offered.

Clarity in Language and Development Goals

There is also a need to respond to public and political expectations, clarifying the needs, the processes, and the current status. In this regard, Inglesby also called for clarity of language used. It is often written in journals or the media that there is a new vaccine for MERS, or for Ebola. In fact, it is not a vaccine, but a vaccine candidate, and it will only be a vaccine when it gets through the development system and is approved for use. Osterholm concurred that language is important, and he added that the data used are also very important. Various participants stressed the need for better risk communication strategies so that the media, policy makers, and the public can relate to the real potential implications of outbreaks and interventions, or lack thereof when applicable. Personal stories of how an outbreak can affect daily life can be as powerful in getting the message out as a numerical estimate, which is based on modeling that comes with caveats and is often misunderstood.

Conversations also surrounded the need for more clarity and agreement around rational stopping points in development, as Larsen noted previously. Licensure may not be feasible, but perhaps Phase III–ready assets can be achieved and shelved for use when needed. Mansoura of Novartis cautioned that late-stage development, scale-up, and manufacturing are complicated, and it is important to be aware that there is a 50 percent failure rate even for products that make it to Phase III. Ensuring the public and policy makers understand this statistic as well could help dissuade the thought that a robust pipeline for MCMs is ready and waiting to respond quickly for an array of threats. Across the panel discussions, the point was made that moments of crisis are windows of opportunity for change. Many participants commented that it is important to capture the attention of funders, policy makers, and the public and make the case for sustainable preparedness. Throughout the workshop, participants reiterated that the public health sector is hugely under-estimating and not asking enough for what is needed to protect Americans from these threats.

SUSTAINABLE BUSINESS MODELS

Participants discussed sustainability as it applies to research and development programs; markets for products, partnerships, and networks; and talent and resources. Lessons learned from several examples of live research and development infrastructures were discussed (e.g., VHFC, CPTR). Providing a sustainable market for developers is a persistent challenge, and a variety of push and pull incentives were discussed to help de-risk the investment by companies. One of the themes across the discussions highlighted by several participants was the need to recognize that profit is part of the requirement for companies to be engaged. Similarly, examples described by Rex in Chapter 7 showed that society can underestimate true societal value of MCMs separate from financial value. Rex suggested four long-term goals based on the discussions:

1. Fund an active basic science infrastructure. Technology is enabling great things, but there is a need for trained scientists to know what to do with that technology, he said. Maintaining live infrastructures, such as vaccine treatment evaluation units, allows for research and practice.
2. Develop a framework for taking programs to stopping points, such as the end of Phase I, or the end of Phase II (i.e., Phase III ready). The notion of stopping partway needs to be examined in some detail, Rex said. There are elements that must be ready at the end of Phase III for registration (e.g., studies of safety, toxicology, carcinogenicity). These elements are not necessarily consecutive, but are layered into the development process. If a program is stopped partway, and some elements are not completed, it may take longer than expected when starting up again if it is necessary to go back and fill in the missing elements.
3. Pick a program and complete it. For example, BARDA could select a product for a priority threat that has succeeded in getting to a stopping point, and call for its completion. By virtue of running the drill, Rex said, there will be a product (or not), people who have practiced and learned, and the system will have been tested.
4. Encourage/permit multinational funding. For example, Hatchett of BARDA said some companies are working on new anti-

bacterial products and are receiving support from both BARDA and the EU Innovative Medicines Initiative. How can other nations be encouraged to participate in multinational efforts?

Moving forward, Rex recommended that a future Academies workshop consider the economic and societal value of having and not having MCMs. The workshop could delve into understanding the $30 billion that SARS is said to have cost, or how reactionary closing of borders might impact the economy. The workshop could also consider the true feasibility and usefulness of taking product development only partway. He'd like to see education of a broad group of stakeholders as to what is required to take an investigational product from Phase I, to Phase II, to Phase III, and what is the likelihood a product parked at the end of Phase I could eventually become a licensed product. Participants should include representatives of the Department of the Treasury, economists, as well as policy and public health experts, he said. Several participants suggested that co-convening with the Brookings Institution or the American Enterprise Institute could provide a different perspective with important audiences, but it would be essential to maintain the science and health focus.

Acknowledging Past Successes

Participants discussed the existence of success stories and models from which to learn. Project Bioshield, after 10 years and $5.6 billion, has yielded 12 MCMs against CBRN threats, 10 of them licensed. Twenty products supported by BARDA have been licensed since BARDA was created in 2006. The animal rule has been used successfully to approve a monoclonal antibody for the treatment of inhalation anthrax. The solutions that have worked in CBRN, influenza, and global health domains were all adapted to the problems they were seeking to solve in those spaces, offered Abdun-Nabi of Emergent BioSolutions. The solution that is going to work for emerging infectious diseases will likely need to be specifically adapted to that domain, he noted. It can draw on many of the other solutions and tools that have been developed in other spaces, but how they are assembled and used will be unique to the emerging infectious disease space.

Importantly, concluded Hatchett of BARDA, a lesson from the Ebola epidemic response is that responding to emerging infectious diseases must be institutionalized as something that the government values, such

that it sufficiently organizes, funds, and conducts preparedness and response activities. This will need to involve government partnership with industry partners, and ideally, engagement of global partners. Several participants likened the approach and level of organization and commitment that is needed to the Manhattan Project.[1] In closing, Mansoura acknowledged the progress made and the successes seen thus far, but cautioned that there is much to be done. We must continue to develop, test, and exercise as we are striving toward next-generation capabilities to address known and unknown infectious diseases that will continue to threaten the national health security of the United States for many years to come.

[1]The Manhattan Project is the unofficial designation for the former U.S. War Department's secret program, organized in 1942, to explore the isolation of radioactive isotopes and the production of an atomic bomb. Initial research was conducted at Columbia University in New York City, New York.

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B

Acronyms and Abbreviations

ASPR	Office of the Assistant Secretary for Preparedness and Response
BARDA	Biomedical Advanced Research and Development Authority
BIO	Biotechnology Industry Organization
BLA	biologics license application
CBRN	chemical, biological, radiological, and nuclear
CDC	Centers for Disease Control and Prevention
CIDRAP	Center for Infectious Disease Research and Policy
CMC	chemistry, manufacturing, and controls
CPTR	Critical Path to TB Drug Regimens
DMID	Division of Microbiology and Infectious Diseases (NIAID)
DoD	Department of Defense
DST	drug susceptibility testing
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EU	European Union
EUA	emergency use authorization (FDA)
EVD	Ebola virus disease

FDA	Food and Drug Administration
FRMM	Flu Risk Management Meeting
FSG	Foundation Strategy Group
GSK	GlaxoSmithKline
HHS	Department of Health and Human Services
IND	investigational new drug application
IOM	Institute of Medicine
IRAT	Influenza Risk Assessment Tool
MCM	medical countermeasure
MERS	Middle East respiratory syndrome
MERS-CoV	Middle East respiratory syndrome coronavirus
NGDS	Next Generation Diagnostics System
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NPV	net present value
OTA	Other Transactions Authority
PCAST	President's Council of Advisors on Science and Technology
PHEMCE	Public Health Emergency Medical Countermeasures Enterprise
PMO	phosphorodiamidate morpholino oligomer (Sarepta Platform)
qPCR	quantitative reverse transcriptase polymerase chain reaction
rVSV-ZEBOV-GP	recombinant vesicular stomatitis virus-based vaccine for the Zaire ebolavirus expressing EBOV glycoprotein (Merck Ebola Vaccine candidate)

SARS	severe acute respiratory syndrome
SNS	Strategic National Stockpile
TB	tuberculosis
USAID	U.S. Agency for International Development
USAMRID	U.S. Army Medical Research Institute of Infectious Diseases
VHFC	Viral Hemorrhagic Fever Consortium
WHO	World Health Organization

C

Statement of Task

Enabling Rapid Medical Countermeasure Research, Discovery, and Translation to Emerging Threats: A Workshop

An ad hoc committee will organize a public workshop that will examine how to better enable rapid and nimble private-sector engagement in the discovery, development, and translation of medical countermeasures (MCMs). The workshop will explore what policies, guidance, and resources exist to guide decision making within the government and how the business and operational models employed by the private sector are impacted by policies and guidance (formal and informal) and available resources set forth by the U.S. government. Furthermore, the workshop will explore what is needed to ensure that the private sector can respond in a rapid, nimble manner to ensure the availability of MCMs. The committee will develop the workshop agenda, select and invite speakers and discussants, and moderate the discussions. The workshop participants will:

- Explore advances made by the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) to improve MCM development and translation.
  - Consider successful public–private partnership strategies, and other challenges or opportunities that might help incentivize MCM product development

  - Consider implications of recent decreases in funding and the impact on whether gains made by the sector since the initial PHEMCE Strategy are able to be sustained.
  - Discuss whether the establishment of a strategic reserve fund may further enable rapid and nimble MCM development to emerging diseases.
- Identify and discuss policy and regulatory issues that either enable or become barriers to an operational model with strong public–private partnerships.
  - Discuss principles that would strengthen capability-based approaches instead of looking to past events for future direction.
- Explore what is needed from the private-sector perspective in order to support this type of rapid response.
  - Consider the need for formal guidance on the indicators and triggers that are used by the U.S. government to guide decisions.

For the workshop presentations the committee may use examples from recent emerging infectious diseases, such as Ebola virus disease, H7N9, and MERS-CoV, to help frame the discussions. An individually authored summary of the presentations and discussions at the workshop will be prepared by a designated rapporteur in accordance with institutional guidelines.

D

Agenda

AGENDA
March 26-27, 2015
Room 125 of the National Academy of Sciences Building
2101 Constitution Avenue, NW, Washington, DC 20418

Enabling Rapid Response and Sustained Capability with Medical Countermeasures to Mitigate Risk of Emerging Infectious Diseases: An Institute of Medicine Workshop

Background:

Ensuring ready access to medical countermeasures (MCMs) for emerging infectious diseases such as pandemic influenza has been an issue accumulating national attention. With the 2013 emergence and persistence of the H7N9 pandemic influenza threat, the 2014 Ebola outbreak affecting West Africa and several countries around the globe, and a recent surge in cases of Middle East respiratory syndrome coronavirus (MERS-CoV) in the Middle East, the real and present danger of these emerging infectious diseases, which know no borders, are increasingly a national security issue. As the National Health Security Strategy states, "As the movement of people, goods, and services across borders increases, our national health security is increasingly dependent on global health security." Though similar in some ways to intentional biological threats like anthrax, these naturally occurring threats present a unique challenge to the medical countermeasures enterprise given the persistent, dynamic,

and unpredictable nature of their epidemiological trajectories. Traditional means of risk assessment and mitigation may require novel approaches. Is rapid response with MCMs a reality now or in the future, if the MCM is not already in advanced development or available in stockpiles? Are public–private partnerships well positioned to respond in a timely manner?

Current operational and business models to build and sustain this capability are limited. Secure multiyear markets, a fundamental tenet of the public–private partnership for MCM advanced development and acquisition programs for intentional CBRN (chemical, biological, radiological, and nuclear threats) (e.g., Project BioShield), and the initial phase of pandemic preparedness have been dramatically reduced. In a Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) now dependent on annual appropriations, and with limited funding to support rapid response as evidenced in 2014 with the Ebola outbreak, these models face new challenges. PHEMCE in 2009 proposed new strategies and approaches to MCM development. However, it did not solve all challenges, and recent decreases in funding and shifts to annual appropriations may prove to negate some initial successes. Between events such as H1N1 influenza outbreaks, mission capabilities need to be sustained so capacity is not lost when the next event emerges. Additionally, many regulations and policies have been developed in response to past events, instead of looking forward to potential future needs and creating capabilities and partnerships in a systematic manner.

This workshop, hosted by the Forum on Medical and Public Health Preparedness for Catastrophic Events; the Forum on Drug Discovery, Development, and Translation; and the Forum on Microbial Threats, will bring together public- and private-sector stakeholders to discuss how to achieve rapid and nimble MCM availability for new and emerging threats. Discussions will include real-world case studies to elucidate how past events were handled from a policy, budget, and operational standpoint, and contribute to a better aggregate picture of what capabilities and resources are needed moving forward.

Meeting Objectives:

- Discuss the nation's capacity to provide rapid access to MCMs for EIDs (emerging infectious diseases), delineate preparedness gaps, and identify activities required by all stakeholders to improve capabilities.

  - Consider the impact of the current fiscal environment and reasonable expectations.
- Examine the sustainability of public–private partnerships.
- Examine the role of MCMs for emerging infectious disease threats as a national security issue.
  - Discuss the ethical, economic, and global dimensions of these threats and the public–private partnerships required to establish robust capabilities.
- Discuss case studies of past incidents of emerging threats to understand government and private-sector decisions and lessons learned.
  - Evaluate potential strategies for rapid availability of needed MCMs; examine the operational and business models required to enable post-event rapid development, translation, and response in terms of regulatory pathways, financing and market opportunities, and the value proposition to private-sector partners.
  - Discuss the integration of One Health efforts into ongoing threat assessments prior to a declared emergency.
- Consider how to operationalize next steps for the public and private sectors to coordinate a more rapid and nimble response to global emerging threats.
  - Discuss common elements across a range of threats.
  - Consider the sustainability of business models to keep stakeholders invested.

March 26, 2015

8:30 a.m. Welcome and Introductions: Workshop Co-Chairs

RICHARD HATCHETT
Chief Medical Officer, Deputy Director Biomedical Advanced Research and Development
(HHS/ASPR/BARDA)

MONIQUE K. MANSOURA
Head, Medical Countermeasures & Government Affairs, Americas
Novartis Influenza Vaccines

8:35 a.m. Global Health Security Initiative Update

VICTOR DZAU
President
Institute of Medicine

8:55 a.m. Opening Keynote

JEREMY FARRAR
Director
Wellcome Trust

SESSION I: Framing Preparedness for Emerging Infectious Diseases as a National Security Imperative

Session Objectives:

- Provide an overview of the current ability to have MCMs available to effectively respond to EIDs of high (national security) impact.
- Discuss budgetary and policy issues that have challenged rapid and nimble response.
- Identify barriers that might prevent a prospective framework for managing future needs.

9:15 a.m. Session Chair: Introduction and Overview of Objectives

GERALD W. PARKER, Vice President, Public Health Preparedness and Response, Texas A&M Health Science Center

9:25 a.m. Panel Discussion: Rapid MCM Response as a National Security Imperative

National Security: ANDREW C. WEBER, Deputy Coordinator for Ebola Response, Department of State

Biosecurity Strategy: TARA O'TOOLE, Senior Fellow, In-Q-Tel, Inc.

Department of Defense/Warfighter Perspective:
CDR FRANCA JONES, Medical Director, Office of the Deputy Assistant Secretary of Defense for Chemical and Biological Defense Programs

Economics: ROBERT SHAPIRO, Co-founder and Chairman, Sonecon, LLC, former Undersecretary of Commerce for Economic Affairs

Global Risk Report: SURESH KUMAR, Senior Partner, Oliver Wyman Public Sector and Health & Life Sciences Practice, Marsh & McLennan Companies

Industry Perspective: DANIEL J. ABDUN-NABI, President and CEO, Emergent BioSolutions, Inc.

Ethical Considerations: LISA M. LEE, Executive Director, Presidential Commission for the Study of Bioethical Issues

10:40 a.m. BREAK

11:00 a.m. Facilitated Discussion with Attendees (1 hr)

Potential Discussion Questions "In your experience…":

- *What is the cost and social impact of inaction and remaining reactionary?*
- *How can we bridge the gap between the value to society versus the value to the industry?*
- *What high-level budget and policy gaps do you see that present a challenge to rapid response?*
- *How could international collaboration support rapid response?*

12:00 p.m. U.S. Preparedness Perspective: Sustainability and Threat Assessment

NICOLE LURIE
Assistant Secretary for Preparedness and Response
Department of Health and Human Services

12:30 p.m. LUNCH

SESSION II: 2014 Ebola Outbreak Response

Session Objectives:

- Discuss methods and findings of recently released Ebola Team B report.
- Discuss budgetary and policy issues that have challenged rapid and nimble response.
- Highlight issues that have caused fast-acting companies to withdraw from response efforts.
  - How can partners think creatively to demonstrate efficacy when disease incidence decreases?

1:15 p.m. Session Chair: Introduction and Overview of Objectives

MICHAEL T. OSTERHOLM, McKnight Presidential Endowed Chair in Public Health Director, Center for Infectious Disease Research & Policy (CIDRAP), University of Minnesota

1:25 p.m. Panel Discussion: Fast-Track Development of Ebola Vaccines and Testing: Reviewing Successes and Understanding Remaining Barriers to a "Rapid" Response in Real Time

ROBIN ROBINSON, Director, Biomedical Advanced Research and Development Authority (BARDA)

MARK FEINBERG, Vice President and Chief Public Health and Science Officer, Merck Vaccines

MARION GRUBER, Director, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration

WOUTER LATOUR, CEO, Vaxart

THOMAS A. DUNN, Program Manager for the Next Generation Diagnostics System Increment 1, Joint

Project Management Office for Medical Countermeasures Systems (JPM-MCS)

2:15 p.m. Facilitated Discussion with Attendees (1 hr)

"In your experience…":

- *How did the uncertainty about the market impact your investment decision?*
  - *What guarantees would you need to move forward? Who can be looked to for purchasing and continuity once they are finalized?*
- *What did you wish was in place ahead of the response or while it unfolded?*
  - *Were there components of the response that worked well compared to prior emerging threat situations?*
- *How did the evolving ethical considerations in performing clinical trials impact your decisions?*
  - *Do we need an ethical framework for questions about allocation of scarce investigational agents?*
- *How did the existing regulatory framework influence decisions regarding your clinical trials?*
- *Knowing that cases are winding down and clinical trials will be difficult to execute, how will that impact future development or motivation to respond?*
  - *What does this mean for the products now in development?*
  - *Will these products become registered?*
  - *How will any registered products be sustained after registration? Who will manage the supply chain? Who will manage pharmacovigilance? Who will drive registration in the relevant territories?*

3:15 p.m. BREAK

SESSION III: Pandemic Influenza

Session Objectives:

- Discuss policy, budgetary, and operational challenges for companies to continue work in pandemic influenza countermeasure development.
- Explore risk assessment needs and opportunities for current tools and frameworks
- Consider needs for balancing a rapid timeline with sustainable stockpiles
  - How fast is "rapid"?
  - What must be stockpiled and what can wait?

3:30 p.m. Session Chair: Introduction and Overview of Objectives

ANDREW PAVIA, George and Esther Gross Presidential Professor, Chief, Division of Pediatric Infectious Diseases, University of Utah

3:40 p.m. Panel Discussion: Opportunities and Challenges in Preparedness and Response to Pandemic Influenza Threats

JACQUELINE KATZ, Deputy Director (acting), Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC)

RICK BRIGHT, Director of the Influenza Division, Biomedical Advancement Research and Development Authority (BARDA)

LOUIS FRIES III, Vice President, Chief Medical Officer, Novavax

MONIQUE K. MANSOURA, Head, Medical Countermeasures & Government Affairs, Americas, Novartis Influenza Vaccines

DAVID W. VAUGHN, Head of External R&D, North America, GSK Vaccines

4:30 p.m. Facilitated Discussion with Attendees (1 hr)

"In your experience…":

- *What are the questions that are asked when making decisions?What factors impact each of those decisions?*
- *What regulatory challenges have you encountered during development?*
- *What financing strategies are needed to enable continued capacity to rapidly produce new anti-viral countermeasures?*
- *How fast is "rapid"? What must be stockpiled and what can wait?*
- *How do you sustain development and production of stockpiled products?*
  - *Does this process change once a threat has been reduced or eliminated?*

5:30 p.m. ADJOURN

March 27, 2015

8:30 a.m. Welcome and Introductions

RICHARD HATCHETT, Workshop Co-Chair
Chief Medical Officer and Deputy Director
Biomedical Advanced Research and Development Authority (HHS/ASPR/BARDA)

MONIQUE K. MANSOURA, Workshop Co-Chair
Head, Medical Countermeasures & Government Affairs, Americas
Novartis Influenza Vaccines

8:35 a.m. Opening Remarks

RAJEEV VENKAYYA
President, Global Vaccine Business Unit
Takeda Pharmaceuticals

SESSION IV: Developing Vaccines and Therapeutics to Emerging Infectious Diseases Prior to the Emergency Threshold: Coronaviruses

Session Objectives:

- Consider the implications of negative funding following the 2003 severe acute respiratory syndrome (SARS) outbreak.
- Discuss the need for ongoing threat and risk assessments and implications for MCM development before an outbreak reaches public health emergency threshold.
- Discuss the integration of One Health Initiative efforts prior to diseases reaching a public health emergency threshold.

9:00 a.m. Session Chair: Introduction and Overview of Objectives (10 min)

TOM INGLESBY, Director, UPMC Center for Health Security

9:10 a.m. Panel Discussion: Challenges and Opportunities in Responding to Coronaviruses: Past and Present (10 min each)

DAVID SWERDLOW, Associate Director for Science, National Center for Immunization and Respiratory Diseases (NCIRD), CDC

FRED CASSELS, former SARS Program Officer, current Chief of Enteric and Hepatic Diseases Branch, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases

JEFFREY ULMER, Global Head, External Research, GSK Vaccines

MICHAEL WONG, Senior Medical Director for Infectious Diseases, Sarepta Therapeutics

PETER DASZAK, President, EcoHealth Alliance

10:00 a.m. BREAK

10:20 a.m. Facilitated Discussion with Attendees (1hr)

"In your experience…":

- *What are the questions that are asked when making decisions? What factors impact each of those decisions?*
- *Can we anticipate future regulatory needs for unknown agents?*
- *Are new financing vehicles necessary to enable rapid response to emerging threats?*
- *When there are multiple issues to worry about, how can you prioritize which diseases and countermeasures should get attention and funding?*
- *How can threat assessments be improved so decision support exists on when to move forward and when to wait?*
- *How can you minimize the risk to existing programs in the face of re-prioritization of resources for an escalating threat?*

11:20 a.m. LUNCH

SESSION V: Sustainability and Maintenance of Business Models to Ensure Rapid and Nimble Response to Emerging Threats of National Security Concern

Session Objectives:

- Discuss internal and external ideas to mounting a rapid response to emerging threats that are presented by current business models and public–private partnerships in other sectors.

  - Consider opportunities for companies to collaborate in pre-competitive areas and solve antitrust issues and perceptions.
- Discuss ways to better leverage public–private partnerships for future emerging threats.
- Consider how to operationalize next steps for the public and private sectors to coordinate a more rapid and nimble response to global emerging threats.
  - Discuss common elements across a range of threats.
  - Consider the sustainability of business models to keep stakeholders invested.

12:20 p.m. Session Chair: Introduction and Overview of Objectives

JOHN REX, Senior Vice President and Head of Infection, Global Medicines Development, Astrazeneca

12:30 p.m. Panel Discussion: Lessons Learned from Sectors and Potential Future Strategies for Infectious Diseases of National Security Concern (5-10 min each)

JOE LARSEN, Deputy Director, Division of CBRN Medical Countermeasures, Biomedical Advanced Research Development Authority (BARDA)

ROBERT GARRY, Program Manager, Viral Hemorrhagic Fever Consortium, Tulane University

MEGHAN MAJOROWSKI, Global Health Director, FSG

DEBRA HANNA, Executive Director for the Critical Path to TB Drug Regimens Consortium, Critical Path Institute

1:10 p.m. Facilitated Discussion with Attendees (1 hr)

"In your experience…":

- *What is needed to ensure that business models are more resilient to the inherent uncertainly associated with potential MCM markets?*
- *Where are policies needed to improve market conditions for industry investment?*
- *Are there business models from other industries that are relevant?*
  - *How do we maintain the discovery apparatus? Would real-world challenges with priority pathogens be a way to sustain interest and focus?*
  - *How do we maintain registered products? Please address issues of post-registration commitments, supply chain maintenance, global registration (and regulatory maintenance), and pharmacovigilance.*
  - *How should these products be valued? What is the correct reward model?*
- *What regulatory policies have influenced sustainability of alternative business models?*
- *What are strategies for managing both sides of the risk/benefit equation for public and private partners?*
  - *How can the perceived value to society be separated from the perceived value to market?*
- *How do you sustain this new priority area?*

2:10 p.m. BREAK

2:30 p.m. Response Panel: Report Out from Discussions—Common Elements and Priorities Identified Across Threats

Evaluate potential strategies in terms of regulatory pathways, financing and market opportunities, and value proposition to private-sector partners. How can we get to the next level?

Session Chairs:

GERALD W. PARKER, Texas A&M Health Science Center

MICHAEL T. OSTERHOLM, CIDRAP

ANDREW PAVIA, University of Utah

TOM INGLESBY, UPMC Center for Health Security

JOHN REX, Astrazeneca

3:15 p.m. Discussion with Attendees:

Potential Discussion Questions:

- *How can we create policies to support MCM development across threat levels, countermeasure types, and funding cycles?*
- *How can business models be created to engage the private sector and maintain interest of stakeholders across the MCM response spectrum?*

4:15 p.m. Next Steps: Key Takeaway Messages

4:30 p.m. ADJOURN

E

Biosketches of Invited Speakers and Facilitators

Daniel Abdun-Nabi, J.D., M.L.T., has been President and CEO of Emergent BioSolutions, Inc. since 2012. Emergent is a specialty pharmaceutical company listed on the New York Stock Exchange with operations across North America and within Germany and Singapore. As a long-standing, reliable partner to the U.S. government, the company is dedicated to the development, manufacture, and delivery of a portfolio of medical countermeasures that address biological and chemical threats, including anthrax, botulinum, smallpox, and chemical agents as well as emerging infectious diseases. The company also develops and commercializes therapeutics and other specialty products for hospitals and clinics to address hematology/oncology, transplantation, infectious disease, and autoimmune disorders. Mr. Abdun-Nabi's career in the life science industry spans more than 25 years. Prior to his appointment as CEO of Emergent BioSolutions, Mr. Abdun-Nabi served in several roles within the company, including as president, chief operating officer. Mr. Abdun-Nabi served as senior vice president for Corporate Affairs and general counsel, secretary, and vice president and general counsel. Prior to joining the company, Mr. Abdun-Nabi served as general counsel for IGEN International, Inc. and its successor BioVeris Corporation, and as senior vice president, legal affairs, general counsel and secretary of North American Vaccine, Inc. Mr. Abdun-Nabi is member of the Board of Directors of Emergent BioSolutions as well as the National Association of Manufacturers. Mr. Abdun-Nabi serves as vice chairman of the Board of BioHealth Innovation, a public–private partnership focused on accelerating innovative, market-relevant technologies across the biohealth sector in Central Maryland. Mr. Abdun-Nabi also serves as a member of the Montgomery County Executive Business Advisory

Group and as vice chair for the Montgomery County Community Advisory Group charged with assisting in the development of a Comprehensive Economic Strategy for Montgomery County. Mr. Abdun-Nabi served as chairman of the Board for the Oxford Emergent Tuberculosis Consortium (a UK joint venture established with Oxford University to develop a novel TB vaccine) and as chairman of the Board of EPIC BIO (a Singapore joint venture established to develop a novel pandemic flu vaccine). Mr. Abdun-Nabi is a member of the National Association of Corporate Directors and has served as a member of the American Society of Corporate Secretaries, the American Corporate Counsel Association and the Licensing Executives Society. Mr. Abdun-Nabi has been a speaker before professional and business groups on a variety of business topics. Mr. Abdun-Nabi received a Master of Laws in Taxation (M.L.T.) from Georgetown University Law Center, a J.D. from the University of San Diego School of Law, and a B.A. in political science from the University of Massachusetts, Amherst.

Rick Bright, Ph.D., is director of the Influenza Division in the Biomedical Advancement Research and Development Authority (BARDA) in the Office of the Assistant Secretary for Preparedness and Response within the Department of Health and Human Services (HHS). The Influenza Division is responsible for preparing the nation for influenza pandemics and coordinating production, acquisition, and delivery of medical countermeasures during a pandemic response. Dr. Bright joined BARDA in 2010. He manages a portfolio of projects for advanced development of vaccines, therapeutics, diagnostics, and respirator devices to aid in the response and protection against pandemic and seasonal influenza. He also leads the BARDA Influenza Division International Program, supporting programs to build and enhance global capacity for influenza vaccine production and evaluation in developing countries. Dr. Bright serves as an international subject-matter expert on influenza, vaccine and therapeutics development, and diagnostic programs. He has also served as an adviser to the World Health Organization (WHO) and the Department of Defense. Dr. Bright began his career in influenza vaccine and therapeutics development during a 9-year combined tenure at the Centers for Disease Control and Prevention (CDC), Influenza Division, where he focused on avian and human influenza viruses from multiple perspectives, including immunology and vaccine development, viral pathogenesis and molecular correlates of pathogenicity, as well as antiviral drugs and the development of novel

assays for high-throughput surveillance for resistance to antiviral drugs. Dr. Bright was a recipient of the Charles C. Shepard Science Award for Scientific Excellence. He has also worked in the biotechnology industry, where he served as the Director of Immunology at Altea Therapeutics and Vice President of Research and Development and Global Influenza Programs at Novavax, Inc. In 2008, he joined PATH (Program for Appropriate Technology in Health) as the Scientific Director of the Influenza Vaccine Project in the Vaccine Development Global Program and as the Director of the Influenza Vaccine Capacity Building Project in Vietnam. In this capacity, he provided technical leadership to accelerate the development of innovative vaccine and adjuvant candidates against influenza to ensure protection and access to vaccines for populations of developing countries. Dr. Bright received his Ph.D. in Immunology and Molecular Pathogenesis from Emory University and his B.S. in Biology (Medical Technology) and Physical Sciences from Auburn University.

Fred Cassels, Ph.D., serves as the Chief of the Enteric and Hepatic Diseases Branch of the Division of Microbiology and Infectious Diseases (DMID), National Insitute of Allergy and Infectious Diseases (NIAID). The branch has a range of grant portfolios with bacterial (e.g., *E. coli*, *Salmonella*, *Helicobacter pylori*, *Clostridium difficile*, cholera, gut microbiome) and viral pathogens (hepatitis A through E, rotavirus, norovirus), as well as biodefense toxins (botulinum, ricin, SEB). Multiple products are in development, arising from the grant portfolios and as submitted from academia and industry, including vaccines, small molecule and immuno-therapeutics, and diagnostics. These products are in the preclinical stage as well as in clinical trials, all with support through DMID grants or contracts. Previously, he served as the severe acute respiratory syndrome (SARS) (2004-2011), and as the Influenza Vaccine Program Officer (2008-2011), managing grants, and contracts and serving as scientific lead for vaccine clinical trials. Prior to DMID, Dr. Cassels worked at the Walter Reed Army Institute of Research (1988-2004) on enterotoxigenic *E. coli* (traveler's diarrhea) pathogenesis, antigen purification and character-ization, and vaccine discovery, scale-up, delivery, Current Good Manufacturing Practice regulations (CGMP), and clinical trials.

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 re-

search has been instrumental in identifying and predicting the impact 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, identifying the first case of a species extinction due to disease, coining the term "pathogen pollution," and discovering the disease chytridiomycosis as the cause of global amphibian declines. Dr. Daszak is a member of the National Academies of Sciences, Engineering, and Medicine's Forum on Microbial Threats, the Academies Advisory Committee to the U.S. Global Change Research Program (USGCRP), the Supervisory Board of the One Health Platform, the One Health Commission Council of Advisors, and the Center of Excellence for Emerging and Zoonotic Animal Diseases (CEEZAD) External Advisory Board. He has served on the Institue of Medicine (IOM) committee on global surveillance for emerging zoonoses, the National Research Council (NRC) committee on the future of veterinary research, the International Standing Advisory Board of the Australian Biosecurity CRC; and has advised the Director for Medical Preparedness Policy on the White House National Security Staff on global health issues. Dr. Daszak won the 2000 CSIRO medal for collaborative research on the discovery of amphibian chytridiomycosis, is the EHA institutional lead for the United States Agency for International Development (USAID) Emerging Pandemic Threats-PREDICT and PREDICT-2, is on the editorial board of *Conservation Biology and Transactions of the Royal Society of Tropical Medicine & Hygiene*, and is Editor-in-Chief of the journal *Ecohealth*. He has authored more than 200 scientific papers, and his work has been the focus of extensive media coverage, ranging from popular press articles to television appearances.

Thomas A. Dunn, M.S., M.B.A., is an Assistant Product Manager for the Diagnostics Joint Product Management Office within the Medical Countermeasure Systems Joint Project Management Office (MCS JPMO) headquartered at Fort Detrick, Maryland. In this role, he provides scientific, technical, acquisition, and programmatic direction as the Next Generation Diagnostics System Increment 1 (NGDS Inc 1) Deployable Component Device Manager for the development of Food and Drug Administration (FDA) cleared in vitro diagnostic (IVD) kits and environmental surveillance assays for biological warfare agents. He collaborates with joint service, interagency, and international partners and acquisition professionals in the development, acquisition, and

fielding of FDA-cleared IVDs and surveillance countermeasures. Mr. Dunn graduated with honors from Johns Hopkins University with a bachelor's degree in Interdisciplinary Science Studies. He continued his graduate studies at Johns Hopkins University, earning master's degrees in Biotechnology and Business Administration. He is Defense Acquisition Workforce certified at Level II in Science and Technology as well as Level I in Program Management. Mr. Dunn has held numerous positions in academia and clinical diagnostics. His scientific career began at the Henry M. Jackson Foundation and University of Maryland School of Medicine, characterizing adaptive immunity for vaccine and preclinical drug trials. He transitioned into clinical genetics and molecular diagnostics discovery at the Institute for Genetic Medicine and the Department of Urology as a technologist and researcher at the Johns Hopkins University School of Medicine. Mr. Dunn also served as a faculty research assistant with the Department of Bioengineering at the University of Maryland. He has authored 13 peer-reviewed scientific publications and holds a patent for a novel cancer treatment, prevention, and detection method. Prior to his role in the NGDS Inc 1 program, Mr. Dunn served as a program analyst/project coordinator for the Joint Biological Agent Identification and Diagnostic System and science manager for the Critical Reagents Program, both within the Chemical Biological Medical Systems (CBMS) JPMO. Mr. Dunn then became an assistant product manager with CBMS in January 2013 and continued in this position through the transition of CBMS into the activation of the MCS JPMO. Mr. Dunn assumed his current role at MCS as an assistant product manager in June 2013. Academia and industry have recognized Mr. Dunn's scientific accomplishments and leadership with the Judge Ralph M. Burnett Prostate Cancer Research Award, Johns Hopkins University General Honors, and a Certificate of Commendation from the Henry M. Jackson Foundation.

Victor J. Dzau, M.D., is the eigth president of the National Academy of Medicine (NAM). He is Chancellor Emeritus for Health Affairs and James B. Duke Professor of Medicine at Duke University and the past President and CEO of the Duke University Health System. Previously, Dr. Dzau was the Hersey Professor of Theory and Practice of Medicine and Chairman of Medicine at Harvard Medical School's Brigham and Women's Hospital, as well as Chairman of the Department of Medicine at Stanford University. Dr. Dzau has made a significant impact on medicine through his seminal research in cardiovascular medicine and

genetics, pioneering the discipline of vascular medicine, and leadership in health care innovation. His important work on the renin angiotensin system (RAS) paved the way for the contemporary understanding of RAS in cardiovascular disease and the development of RAS inhibitors as therapeutics. Dr. Dzau also pioneered gene therapy for vascular disease, and his recent work on stem cell "paracrine mechanisms" and the use of microRNA in direct reprogramming provides novel insight into stem cell biology and regenerative medicine. In his role as a leader in health care, Dr. Dzau has led efforts in health care innovation. His vision is for academic health sciences centers to lead the transformation of medicine through innovation, translation, and globalization. Leading this vision at Duke, he and his colleagues developed the Duke Translational Medicine Institute, the Duke Global Health Institute, the Duke-National University of Singapore Graduate Medical School, and the Duke Institute for Health Innovation. These initiatives create a seamless continuum from discovery and translational sciences to clinical care, and they promote transformative innovation in health. As one of the world's preeminent academic health leaders, Dr. Dzau advises governments, corporations, and universities worldwide. He has served as a member of the Council of the IOM and the Advisory Committee to the director of the National Institutes of Health (NIH) and as chair of the NIH Cardiovascular Disease Advisory Committee and the Association of Academic Health Centers. Currently he is a member of the board of directors of the Singapore Health System, Governing Board of Duke-National University of Singapore Graduate Medical School, and Senior Health Policy Advisor to Her Highness Sheikha Moza (Chair of the Qatar Foundation). He is also on the Board of Health Governors of the World Economic Forum and chaired its Global Agenda Council on Personalized and Precision Medicine. In 2011, he led a partnership between Duke University, the World Economic Forum and McKinsey. He founded the nonprofit International Partnership for Innovative Healthcare Delivery and chairs its board of directors. Among his honors and recognitions are the Gustav Nylin Medal from the Swedish Royal College of Medicine; the Max Delbruck Medal from Humboldt University, Charité, and the Max Planck Institute; the Commemorative Gold Medal from the Ludwig Maximilian University of Munich; the Inaugural Hatter Award from the Medical Research Council of South Africa; the Polzer Prize from the European Academy of Sciences and Arts; the Novartis Award for Hypertension Research; the Distinguished Scientist Award from the American Heart Association (AHA); and the AHA Research

Achievement Award for his contributions to cardiovascular biology and medicine. He has received six honorary doctorates.

Jeremy Farrar, Ph.D., is director of the Wellcome Trust, a global charitable foundation dedicated to achieving extraordinary improvements in health by supporting the brightest minds. Before joining the Trust he was director of the Oxford University Clinical Research Unit in Vietnam, where his research interests were in infectious diseases, tropical health and emerging infections. He has contributed to 500 peer-reviewed scientific papers, and served on several WHO advisory committees. Dr. Farrar was appointed OBE in 2005 for services to Tropical Medicine, and he has been awarded the Memorial Medal and Ho Chi Minh City Medal from the Government of Vietnam, Frederick Murgatroyd Prize for Tropical Medicine by the Royal College Physicians, and the Bailey Ashford Award by the American Society for Tropical Medicine and Hygiene. He is a fellow of the Academy of Medical Sciences.

Mark F. Feinberg, M.D., Ph.D., is the Vice President for Medical Affairs and Policy in Merck Vaccines and Infectious Diseases at Merck & Co., Inc. He is responsible for global efforts to implement vaccines and anti-infective therapies to achieve their greatest individual and public health benefits. Dr. Feinberg received his B.A., magna cum laude in biology and anthropology from the University of Pennsylvania, and his M.D. and Ph.D. from Stanford University School of Medicine. His Ph.D. research at Stanford was supervised by Dr. Irving Weissman and included time spent studying the molecular biology of the human retroviruses —HTLV-I and HIV—as a visiting scientist in the laboratory of Dr. Robert Gallo at the National Cancer Institute. Dr. Feinberg served as a project officer for the Committee on a National Strategy for AIDS of the IOM and the National Academy of Sciences (NAS). Dr. Feinberg pursued postgraduate residency training in internal medicine at the Brigham and Women's Hospital of Harvard Medical School and postdoctoral fellowship research in the laboratory of Dr. David Baltimore at the Whitehead Institute for Biomedical Research. Dr. Feinberg was an assistant professor of medicine and microbiology & immunology at the University of California, San Francisco (UCSF), where he also served as an attending physician in the AIDS/Oncology Division and as director of the Virology Research Laboratory at San Francisco General Hospital. Dr. Feinberg was a medical officer in the Office of AIDS Research in the Office of the Director of the National Institutes Attending Physician at

the NIH Clinical Center. During this period, he also served as executive secretary of the NIH Panel to Define Principles of Therapy of HIV Infection. Prior to joining Merck in 2004, Dr. Feinberg served as professor of medicine and microbiology & immunology at the Emory University School of Medicine, as an Investigator at the Emory Vaccine Center, and as an attending physician at Grady Memorial Hospital. At UCSF and Emory Dr. Feinberg and colleagues were engaged in the research studies focused on revealing fundamental aspects of the pathogenesis of AIDS. Dr. Feinberg also founded and served as the medical director of the Hope Clinic of the Emory Vaccine Center—a clinical research facility devoted to the clinical evaluation of novel vaccines for HIV and other infectious diseases, and in basic research studies focused on revealing fundamental aspects of the pathogenesis of AIDS. Dr. Feinberg also founded served as the medical director of the Hope Clinic of the Emory Vaccine Center—a clinical research facility devoted to the clinical evaluation of novel vaccines and to the translation research studies of human immune system biology. In addition to his other professional roles. Dr. Feinberg has also served as a consultant to and a member of several committees of the IOM and the NAS. Dr. Feinberg currently serves as a member of the National Advisory Committee, the Academies' Forum on Microbial Threats, and the board of trustees of the National Foundation for Infectious Diseases. He has also earned board certification in internal medicine, is a fellow of the American College of Physicians, and a member of the Association of American Physicians. He was the recipient of an Elizabeth Glaser Scientist Award from the Pediatric AIDS Foundation and an Innovation in Clinical Research Award from the Doris Duke Charitable Foundation.

Louis Fries III, M.D., joined the Novavax team in 2011. He has 22 years of experience in the clinical testing and development of human vaccines in academic, small biotech, and major biopharmaceutical environments. While a major career focus has been influenza, he has also had extensive involvement with bacterial and parasitic vaccines and therapeutic and prophylactic immunoglobulins. Most recently, following the acquisition of ID Biomedical by GSK Biologicals, Dr. Fries served as Director of Clinical Development from 2005 to 2011. He had previously served as Vice President of Clinical and Regulatory Affairs for Intellivax and ID Biomedical GSK Biologicals, which he had joined after 4 years as Director of Clinical Development for Univax and Nabi. Prior to joining the biotechnology industry, Dr. Fries served for 4 years as a

faculty member in the Department of International Health, Johns Hopkins Univerisity School of Hygiene and Public Health. He has been an author of more than 60 peer-reviewed publications. Dr. Fries received his undergraduate training at the Johns Hopkins University and his M.D. from Duke University. He trained in internal medicine at Johns Hopkins University and infectious disease at the NIAID, where he was a member of the Laboratory of Clinical Investigation from 1979 to 1989.

Robert F. Garry, Ph.D., is a professor of Microbiology and Immunology at Tulane University School of Medicine. He serves in the Tulane University administration as Assistant Dean for Graduate Studies in Biomedical Sciences. He is also an associate member of the Broad Institute of Harvard and Massachusetts Institute of Technology (MIT) and an adjunct professor at Tuskegee University and Redeemers University (Nigeria). He is currently managing the Viral Hemorrhagic Fever Consortium (VHFC), which is developing countermeasures against Lassa virus, Ebola virus, and other severe pathogens. The team developed point-of-care and confirmatory diagnostics for Lassa fever to commercial standards. The VHFC leveraged these advances to develop high-sensitivity and specificity immunoassays for Ebola virus and other filoviruses, including an Ebola Rapid Diagnostic Test (Ebola RDT) that can be used in austere settings. The West African Ebola outbreak is the first to have occurred in an area with an advanced clinical and laboratory infrastructure for study of viral hemorrhagic fevers. VHFC scientists analyzed Ebola virus genetics/genomics as the virus initially spread into Sierra Leone. The study demonstrated a single introduction of Ebola virus into humans with subsequent human-to-human spread and documented a rapid accumulation of mutations in the viral genome. A clinical study showed that the West African variant of Ebola virus causes predominantly a gastrointestinal illness and focused attention of this aspect of the disease for control of disease spread. Dr. Garry has served on numerous National Institutes of Health review panels, principally in the areas of AIDS, Small Business and Biodefense. Dr. Garry completed his undergraduate education at Indiana State University and performed doctoral studies at the University of Texas at Austin.

Marion F. Gruber, Ph.D., is the director of the Office of Vaccines Research and Review (OVRR) in the Center for Biologics Evaluation and Research, FDA. In this position, she directs the review, monitoring, and evaluation of investigational new drug applications and biologic

license applications encompassing vaccines and related biological products as well as research pertaining to the development, manufacturing, and testing of vaccines. Before her current role she served as OVRR deputy director and as OVRR associate director for policy. In these positions she gained extensive experience in developing policies and programs affecting vaccine regulations. Dr. Gruber has served on numerous agency and interagency working groups and committees. She has represented the OVRR in numerous FDA-wide initatives, at the national and international meetings, and on national and international task forces to foster communications and collaborations related to the safety, quality, and efficacy of vaccines. Dr. Gruber has more than 20 years of experience in the regulatory review and approval of preventive vaccines and related biologics. She has generated guidance for industry documents critical to the development of preventive vaccines and has contributed to rule making affecting the regulation of vaccines.

Debra Hanna, Ph.D., is currently the executive director of Critical Path to TB Drug Regimens (CPTR) at the Critical Path Institute. Her primary responsibilities include leading a team of more than 300 scientists to facilitate the development of novel tuberculosis (TB) drug regimens through development of innovative regulatory science approaches, qualification of novel drug development tools and biomarkers, and development of rapid drug susceptibility assays and diagnostics for TB. Dr. Hanna is a trained microbiologist and immunologist. Prior to joining Critical Path Institute, she spent 11 years within the Antibacterial Research and Development Unit with Pfizer Global Research and Development. She was the research project leader for multiple antibacterial drug development programs. Her laboratory focused on the pre-clinical evaluation of novel antibiotics and their combination using multiple in vitro systems including the hollow fiber model. Additionally, Dr. Hanna led a dynamic translational research team focused on understanding pre-clinical pharmacodynamics and pharmacokinetic relationships for novel antibacterial agents from early discovery to Phase II development. Dr. Hanna's passion for TB research began during her postdoctoral fellowship at the University of California, San Diego, where she studied the impact of virulence genes for survival of *Mycobacterium tuberculosis* in the host lung. She received her doctorate in microbiology from North Carolina State University and her B.S. degree in microbiology and immunology from Colorado State University.

Richard Hatchett, M.D., is chief medical officer and deputy director for Strategic Sciences and Management at BARDA within HHS. His primary responsibilities include oversight of programs relating to strategic science and innovation, strategic affairs and reporting, development of science and preparedness policy, human resources, communications, and organizational marketing. Previously, he served as Director for Medical Preparedness Policy on the White House National Security Staff, where he worked on a wide array of issues related to medical countermeasures development, the 2009 H1N1 pandemic, and pandemic preparedness more broadly. In 2005–2006, he served as Director for Biodefense Policy on the White House Homeland Security Council and was a principal author of the National Strategy for Pandemic Influenza Implementation Plan. In this capacity, he helped set policy and devise strategies to mitigate the consequences of a pandemic and promote pandemic preparedness. From 2005 to 2011, he served as associate director for Radiation Countermeasures Research and Emergency Preparedness at NIAID. Dr. Hatchett completed his undergraduate and medical educations at Vanderbilt University, an internship and residency in Internal Medicine at New York Hospital–Cornell Medical Center, and a fellowship in Medical Oncology at the Duke University Medical Center.

Thomas V. Inglesby, M.D., chief executive officer and director of the UPMC Center for Health Security, a nongovernmental organization dedicated to protecting people's health from the consequences of epidemics and disasters and to ensuring that communities are resilient to those challenges. Dr. Inglesby's work is internationally recognized in the fields of public health preparedness, pandemic flu and epidemic planning, and biosecurity. He is chair of the Board of Scientific Counselors, Office of Public Health Preparedness and Response, CDC. He is co-chair of the National Health Security Preparedness Index initiative. He has been chair or a member of a number of the Academies committees, and he has served in an advisory capacity to the Defense Science Board, HHS and the Department of Homeland Security, and NIH. He has been invited to brief White House officials from the past three presidential administrations on national biosecurity challenges and priorities, and he has delivered congressional testimony on public health preparedness and biosecurity. He is also on the board of directors of PurThread, a company dedicated to developing antimicrobial textiles.

During the past 15 years, Dr. Inglesby has authored or co-authored more than 80 peer-reviewed articles, reports, and commentaries on a wide range of issues related to health and security. He is co-editor-in-chief of the journal *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science*, which he helped to establish a decade ago as the first peer-reviewed journal in its field. He was principal editor of the 2002 JAMA book *Bioterrorism: Guidelines for Medical and Public Health Management*. He is regularly consulted by major news outlets. Dr. Inglesby is associate professor of medicine and public health at the University of Pittsburgh Schools of Medicine and Public Health. He completed his internal medicine and infectious diseases training at Johns Hopkins University School of Medicine, where he also served as assistant chief of service. Dr. Inglesby received his M.D. from Columbia University College of Physicians and Surgeons and his B.A. from Georgetown University. He continues to see patients in a weekly infectious disease clinic.

CDR Franca R. Jones, M.S., Ph.D., is Director of Medical Programs in the Office of the Assistant Secretary of Defense for Nuclear, Chemical, and Biological Defense Programs (Chemical and Biological Defense). In 2010, CDR Jones was selected for a detail in the White House Office of Science and Technology Policy, where she led the administration's biological defense research, development, testing, and evaluation policy, and biosecurity and biosurveillance policy. CDR Jones has made significant strides toward developing national security policy and coordinating interagency research and development policies in the areas of chemical and biological defense. She has led or co-led the development of the National Biological Response and Recovery Science and Technology Roadmap; National Biosurveillance Science and Technology Roadmap; National Strategy for Chemical, Biological, Radiological, Nuclear, and Explosives Standards; National Non-Traditional Chemical Agent Research, Development, Testing, and Eval-uation Strategy; National Strategy for Biosurveillance; and United States Government Policy for Oversight of Dual Use Research of Concern.

Jacqueline Katz, Ph.D., was appointed chief of the Immunology and Pathogenesis Branch of CDC's Influenza Division in 2006. Under her leadership, the Branch has received three Charles C. Shepard Science Awards for excellence in laboratory methods publications. Dr. Katz and her group are inter-nationally renowned for their research on the

pathogenesis, immunity, and transmission of seasonal and pandemic influenza viruses, specifically in the area of human infection with novel influenza viruses of animal origin. Dr. Katz earned her B.S. degree in microbiology and biochemistry and her Ph.D. in microbiology from the University of Melbourne, Australia. After completing her postdoctoral training in influenza virology, she worked as an assistant member of the Department of Virology and Molecular Biology at St. Jude's Children's Research Hospital. Dr. Katz joined CDC in 1992 as chief of the Immunology and Viral Pathogenesis Section in the Influenza Branch within the Division of Viral and Rickettsial Diseases. During the 2009 H1N1 pandemic, Dr. Katz and her group conducted serologic studies, provided laboratory support for seroepidemiologic investigations, and supplied technical support to public health partners. Using existing models system, her team studied the properties of virulence (disease severity) and transmissibility of pandemic 2009 H1N1 viruses in comparison to seasonal viruses. This research provided a platform for the ongoing assessment of multiple preventive and treatment strategies against pandemic 2009 H1N1 infection. In addition to her role at CDC, Dr. Katz has adjunct appointments at Emory University in the Departments of Microbiology and Immunology and Pathology, and is an adjunct member of the graduate faculty in the Immunology and Molecular Pathogenesis Program of the Division of Biological and Biomedical Sciences. She also serves as an associate editor for the *International Society for Influenza and Other Respiratory Virus Diseases*. Dr. Katz's work is documented in more than 150 research articles, reviews, and books.

Suresh Kumar, M.M.S., is a senior partner in Oliver Wyman's Public Sector and Health & Life Sciences practice groups in New York. He previously spearheaded U.S. Trade Promotions and Exports in the Obama Administration as Assistant Secretary of Commerce & Director General of the U.S. & Foreign Commercial Service. Mr. Kumar served on the Group Operating Committee of Johnson & Johnson. A "trifecta athlete," he has contributed much to private enterprise, public service, and the social sectors as an executive, administrator, consultant, and professor of management. He has led innovative process transformation initiatives and identified billion-dollar cost avoidance and efficiencies. Throughout his business, government, and consulting careers, Mr. Kumar has led projects to create enduring value, facilitate global expansion, and enhance leadership positions. His global operating

experiences included leading the Worldwide Consumer Pharmaceuticals businesses at Johnson & Johnson, where he served on the Group Operating Committee, and Warner Lambert's Latin America and Asia Consumer Products businesses as vice president. Mr. Kumar has established global organizations and turned around Emerging Markets businesses. He has established programs to expand access to health care and improve population health. He served on the boards/global councils of the World Self-Medication Industry, American Management Association, Association of National Advertisers, and Consumer Health-care Products Association. He has served the Bill & Melinda Gates and Clinton Foundations, the Alliance for a Green Revolution in Africa, and the African Development Bank to "improve lives and livelihoods." Engagements helped shape policies, programs, and financing mech-anisms to reduce hunger and led to food security in Rwanda and Malawi. He has worked extensively in Africa. He has helped companies develop growth strategies, go to market programs, and enter new markets. He has led organizational transformation to leverage assets and resources across sectors, functions, and geographies. He has helped create cohesive enterprise-wide processes to enhance market agility, and integrated businesses and acquisitions to improve operational effect-iveness across the Americas, Europe, and Asia. Mr. Kumar is a Distinguished Visiting Professor of International Business at George Washington University and has previously held faculty appointments at Rutgers University, Schulich School of Business at York University in Toronto, Canada, and Bombay University in India. He was Distinguished Executive-in-Residence at Thunderbird School of Global Management. Mr. Kumar has led business initiatives on every continent and speaks six languages. He has published on globalization and management practices. He has an economics degree from Delhi University and a master's in management from Bombay University. He is an alumnus of the Thunderbird International Consortium Program.

Joe Larsen, Ph.D., is the chief of the Broad Spectrum Antimicrobials program at the BARDA. The goals of BARDA's Broad Spectrum Antimicrobials program are to enable the U.S. government to acquire medical countermeasures (MCMs) to protect the American public against bioterrorist threats and to develop additional antimicrobial treatment options to counter the growing threat of antimicrobial resistance in clinically prevalent bacterial pathogens. He currently oversees a portfolio of approximately $800M in programs that support the development of

novel antibacterial and antiviral drugs. Dr. Larsen also serves as the BARDA representative on the U.S. Interagency Task Force on Antimicrobial Resistance. Previously, Dr. Larsen served as a senior science and technology manager at the Joint Science and Technology Office for Chemical and Biological Defense within the Defense Threat Reduction Agency. In that position he managed an ~$50M applied research program aimed at the development of medical therapeutics against viral, bacterial, and toxin threat agents. From 2005 to 2006, Dr. Larsen was an American Association for the Advancement of Science Fellow at the Department of Homeland Security, where he managed university-based research programs aimed at the development of enhanced food safety detection systems and MCMs for agricultural threat agents. He was a 2005 NAS Christine Mirzayan Fellow with the Board of Life Sciences. Dr. Larsen received his Ph.D. in microbiology from the Uniformed Services University of the Health Sciences and his B.A. with honors from the University of Kansas.

Wouter Latour, M.D., M.B.A., is chief executive officer and director of Vaxart, a company that develops oral vaccines. Dr. Latour brings more than 20 years of industry experience to Vaxart, including roles as vice president and director, Global Strategy and Business Development at SmithKline Beecham Biologicals (now GSK Vaccines) and as strategic adviser for Novartis Pharma, Novavax, and Berna Biotech (now J&J/Crucell). Most recently, Dr. Latour served as CEO and director at Trinity Biosystems, Inc., a company focusing on oral delivery of biopharmaceuticals. Dr. Latour earned his M.D. from the University of Amsterdam and his M.B.A. from Stanford University.

Lisa M. Lee, Ph.D., M.A., M.S., is executive director of the Presidential Commission for the Study of Bioethical Issues. Dr. Lee, who has a Ph.D. from Johns Hopkins University, an M.A. in educational psychology from the University of Colorado, and an M.S. in bioethics from Alden March Bioethics Institute at Albany Medical College, is an epidemiologist and public health ethicist. The focus of Dr. Lee's current work is bioethics pedagogy and public health ethics. Her prior work at CDC included the ethics of public health surveillance, privacy and public health data use, scientific integrity, research ethics, development and evaluation of surveillance systems, research on HIV and fertility, HIV/AIDS survival, HIV and tuberculosis, and data quality. During her 14-year career at CDC, she held several leadership positions, including as the agency's

assistant science officer and director of the Office of Scientific Integrity. Dr. Lee is the lead editor *of Principles and Practice of Public Health Surveillance*, 3rd edition (Oxford University Press, 2010). She has authored numerous publications in both science and ethics. She has served as a peer reviewer for many scientific conferences and journals, and as associate editor for the *Journal of Bioethical Inquiry and Public Health Reviews*. Dr. Lee is adjunct professor at the Center for Biomedical Ethics Education & Research at Albany Medical College, where she teaches ethics. She is the recipient of the 2014 Pellegrino Medal for excellence in bioethics.

Nicole Lurie, M.D., M.S.P.H., is the Assistant Secretary for Preparedness and Response at HHS. The mission of her office is to lead the nation in preventing, responding to, and recovering from the adverse health effects of public health emergencies and disasters, ranging from hurricanes to bioterrorism. Dr. Lurie was previously senior natural scientist and the Paul O'Neill Alcoa Professor of Health Policy at the RAND Corporation, where she directed RAND's public health and preparedness work as well as RAND's Center for Population Health and Health Disparities. She also served as Principal Deputy Assistant Secretary of Health at HHS; in state government, as medical adviser to the commissioner at the Minnesota Department of Health; and in academia, as professor in the University of Minnesota Schools of Medicine and Public Health. Dr. Lurie has a long history in the health services research field, primarily in the areas of access to and quality of care, mental health, prevention, public health infrastructure, and preparedness and health disparities. Dr. Lurie attended college and medical school at the University of Pennsylvania, and completed her residency and M.S.P.H. at the University of California, Los Angeles, where she was also a Robert Wood Johnson Foundation Clinical Scholar. She is the recipient of numerous awards and is a member of the National Academy of Medicine. Dr. Lurie continues to practice clinical medicine in Washington, DC.

Meghan Majorowski, M.Sc., leads the Global Health practice at FSG, a mission driven consulting firm committed to reimaging social change that serves foundations, businesses, non profits and governments around the world. She brings nearly 15 years of experience in strategic and tactical consulting as well as management of development programs in emerging economies. She started her career as a strategy consultant for

McKinsey & Company and became vice president of global health operations at BroadReach Healthcare and a private consultant serving tech start-ups and philanthropic organizations, including the Bill & Melinda Gates Foundation.

Monique K. Mansoura, Ph.D., M.B.A., M.S., is the senior director of the Medical Countermeasures Franchise at Novartis Vaccines (NVx). She manages daily operations for the cross-functional Global Program Team. She leads policy and business development efforts to identify and pursue opportunities to develop the franchise through alignment of NVx capabilities with U.S. government policies and strategies to develop MCM abilities to support the national health security mission. NVx is recognized as a critical partner of the U.S. government's MCM enterprise, particularly for pandemic influenza preparedness and response, and also for broader MCM goals as one of three HHS Centers for Innovation in Advanced Development and Manufacturing. This was most recently demonstrated in the Novartis rapid response to the H7N9 outbreak and persistent pandemic threat. Novartis developed and demonstrated the protective value of a novel H7N9 vaccine and delivered a pre-pandemic stockpile with less than 9 months of initial notification of the outbreak, and drove the integration of novel synthetic seed technology in clinical development and commercial-scale manufacturing. From 2002 to 2010, she led MCM policy and strategy efforts for HHS, establishing the inaugural Public Health Emergency Medical Countermeasures Enterprise Strategy and Implementation Plan, which provided the framework for priority setting and a roadmap for the allocation of the $5.6 billion Special Reserve Fund provided under Project BioShield from FY04 to FY13. The requirements for chemical, biological, radiological, and nuclear MCMs established under her leadership have provided the foundation for the HHS product development pipeline at NIH and BARDA, and for the BioShield acquisition programs. She has worked at the NIH National Human Genome Research Institute as a policy analyst in support of the Human Genome Project and as a postdoctoral fellow conducting cystic fibrosis research. She earned a Ph.D. in bioengineering and an M.S. in human genetics from the University of Michigan and a B.S. in chemical engineering from Wayne State University. She earned an M.B.A. in the MIT Sloan Fellows Program in Innovation and Global Leadership, served as a consultant to the MIT Center for Biomedical Innovation, and supported program and planning efforts for the NIH Therapeutics for

Rare and Neglected Diseases program, now part of the National Center for Advancing Translational Science.

Michael T. Osterholm, Ph.D., M.P.H., is the McKnight Presidential Endowed Chair in Public Health at the University of Minnesota and director of the Center for Infectious Disease Research and Policy (CIDRAP). In addition, he is a professor in the Division of Environmental Health Sciences, School of Public Health; a professor in the Technological Leadership Institute, College of Science and Engineering; and an adjunct professor in the Medical School, University of Minnesota. He is also a member of the National Academy of Medicine and the Council of Foreign Relations. In 2005 Dr. Osterholm was appointed by the secretary of HHS to be on the newly established National Science Advisory Board on Biosecurity. In 2008, he was named to the University of Minnesota Academic Health Center's Academy of Excellence in Health Research. Later that year, he was appointed to the World Economic Forum Working Group on Pandemics. From 2001 through early 2005, Dr. Osterholm, in addition to his role at CIDRAP, served as a special adviser to then-HHS Secretary Tommy G. Thompson on issues related to bioterrorism and public health preparedness. He was also appointed to the Secretary's Advisory Council on Public Health Preparedness. In 2002, Dr. Osterholm was appointed by Thompson to be his representative on the interim management team to lead CDC. With the appointment of Dr. Julie Gerberding as director of CDC in 2002, Dr. Osterholm was asked by Thompson to assist Dr. Gerberding on his behalf during the transition period. Previously, Dr. Osterholm served for 24 years at the Minnesota Department of Health (MDH), the past 15 as state epidemiologist and chief of the Acute Disease Epidemiology Section. While at MDH, he and his team were leaders in the area of infectious disease epidemiology. He has led numerous investigations of outbreaks of international importance, including foodborne diseases, the association of tampons and toxic shock syndrome, the transmission of hepatitis B in health care settings, and HIV infection in health care workers. In addition, his team conducted many studies on infectious diseases in child-care settings, vaccine-preventable diseases (particularly *Haemophilus influenzae type b* and hepatitis B), Lyme disease, and other emerging infections. They were also among the first to call attention to the changing epidemiology of foodborne diseases. He was the principal investigator and director of NIH-supported Minnesota Center of Excellence for Influenza Research and Surveillance and chaired the

executive committee of the Centers of Excellence Influenza Research and Surveillance network. Dr. Osterholm has been an international leader on the critical concern regarding our preparedness for an influenza pandemic. His invited papers in the journals *Foreign Affairs*, the *New England Journal of Medicine*, and *Nature* detail the threat of an influenza pandemic before the recent pandemic and the steps we must take to better prepare for such events. Dr. Osterholm has also been an international leader on the growing concern regarding the use of biological agents as catastrophic weapons targeting civilian populations. In that role, he served as a personal adviser to the late King Hussein of Jordan. Dr. Osterholm provides a comprehensive and pointed review of America's current state of preparedness for a bioterrorism attack in his *New York Times* best-selling book, *Living Terrors: What America Needs to Know to Survive the Coming Bioterrorist Catastrophe*. The author of more than 315 papers and abstracts, including 21 book chapters, Dr. Osterholm is a frequently invited guest lecturer on the topic of epidemiology of infectious diseases. He serves on the editorial boards of nine journals, including *Infection Control and Hospital Epidemiology and Microbial Drug Resistance: Mechanisms, Epidemiology and Disease*, and he is a reviewer for 24 other journals. He is past president of the Council of State and Territorial Epidemiologists (CSTE) and has served on CDC's National Center for Infectious Diseases Board of Scientific Counselors. Dr. Osterholm has served on the Academies Forum on Microbial Threats, the IOM Committee on Emerging Microbial Threats to Health in the 21st Century, and the IOM Committee on Food Safety, Production to Consumption. He was a reviewer for the IOM's *Report on Chemical and Biological Terrorism: Research and Development to Improve Civilian Medical Response*. As a member of the American Society for Microbiology, Dr. Osterholm was on the Committee on Biomedical Research of the Public and Scientific Affairs Board, the Task Force on Biological Weapons, and the Task Force on Antibiotic Resistance. He is a frequent consultant to WHO, NIH, FDA, the Department of Defense, and CDC. He is a Fellow of the American College of Epidemiology and the Infectious Diseases Society of America (IDSA). Dr. Osterholm has received numerous honors for his work, including an honorary doctorate from Luther College; the Pump Handle Award, CSTE; the Charles C. Shepard Science Award, CDC; the Harvey W. Wiley Medal, FDA; the Squibb Award, IDSA; Distinguished University Teaching Professor, Environmental Health Sciences, School of Public Health, UMN; and the Wade Hampton Frost Leadership

Award, American Public Health Association. He also has been the recipient of six major research awards from NIH and CDC.

Tara O'Toole, M.D., M.P.H., is senior fellow and executive vice president at In-Q-Tel (IQT), a private, nonprofit strategic investment firm that links the U.S. Intelligence Community and venture-backed start-up firms on the leading edge of technological innovation. Dr. O'Toole is leading a strategic IQT initiative to explore opportunities and risks likely to arise in the next decade as a result of advances in the biological sciences and biotechnologies, with a particular focus on detection of and defense against biological attacks. From 2009 to 2013, Dr. O'Toole served as under secretary of Science and Technology (S&T) at the Department of Homeland Security, the principal adviser to the secretary on matters related to science and technology. Under Dr. O'Toole's leadership, S&T created the department's first division of cybersecurity research, a division devoted to delivering technologies to first responders, and a system engineering division. She won approval and funding from the Administration and Congress to begin construction of an urgently needed, long-delayed high containment laboratory for emergent and contagious animal diseases. In the decade before becoming under secretary, Dr. O'Toole founded and directed two university-based think tanks devoted to civilian biodefense. She was a professor of public health and director of the Johns Hopkins University Center for Civilian Biodefense Studies at the Johns Hopkins Bloomberg School of Public Health, which was the first academic center devoted to biosecurity policy and practices, and played a major role in defining the nature and consequences of major biological threats, both natural and deliberate. In 2003, Dr. O'Toole was CEO and director of the Center for Biosecurity of the University of Pittsburgh Medical Center and professor of medicine and public health at the University of Pittsburgh. From 1994 to 1998, Dr. O'Toole served in President Clinton's administration as assistant secretary for Environment Safety and Health in the Department of Energy. From 1989 to 1993, Dr. O'Toole was a senior analyst at the Congressional Office of Technology Assessment (OTA). Prior to OTA, she practiced internal medicine in community health centers in east Baltimore as part of the Public Health Service. Dr. O'Toole is a past chair of the board of the Federation of American Scientists, and is a member of the Council on Foreign Relations. She received her B.A. from Vassar College, her M.D. from the George Washington University School of Medicine, and her M.P.H. from the Johns Hopkins Bloomberg

School of Public Health. She is board certified in internal medicine and occupational and environmental medicine.

Gerald W. Parker, Jr., D.V.M., Ph.D, M.S., joined the Texas A&M Health Science Center in 2013 as vice president for public health preparedness and response, and as Principal Investigator for the Texas A&M Center for Innovation in Advanced Development and Manufacturing, a public–private partnership with the HHS designed to enhance the nation's emergency preparedness against emerging infectious diseases, including pandemic influenza, and chemical, biological, radiological, and nuclear threats. Earlier, Dr. Parker served as the Deputy Assistant Secretary of Defense for Chemical and Biological Defense and was responsible for Chemical and Biological Defense Program oversight throughout the Department of Defense and integration with interagency and international partners. He previously served as the Principal Deputy Assistant Secretary, Office of the Assistant Secretary for Preparedness and Response at HHS. In that role, Dr. Parker provided leadership in coordinating HHS-wide efforts with respect to preparedness for and response to public health and medical emergencies, and served as a focal point for operational and policy coordination with the White House, other federal departments, Congress, state and local officials, private-sector leaders, and international authorities responsible for emergency medical preparedness and the protection of the civilian population from acts of terrorism and other public health emergencies. Dr. Parker also served at the Department of Homeland Security from 2004 to 2005. He was awarded the Distinguished Executive Presidential Rank Award in 2009, and the Secretary of Defense Medal for Meritorious Civilian Service in 2013. Prior to his selection into the Senior Executive Service in 2004, Dr. Parker had 26 years of distinguished active U.S. Army service as a researcher, team leader, division director, program director, and laboratory Commander. During his military career, Dr. Parker held a variety of positions, including assistant deputy for research and development, director for the Medical Chemical and Biological Defense Research Program, and deputy director for the Combat Casualty Research Program at the U.S. Army Medical Research and Materiel Command. He is a former Commander and Deputy Commander of the U.S. Army Medical Research Institute of Infectious Diseases. Dr. Parker graduated from Texas A&M University with a B.S. in veterinary medicine and a Doctor of Veterinary Medicine the following year. He holds a doctorate in physiology from Baylor

College of Medicine in Houston and an M.S. in Resourcing the National Strategy from the Industrial College of the Armed Forces.

Andrew Pavia, M.D., FAAP, FIDSA, is the George and Esther Gross Presidential Professor and chief of the Division of Pediatric Infectious Diseases at the University of Utah and director of hospital epidemiology at Primary Children's Medical Center. His current research focuses on the epidemiology, diagnosis, and management of influenza and other respiratory and emerging infections. He is a member of the board of directors of the Infectious Diseases Society of America and chairs the Pandemic Influenza and Bio-emergencies Task Force. He is also a member of the Board of Scientific Counselors of the Director of the Office of Infectious Diseases at CDC and has served as a member of the National Biodefense Science Board and the National Vaccine Advisory Board. He has been an adviser to CDC on pandemic influenza- and anthrax-related issues. He has served on committees for the Institute of Medicine exploring the distribution of antivirals during influenza pandemics and the pre-positioning of countermeasures for anthrax. He received his B.A. and M.D. at Brown University. He trained as a resident and chief resident at Dartmouth Hitchcock Medical Center, as an Epidemic Intelligence Service officer and preventive medicine resident at CDC, and as an infectious disease fellow at the University of Utah.

John H. Rex, M.D., FACP, is a distinguished research scientist and recognized as an opinion leader in the field of infectious disease therapy, in particular, for antifungal agents. He is vice president and head of infection, Global Medicines Development, at AstraZeneca. Dr. Rex is a science-based leader with more than 25 years of preclinical and clinical drug development experience, including 15 years as an academic investigator (NIH; University of Texas Medical School–Houston; preclinical translation work; investigator across all clinical phases and multiple indications, including pharmacology studies; clinical trial design; overall clinical development plan design; biomarker development and integration; regulatory interactions in the United States and European Union). This was followed by direct industry experience since 2003 at AstraZeneca Pharmaceuticals as vice president, clinical infection (2003-2012) and then vice president and head of infection, Global Medicines Development (2012-present). His industry experience includes program building via business development (AstraZeneca now has a strong anti-infective pipeline built via three acquisitions and four

licensing deals), extensive regulatory interactions, and external influencing focused on changing the development and reimbursement environments for antimicrobial agents. Since 2012, Dr. Rex has been a non-executive director at F2G Ltd., a U.K.-based biotechnology company dedicated to the discovery and development of new and clinically superior drug classes to treat life-threatening, systemic fungal infections in at-risk patient populations. Dr. Rex has been the industry representative on the Food and Drug Administration Anti-Infective Drug Advisory Committee, is vice chair of the Consensus Committee on Microbiology for the Clinical Laboratory Standards Institute, is a highlights adviser for Nature Reviews Microbiology, is a member of the Wellcome Trust Seeding Drug Discovery Committee, serves on several editorial boards, and was formerly an editor for *Antimicrobial Agents and Chemotherapy*. He has a B.A. in biochemistry from Rice University and an M.D. from Baylor College of Medicine.

Robin Robinson, Ph.D., was appointed in 2008 as the first director of BARDA, and Deputy Assistant Secretary in the Office of the Assistant Secretary for Preparedness and Response within HHS. Dr. Robinson previously served as director for the Influenza & Emerging Disease Program within BARDA and its predecessor agency at HHS. Dr. Robinson was recruited by HHS from the vaccine industry in 2004 to establish a program with scientific and technical experts to implement the strategic plans and policies for MCMs outlined in the National Strategy for Pandemic Influenza. These measures included development, acquisition, and establishment of national MCM stockpiles, and expansion of domestic manufacturing surge capacities for influenza vaccines, antiviral drugs, rapid diagnostics, and nonpharmaceutical countermeasures, including respiratory devices. For his leadership in this role, Dr. Robinson was the recipient of the Department of Defense's Clay Dalrymple Award in 2008 and a finalist for the Service to America Medal in 2009. Dr. Robinson received a bachelor's degree in biology from Millsaps College, and a doctoral degree from the University of Mississippi Medical School in medical microbiology. He completed a National Institutes of Health postdoctoral fellowship with the State University of New York at Stony Brook in molecular oncology. As director of vaccines at Novavax, Inc., he developed patented platform vaccine technologies, including virus-like particles and subunit protein vaccines for human pathogens, including malaria, human papilloma virus, hepatitis, and influenza and for prostate, melanoma, and cervical

cancers. Dr. Robinson also serves on WHO international expert teams on pandemic influenza vaccines. Additionally, he continues to serve as an editorial board member and reviewer for several professional scientific and technical journals on virology, vaccines, public health, and biotechnology.

Robert J. Shapiro, Ph.D., M.A., M.Sc., is chair of Sonecon, LLC, a private firm that provides economic and security-related advice and analysis to senior officials of the U.S. and foreign governments and senior executives of U.S. and foreign businesses and nonprofit organizations. Dr. Shapiro has advised, among others, President Bill Clinton, Vice President Al Gore, Jr., British Prime Minister Tony Blair, Treasury Secretaries Timothy Geithner and Robert Rubin, British Foreign Secretary David Miliband, and many U.S. senators and representatives. He also has advised senior executives of many global companies, including AT&T, ExxonMobil, Amgen, Gilead Science, Google, Elliot Management, Liberty Mutual Insurance, and Fugitsu, as well as nonprofit organizations such as PhRMA and the Center for American Progress. Dr. Shapiro also is a senior fellow of the Georgetown University McDonough School of Business, an adviser to the International Monetary Fund, co-chair of American Task Force Argentina, and director of the Globalization Initiative at New Democrat Network. Before establishing Sonecon, he was the Under Secretary of Commerce for Economic Affairs; in that position, he directed economic policy at the Commerce Department and oversaw the planning and operations of the Census Bureau and the Bureau of Economic Analysis. Previously, he was co-founder and vice president of the Progressive Policy Institute, associate editor of *U.S. News & World Report*, and *Legislative Director and Economic Counsel* to former Sen. Daniel Patrick Moynihan (D-NY). Dr. Shapiro also was the principal economic adviser to Bill Clinton in his 1991-1992 campaign and an economic adviser in the campaigns of Barack Obama, John Kerry, and Al Gore. He has been a fellow of Harvard University, the Brookings Institution, and the National Bureau of Economic Research. He holds a Ph.D. and an M.A. from Harvard University, an M.Sc. from the London School of Economics and Political Science, and an A.B. from the University of Chicago.

David Swerdlow, M.D., is the associate director for science, National Center for Immunization and Respiratory Diseases (NCIRD), CDC, and

the lead of the NCIRD Office of Science and Integrated Programs and the NCIRD Infectious Disease Modeling Unit. He was the CDC Ebola Response, International Task Force lead in August and September 2014 and was incident manager (CDC lead) of CDC's Middle East respiratory syndrome coronavirus Response in 2013 and 2014. He has also held leadership roles during numerous other CDC emergency responses, including CDC's responses to cholera in Haiti, pandemic influenza A (H1N1), Hurricane Katrina, adverse events associated with smallpox vaccine, and the anthrax bioterrorism attacks. Before going to NCIRD, he spent more than a decade at CDC studying the epidemiology of foodborne diseases, and he has held leadership positions in the areas of viral and rickettsial zoonotic diseases and HIV/AIDS behavioral and clinical surveillance. His undergraduate education was at the University of California, San Diego, and he is a graduate of Harvard Medical School. Following medical school he completed an internal medicine residency at the University of Washington in Seattle, an Epidemic Intelligence Service Fellowship at CDC, a preventive medicine residency at the San Diego County Department of Health Services, and an infectious diseases fellowship at the Massachusetts General Hospital. He is Board certified in Internal Medicine and Infectious Diseases. He is a clinical assistant professor of medicine, Emory University School of Medicine, and has worked in the Infectious Diseases Clinic at the Atlanta VA Medical Center since 1993. He is an adjunct assistant professor at Rollins School of Public Health, Emory University, where he has been the lead instructor of two epidemiology courses since 2000, and he is on the faculty council. He is on the HHS Executive Enterprises Committee, the HHS Public Health Emergency Medical Countermeasures Enterprise Emerging Infectious Disease Working Group, and the Program Committee of the Infectious Diseases Society of America. He is co-chair of the Pandemic Prediction and Forecasting Science and Technology Working Group, which is sponsored by the White House Office of Science and Technology Policy, National Science and Technology Council, and he is an academic editor at *PLoS ONE*. He has co-authored more than 200 peer-reviewed publications, book chapters, and government publications.

Jeffrey Ulmer, Ph.D., is global head of external research at GSK Vaccines, where he is responsible for identification and assessment of new opportunities for collaborative research. At Merck Research Laboratories and Chiron Corporation, he conducted seminal studies on

DNA vaccines, and novel vaccine adjuvants and delivery systems. He has published ~200 scientific articles, and is on the editorial boards of *Expert Opinion on Biological Therapy*, *Human Vaccines*, and *Expert Review of Vaccines*. He received his B.Sc. with honors from the Department of Chemistry at the University of Regina and was the recipient of the Merit Award of the Society of Chemical Industry of Canada. He received his Ph.D. in biochemistry from McGill University and completed his postdoctoral training in the laboratory of Nobel laureate Dr. George Palade in the Department of Cell Biology at Yale University School of Medicine.

David W. Vaughn, M.D., M.P.H., joined GSK Vaccines in 2007 serving as director and Clinical Lead for Pandemic Influenza Vaccines, then vice president and head of Global Vaccines Clinical Laboratories, and is now head of External R&D, North America. This followed a 21-year career with the U.S. Army where he served as the chief of the Department of Virology at the Armed Forces Research of Medical Sciences in Bangkok, Thailand, and then the chief of the Department of Virus Diseases, Walter Reed Army Institute of Research. His final position in the military was as the director of the U.S. Military Infectious Diseases Research Program.

Rajeev Venkayya, M.D., is president of the Global Vaccine Business Unit of Takeda Vaccines. He is responsible for Takeda's global vaccine business, including a long-standing business in Japan and a global development pipeline that includes vaccine candidates for norovirus and dengue fever, gained through the acquisitions of LigoCyte Pharmaceuticals and Inviragen Inc. Dr. Venkayya was previously the director of vaccine delivery at the Bill & Melinda Gates Foundation, where he was responsible for the Foundation's top two priorities, polio eradication and new vaccine introduction. This included the Foundation's engagement and investments in the Global Polio Eradication Initiative and GAVI, and an investment portfolio of approximately $500 million/year. He also served as a member of the GAVI Board. Previously, Dr. Venkayya was special assistant to the president and senior director for biodefense at the White House, where he directed the development of policies to prevent, protect, and respond to bioterrorism and naturally occurring biological threats. He led the development and implementation of the National Strategy for Pandemic Influenza, as well as presidential directives on medical countermeasures

and public health preparedness. He was 1 of 13 individuals appointed by President Bush to the nonpartisan White House Fellowship program. Dr. Venkayya was previously an assistant professor of medicine in the Division of Pulmonary and Critical Care Medicine at UCSF. He was co-director of the Medical Intensive Care Unit and director of the High-Risk Asthma Clinic at San Francisco General Hospital, and the principal investigator for a 5-year research grant from the NIH to study the immunologic mechanisms leading to asthma. Dr. Venkayya completed his fellowship training in pulmonary and critical care medicine at UCSF. Earlier, he was a resident and chief medical resident in internal medicine at the University of Michigan Medical Center. He completed his undergraduate and medical school education in the 6-year B.S./M.D. program at the Northeastern Ohio Universities College of Medicine, where he was inducted into the Alpha Omega Alpha honorary medical society. He is a life member of the Council on Foreign Relations.

Andrew C. Weber, M.S., is the deputy coordinator for Ebola response at the Department of State. In this role, Mr. Weber helps to lead diplomatic outreach to ensure a speedy, effective, and truly global response to this crisis. President Obama has declared the Ebola outbreak a national security priority. Mr. Weber has collaborated with partners from across the U.S. government and around the world to bring this epidemic under control. Mr. Weber served until October 2014 as Assistant Secretary of Defense for Nuclear, Chemical, and Biological Defense Programs, focusing on preventing, protecting against, and responding to weapons of mass destruction and terrorism threats. He supported international efforts to eliminate Syrian and Libyan chemical weapons and to strengthen global health security. Prior to his appointment by Obama in 2009, he spent 13 years as an adviser for threat reduction policy in the Office of the Secretary of Defense. He played a key role in the Nunn-Lugar Cooperative Threat Reduction program. He served previously as a U.S. Foreign Service Officer, with diplomatic assignments in Saudi Arabia, Germany, Kazakhstan, and Hong Kong. Mr. Weber also taught a course on Force and Diplomacy at the Edmund A. Walsh Graduate School of Foreign Service at Georgetown University. He has an M.S. in foreign service from Georgetown and is a graduate of Cornell University. Mr. Weber speaks Russian and is a member of the Council on Foreign Relations.

Michael Wong, M.D., is senior medical director of infectious diseases at Sarepta Therapeutics. He hold a dual appointment as associate professor of medicine at Harvard Medical School. His primary responsibilities include oversight of the discovery and development of the proprietary formulation of phosphorodiamidate morpholino oligomers as effective antiviral and antibacterial agents, and of the strategic alliances for the development of those products. Current applications of the antisense oligomers include medical countermeasures for filovirus infections, including Ebola and Marburg viruses and pandemic influenza A, and agents effective against a variety of multidrug-resistant bacteria. Previously, he served as director, transplant infectious diseases. at the Beth Israel Deaconess Medical Center, and he remains active in clinical research on organ transplantation in the HIV+ recipient population. He is also a member of the Massachusetts Public Health Council, which is responsible for reviewing and approving regulations on public health policy for the Commonwealth of Massachusetts. This includes policies in response to endemic zoonoses such as West Nile Virus (WNV) and Eastern Equine Encephalitis (EEE), as well as to potential or real epidemics such as the Ebola threat and pandemic H1N1. Dr. Wong completed his undergraduate education at the University of California, Irvine, and obtained his M.D. at the University of Vermont College of Medicine. He completed an internal medicine residency at the Deaconess Hospital, and a fellowship in infectious diseases at Wilford Hall U.S. Air Force Medical Center. He has held staff positions at Wilford Hall, where he also served as the section chief for applied retroviral research, and the Virginia Commonwealth University/Medical College of Virginia, where he was associate hospital epidemiologist and director of HIV services.