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Exploring Lessons Learned from a Century of Outbreaks

READINESS FOR 2030

PROCEEDINGS OF A WORKSHOP

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Forum on Microbial Threats

Board on Global Health

Health and Medicine Division

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This Proceedings of a Workshop was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published proceedings as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the charge. The review comments and draft manuscript remain confidential to protect the integrity of the process.

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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the content of the proceedings nor did they see the final draft before its release. The review of this proceedings was overseen by **DAVID R. CHALLONER,** University of Florida. He was responsible for making certain that an independent examination of this proceedings was carried out in accordance with standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the rapporteurs and the National Academies.

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BOXES

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Acronyms and Abbreviations

AAAS	American Association for the Advancement of Science
APHA	American Public Health Association
ASPR	Assistant Secretary for Preparedness and Response
BARDA	Biomedical Advanced Research and Development Authority
CBER	Center for Biologics Evaluation and Research
CDC	U.S. Centers for Disease Control and Prevention
CEPI	Coalition for Epidemic Preparedness Innovations
CoV	coronavirus
CVV	candidate vaccine virus
FAO	Food and Agriculture Organization of the United Nations
FBI	Federal Bureau of Investigation
FEMA	U.S. Federal Emergency Management Agency
GDP	gross domestic product
GHSA	Global Health Security Agenda
GISN	Global Influenza Surveillance Network
GISRS	Global Influenza Surveillance and Response System
GLASS	Global Antimicrobial Surveillance System
GOARN	Global Outbreak Alert and Response Network
GPMB	Global Pandemic Monitoring Board

HA	hemagglutinin
HHS	U.S. Department of Health and Human Services
IHR	International Health Regulations
IPAPI	International Partnership for Avian and Pandemic Influenza
IRAT	Influenza Risk Assessment Tool
IVPP	influenza viruses with pandemic potential
JEE	Joint External Evaluation
MERS	Middle East respiratory syndrome
NA	neuraminidase
NIAID	National Institute of Allergy and Infectious Diseases
NPI	nonpharmaceutical intervention
NVPO	National Vaccine Reporting Office
OIE	World Organisation for Animal Health
PAHO	Pan American Health Organization
PIP	Pandemic Influenza Preparedness
SARS	severe acute respiratory syndrome
SDG	Sustainable Development Goal
UN	United Nations
USDA	U.S. Department of Agriculture
WHO	World Health Organization

1

Introduction

In 1918, an influenza pandemic of unparalleled scope and severity swept across the globe. By the time it subsided, the pandemic had infected around 500 million people, roughly one-third of the world's population at the time, and resulted in at least 50 million deaths worldwide (Barry, 2005). One century later, outbreaks and pandemics of influenza and other infectious diseases have caused widespread human suffering and deaths, and continue to pose major threats to public health, health security, and societal and economic stability at the local, national, and global levels. The past several decades alone have seen more than 30 large-scale recurring and emerging infectious disease threats that have caused events ranging from fairly localized outbreaks to pandemics (Mukherjee, 2017). This trend is expected to rise, as the result of many factors such as increased human–animal contact, climate change, land use changes, global population growth, and increased global interconnectedness (Jones et al., 2008).

Advancements in science and technology related to diagnostic capacities, vaccines, and antivirals have provided more effective tools for preventing and responding to infectious disease threats. Given the host of challenges associated with the timely development and deployment of strain-specific influenza vaccines, international efforts for developing a universal influenza vaccine have generated some optimism. The movement toward a One Health approach to pandemic preparedness, which encompasses human, animal, plant, and environmental sectors, is also promising, as many infectious disease threats of significance originate among animals and cross-over

to humans (Morse et al., 2012). While many advances have been made, critical challenges remain in developing, evaluating, and deploying medical countermeasures and other interventions to adequately counter major outbreaks (GHRF Commission, 2016).

On the international front, global health experts have established global governance frameworks, financing mechanisms, and legal instruments to support the global community to respond to infectious disease outbreaks and epidemics. However, the failures in response to the 2014 Ebola outbreak in West Africa suggest that current global governance structures and operational synergies within and among various countries, institutions, and international bodies may be unable to respond adequately to catastrophic infectious disease crises (GHRF Commission, 2016). Progress has also been made in strengthening preparedness from local to national levels, but health systems in many countries and communities still lack day-to-day health delivery functions and have little capacity to surge during an infectious disease outbreak or pandemic.

No other pandemics in the past century have approached the magnitude of the 1918 influenza pandemic. If a pandemic of comparable scale and impact to the 1918 pandemic were to occur today, modeling estimates suggest that the impact could be similarly devastating—killing between 50 and 80 million people worldwide, with expected annual global losses from pandemic risk of around $500 billion per year (Murray et al., 2006; Fan et al., 2018). However, there are opportunities to mitigate these grim scenarios. Collective action at local, national, and global levels could strengthen preparedness for infectious disease outbreaks and pandemics by leveraging and intensifying the scientific and political momentum that has gathered over recent decades.

WORKSHOP OBJECTIVES

In November 2018, an ad hoc planning committee under the auspices of the Forum on Microbial Threats at the National Academies of Sciences, Engineering, and Medicine planned two sister workshops held in Washington, DC, to examine the lessons from influenza pandemics and other major outbreaks, understand the extent to which the lessons have been learned, and discuss how they could be applied further to ensure that countries are sufficiently ready for future pandemics.[1] The first was a public, half-day

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

pre-workshop event held on November 26, 2018, titled A Century After the 1918 Influenza Pandemic—Why Are We Still Concerned Today? This event was co-hosted with the National Academy of Medicine to mark the 100th anniversary of the 1918 influenza pandemic. It provided a platform to highlight the benefits and progress of driving science, public health, global governance, and cross-sectoral alliances for pandemic influenza preparedness. The event opened with a keynote address and featured a session of presentations, followed by a panel discussion with the general audience.

Building on the pre-workshop event, the Forum on Microbial Threats then held a 1.5-day public workshop on November 27 and November 28, 2018, titled Readiness for Microbial Threats 2030: Exploring Lessons Learned Since the 1918 Influenza Pandemic. Keiji Fukuda, director and clinical professor, School of Public Health, The University of Hong Kong, chaired this workshop. The participants in this workshop examined the lessons from major outbreaks and explored the extent to which they have both been learned and applied in different settings. The workshop also focused on key gaps in pandemic preparedness and explored immediate and short-term actions that exhibited potential for the greatest impact on global health security by 2030. Workshop speakers and discussants contributed perspectives from government, academic, private, and nonprofit sectors. This workshop opened with a keynote address and a plenary presentation, followed by three sessions of presentations and discussions. Additionally, panelists, forum members, and attendees were given the opportunity to assemble into small groups and asked to consider potential priority actions and strategies for systematizing and integrating outbreak and pandemic preparedness so that it is a routine activity from the local to global levels.

Specifically, participants discussed the following topics during the 1.5-day workshop[2]:

- Recent progress achieved in monitoring global health security and pandemic preparedness at national and global levels, including advances in developing national action plans that stem from the Joint External Evaluation, building strong public health capacities that incorporate a One Health approach, and developing risk analysis and assessment tools to guide resource allocation;
- Critical challenges and opportunities in developing and evaluating medical countermeasures, including seasonal vaccines, a universal influenza vaccine, and novel diagnostics and therapeutics, as well as strategies to secure their adequate supply and distribution;

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

- Various methods and tools, such as effective surveillance systems and sequencing technologies, to shorten the time between onset and detection, lab confirmation, and public communication of major disease outbreaks;
- Strategies to protect supply chains and build surge capacity for essential services and infrastructure, such as emergency operations centers; and
- Effective mechanisms for stimulating meaningful coordination and communication among various stakeholders, including multilateral organizations, national governments, private sectors, and civil societies.

Finally, to provide a contextual foundation to support the workshop discussions, the Forum on Microbial Threats commissioned a paper that reviews the literature on the observations and lessons that were made previously after major outbreaks in the past century and provides reflections on what needs to be accomplished to make progress in epidemic and pandemic preparedness moving forward (see Appendix A). This paper was distributed to the public audience during the workshop.

ORGANIZATION OF THE PROCEEDINGS OF THE WORKSHOP

In accordance with the policies of the National Academies, the workshop did not attempt to establish any conclusions or recommendations about needs and future directions, focusing instead on information presented, questions raised, and improvements suggested by individual workshop participants. Chapters 2 and 3 are dedicated to the half-day pre-workshop event. Chapter 2 includes highlights from the pre-workshop welcome remarks and the keynote presentation, in which the speaker provided a historical overview of the 1918 influenza pandemic and considered whether the world is ready to respond to the next influenza pandemic. Chapter 3 provides an overview of the pre-workshop panel discussion, in which participants addressed progress in global efforts to prepare for the next influenza pandemic across the realms of virus biology, universal influenza vaccine development, global governance structures, and the One Health approach.

The chapters thereafter focus on presentations and discussions from the 1.5-day workshop. Chapter 4 features the workshop's keynote presentation, which described the impact of outbreaks and pandemics on people, communities, and economies. The chapter also outlines a plenary presentation, which provided an overview of evolving and recurring challenges over a century of pandemics and emerging infectious diseases.

Chapters 5 through 7 cover lessons learned from major outbreaks and the lessons that still need to be applied from the local to global levels. Specifically, Chapter 5 highlights local- and national-level experiences with pandemic preparedness and examines whether adequate national capacities are in place. Chapter 6 offers private-sector and institutional perspectives on lessons learned in vaccine preparedness and examines the spectrum of challenges in vaccine development, manufacturing, and deployment during the 2009 H1N1 pandemic. Chapter 7 explores global perspectives on and lessons learned about equity and fairness related to preparedness, with a focus on the discussions of virus and benefit sharing that arose out of the 2006 H5N1 outbreak and led to the development of the Pandemic Influenza Preparedness Framework.

Finally, the two remaining chapters highlight potential actions for overcoming impediments and achieving greater outbreak and pandemic preparedness moving forward. Chapter 8 summarizes a workshop session that focused on ending the cycle of panic and neglect that often occurs in pandemic preparedness, developing a business case for sustained political and financial support, and systematizing outbreak and pandemic preparedness at local, national, and global levels. Chapter 9 features global health experts' visionary statements on potential immediate and short-term actions in outbreak preparedness that may have the greatest impact on global health security by 2030, and participants' reflections on some top priorities and actions raised throughout the workshop.

2

Is the World Ready to Respond to the Next Influenza Pandemic?

The half-day pre-workshop event opened with welcome remarks from Victor Dzau, president of the National Academy of Medicine (NAM), who provided an overview of the progress, challenges, and opportunities for preparing and responding to the next influenza pandemic. Following his remarks, Laurie Garrett, science journalist and founder of the Anthropos Initiative, delivered a keynote presentation, setting the stage with an overview of historical influenza pandemics. In particular, Garrett explored the 1918 influenza pandemic and the 2009 H1N1 pandemic from both cultural and epidemiological perspectives and examined the potential impact of a severe influenza pandemic under today's conditions.

OPENING REMARKS

In his opening remarks, Victor Dzau, president of the NAM, stated that 2018 marks the 100th anniversary of one of the deadliest disease outbreaks in human history: the 1918 influenza pandemic. Since then, scientific and medical advances in antibiotics, diagnostics, vaccines, and other areas have enabled the international community to better prepare for infectious disease outbreaks. However, outbreaks have continued to cause devastating outcomes over the years, and emerging infectious disease events are increasing significantly over time (Jones et al., 2008). According to Dzau, "The world is ill-prepared for another influenza pandemic."

Dzau pointed out that the 2014–2016 Ebola outbreak in West Africa was a wakeup call with failures at all response levels: local, national, regional, and international (GHRF Commission, 2016). Ultimately, the

epidemic was contained, but the costs in human lives and in economic and social disruption were significant with more than 11,000 deaths. Most recently, the Ebola outbreak in the Democratic Republic of the Congo has resulted in more than 500 deaths so far.[1] The ongoing conflict in the region has complicated this outbreak and has caused tremendous concern within the international community, he said. Although Ebola kills thousands of people and leads to devastating consequences, the health outcomes could be even worse if Ebola were airborne. With the potential for influenza to be transmitted by aerosols, Dzau underscored that the stakes are high and global health experts need to step up their efforts to prepare for the next influenza pandemic.

Dzau then discussed recent progress made that aims to strengthen pandemic preparedness. Since the Ebola outbreak in West Africa, the NAM, the Harvard Global Health Institute, the London School of Hygiene & Tropical Medicine, and the United Nations (UN) High-Level Panel on the Global Response to Health Crises have generated assessment reports to chronicle what went wrong during this outbreak and how infectious disease outbreaks can be managed better in the future (Moon et al., 2015; GHRF Commission, 2016; UN, 2016). These reports generated many common recommendations, and in fact, concrete changes have been made. In particular, the following programs and alliances have been created: the World Health Organization's (WHO's) Contingency Fund for Emergencies[2] and Joint External Evaluation,[3] the World Bank's Pandemic Emergency Financing Facility,[4] and the Coalition for Epidemic Preparedness Innovations.[5]

Furthermore, in response to the United Nations High-Level Panel's recommendations to create a better monitoring system for disease outbreaks,

[1] For the latest numbers, please see https://www.who.int/ebola/situation-reports/drc-2018/en (accessed March 25, 2019).

[2] The Contingency Fund for Emergencies is a voluntary fund that allows WHO to disburse as much as $500,000 within 24 hours, filling the gap from when the need for emergency response is identified to the point when other financing mechanisms can activate. See http://www.who.int/emergencies/funding/contingency-fund/en (accessed February 26, 2019).

[3] The Joint External Evaluation is a voluntary process to assess country capacities to prevent, detect, and respond to public health risks. The goal is to identify critical gaps in national health systems and prioritize actions toward better preparedness and response. See http://www.who.int/ihr/procedures/joint-external-evaluations/en (accessed February 26, 2019).

[4] The Pandemic Emergency Financing Facility is another quick-disbursing financing mechanism that provides surge funds after a major infectious disease outbreak. It also offers the first insurance opportunity for pandemic risk, covering all low-income countries eligible for financing under the International Development Association. See http://www.worldbank.org/en/topic/pandemics/brief/pandemic-emergency-financing-facility (accessed February 26, 2019).

[5] The Coalition for Epidemic Preparedness coordinates financing and research among public, private, philanthropic, and civil society organizations to prioritize development of vaccines against diseases with epidemic potential, and to enable equitable access to the resulting vaccines. See http://www.cepi.net (accessed February 26, 2019).

an independent board titled the Global Preparedness Monitoring Board (GPMB) was recently established for an initial 5 years. WHO's Director-General and the president of the World Bank in 2018 co-led the creation of GPMB, which comprises 13 international members, including Dzau, at that time. He explained that the function of the board is to offer high-level monitoring and develop a framework for global health crisis preparedness; identify and then strategically prioritize gaps in preparedness; and advocate preparedness at the highest political forums (e.g., G7 and G20 summits). He noted that the framework would be organized around four domains: strengthening public health capacities, monitoring progress of research and development, monitoring public and private preparedness financing, and generating risk analyses that include economic and social vulnerabilities. Dzau said that to accomplish some of these goals, GPMB will recruit a secretariat and will commission and publish annual reports on the status of global preparedness for outbreak crises.

According to Dzau, continued progress in science and research, public health, and governance is critical for ensuring pandemic preparedness. He concluded, "Improving pandemic preparedness will require sustained attention to collective action across many sectors. This is why I am so pleased to see all of you come together for this workshop."

HISTORICAL INFLUENZA PANDEMICS

Laurie Garrett, science journalist and founder of the Anthropos Initiative, explained that the historical record of influenza pandemics stretches back to the 1100s. Table 2-1 provides an overview of influenza pandemics known to have occurred from the 12th century through the 19th century. She noted that historical pandemics are often described as originating in Russia, but more likely, initial pandemics originated in China, spread across Siberia, entered Russia, and then moved into Europe. These pandemics probably spread from Europe to colonial outposts in the Americas, Africa, and Asia via trade routes, slavery, and general colonial mechanisms. Several pandemics in the 18th and 19th centuries had high mortality rates and the morbidity of the "Great Pandemic" in 1833 was as high as 80 percent (Patterson, 1986). Notably, the influenza pandemic of 1889, spread by Transatlantic shipping between the Americas and Africa, affected the entire world and had a high death toll for people between 21 and 40 years of age. Similar to subsequent influenza pandemics of the 20th century, peak mortality in several of these historical pandemics occurred among young adult populations (Patterson, 1986).

TABLE 2-1 Historical Influenza Pandemics, 1173–1889

Year	Description and Context
1173	Europe
1387	Europe
1510	Unknown
1557	Unknown
1580	Spread from the Mediterranean to the Baltics in 4 months
1708	Started in Rome at Christmas and swept north
1729	Started in Moscow; swept west and reached North America in 1732
1732	Started in Russia and spread west through Poland[a]
1761	Spread from Poland at the end of the 7 Years War
1781	Spread from China to Russia to Europe[b]
1789	Spread out of Russia through Europe to North and South Americas
1799	Spread from Russia across Europe during the Napoleonic War
1830	Spread from China, India, and Southeast Asia to Russia, Europe, and the Americas
1830–1831	Southeast Asia and Indonesia
1833	Spread out of Russia[c]
1847	Spread west out of Moscow and Constantinople[d]
1889	Spread from China to London[e]

[a] High rate of mortality in the United Kingdom; the outbreak in horses preceded the outbreak in humans.
[b] Highest mortality among young adults.
[c] Also known as the "Great Pandemic"; morbidity as high as 80 percent.
[d] Railroad links were completed across much of Europe by 1847.
[e] Spread by Transatlantic shipping to the Americas and to Africa multiple times; high mortality among adults 21 to 40 years of age.
SOURCES: Garrett presentation, November 26, 2018; Patterson, 1986.

AN IN-DEPTH EXAMINATION OF THE 1918 INFLUENZA PANDEMIC

According to Garrett, the 1918 influenza pandemic was exceptionally virulent because it behaved fundamentally differently from previous outbreaks in its ability to cause disease. The symptoms of the disease in many cases were very severe, including hemorrhage with profound bleeding, blood-laced vomit, high fever, delirium and hallucinations, miscarriage, heliotrope cyanosis, and acute respiratory distress. Garrett explained how the 1918 pandemic spread across the globe in 9 months through three waves: a mild first wave (May–August 1918), a severe second wave

(September–November 1918), and a moderate third wave (December 1918 to mid-1919). Although popularly dubbed "Spanish Influenza" (derived from the country's neutrality during World War I), the pandemic was unrelated to Spain; it actually came out of U.S. military camps in Haskell County, Kansas, and spread through troop movements (Barry, 2005).

Historical and Cultural Context

Garrett then provided historical and cultural context leading to the turning point of the 1918 influenza pandemic (Crosby, 2003; Barry, 2005). She described her uncle's experience as a young boy during the pandemic, noting that the generation who experienced that pandemic is now gone; only their recorded oral histories remain. World War I began in July 1914 and was well under way when the pandemic occurred. Despite the surge in influenza in 1918, the war continued. An estimated 9 million combatants and 7 million civilians died during the war, but it is unclear how many of those deaths may have been caused by the three waves of the influenza pandemic that spread worldwide between April 1918 and February 1919 (Chorba, 2018). The lowest estimate for influenza mortality during the pandemic is 21 million deaths, which represents millions of casualties more than the war claimed (Jordan, 1927; Mougel, 2011).

According to Garrett, warfare tactics likely contributed to influenza transmission. The first widespread use of gas warfare occurred during World War I, and thousands—if not millions—of civilians and soldiers were exposed to mustard gas and chlorine, which left many with permanent damage to their lungs, their eyes, and their general health. The effects of exposure likely contributed to people's susceptibility to respiratory infections such as influenza. In addition, soldiers spent long periods in close contact in below-ground trenches to protect themselves from bombs, and this also may have contributed to increased influenza transmission. She explained that efforts to address the influenza pandemic in the United States were hampered by major deficits in the domestic health workforce during World War I; at the time of the initial outbreak, thousands of physicians were working on foreign battlefields and thousands of nurses had been recruited to serve on battlefields and in rehabilitation centers abroad (Crosby, 2003).

When influenza first emerged in the United States, the framework for public discourse about the pandemic was limited by congressional legislation that sought to suppress government criticism, said Garrett. The Espionage Act of 1917 prohibited many forms of speech, including "disloyal, profane, scurrilous, or abusive language about the form of government of the United States."[6] The Sedition Act, passed in May 1918, amended the

[6] Espionage Act of 1917, Public Law 65-24, 99th Cong. (June 15, 1917).

Espionage Act and prohibited any form of speech or expressed opinion that cast the government or the war effort in a negative light or interfered with the sale of government bonds.[7] She added that any attempts to criticize the government's response to influenza—either among U.S. military personnel abroad or on the domestic front—were considered violations of the Sedition Act. Part of the reason the written history record of the pandemic is sparse, she noted, is because it was illegal to be critical of the influenza response in writing. In fact, media at the time published articles that misrepresented the severity of the pandemic to the public, stating that it was just a typical seasonal influenza outbreak (Bristow, 2010). Ultimately, however, the public in the United States and worldwide came to understand the severity of the pandemic.

Response to 1918 Influenza Pandemic

Garrett explained that because scientific knowledge about virology had just begun to burgeon in 1918, health professionals lacked clarity about what actually constituted the pandemic disease. At the time, the main theory proposed by the U.S. scientific establishment was that the pandemic was caused by *Bacillus influenza*, a bacterial disease. Conjecture and speculation were rampant about the nature and cause of the disease, as well as how people could protect themselves from it.[8] A common presumption was that improved personal hygiene and public space cleanliness would somehow quash the pandemic; people also thought that face masks would provide protection against influenza, but no one understood what type of mask should be used, how it should be used, or how much protection a mask would offer. Nonetheless, many governments implored their populations to wear masks in public spaces, and in one case, a man in San Francisco was shot by law enforcement officers for refusing to wear a mask in public (University of Michigan Center for the History of Medicine, 2016). Because of confusion and misinformation about the disease, responses to the pandemic by state and local governments were disorganized and inconsistent. For example, some cities decided to close schools and cancel public events while others did not.

As the epidemic worsened around the world, quarantines were imposed and public and outdoor activities were restricted. Instances of undue optimism about the pandemic's end were deflated by subsequent resurgences. Because

[7] The Sedition Act was repealed in December 1920; the Espionage Act has been amended many times but still exists under Title 18 of the U.S. Constitution.

[8] Garrett said that nakedness, fish contaminated by Germans, dirt or dust, unclean pajamas, open windows, closed windows, old books, and "cosmic influence" were all popularly posed as causes of influenza.

most of the country's medical establishment was overseas at the time, the U.S. government heavily incentivized people who remained to volunteer to help the response. However, people were largely unwilling to volunteer because of their fears and concerns about becoming infected. Since hospitals and clinics in the United States were filled to capacity, giant warehouses were created worldwide and filled with patients. Garrett described these warehouses as crowded, makeshift wards, and she detailed how volunteers and trained personnel cared for patients and were also responsible for removing dead bodies for burial. She also noted that such warehouses may have contributed to influenza transmission among the uninfected people who entered. At the time, shortages in coffins and grave spaces were rampant across the United States, leading to mass burials and unmarked graves. Law enforcement officers became more aggressive in enforcing closures and prosecuting hygiene offenses such as spitting, coughing, or sneezing in public (Aimone, 2010). Churches and schools were often closed down or converted into orphanages or warehouses for people who were sick. Garrett suggested that Armistice celebrations for the end of World War I contributed to the third wave of the pandemic, because so many people were celebrating in congregate settings without masks (Byerly, 2010).

Mortality of 1918 Influenza Pandemic

The pandemic influenza strain had a distinct presentation in patients as early as July 1918; an excerpt from a coroner's report in London noted, "The lung lesion, complex or variable, struck one as being quite different in character to anything one had met with at all commonly in the thousands of autopsies one has performed during the last 20 years. It was not the common broncho-pneumonia of ordinary years" (Barry, 2005). Garrett provided statistics to illustrate the pandemic's devastating mortality. During the autumn of 1918, more than 20,000 people died of influenza in New York City in only 6 weeks, and during the same period, influenza killed 5 percent of Ghana's population and 19 percent of Western Samoa's population (Garrett, 2005; McLeod et al., 2008). Records from Kentucky indicate that 37 percent of all deaths in 1918 were classified as "respiratory." The United States saw a huge increase in premature mortality among children under 1 year of age (Garrett, 1994).

Garrett explained that the 1918 event was a turning point in the recorded history of influenza pandemics. For the first time, an entirely bird-adapted virus had transformed into a human-to-human transmitting virus—without going through an intermediary species. The pandemic's high mortality was bolstered as the virus spread via networks of expanding railroad and shipping lines across the world. Given the paucity of available records, 1918 death estimates range from 20 to 22 million, which

represented 1 percent of humanity at the time, to 100 million or more, representing about 5 percent of humanity (Jordan, 1927; Johnson and Mueller, 2002). To put this into perspective, Garrett explained that if a pandemic killed between 1 and 5 percent of humanity today, the number of deaths would likely range between 72 and 340 million. However, pandemic mortality rates varied widely across the world. For instance, all-cause mortality between 1918 and 1920 reached 40 percent in parts of Iran and was very high among some rural and indigenous communities in the United States (Brady et al., 2014; Hatami, 2016).

Garrett's own analysis of mortality records suggests that in the United States, more than 1 million people died from any cause in 1917 and almost 1.5 million died in 1918. Death rates during the period increased across every U.S. state, and the number of deaths attributed to influenza and to "respiratory" causes skyrocketed nationwide between 1917 and 1918; according to Garrett, many deaths attributed to respiratory causes were likely caused by influenza.[9] Overall, the generally cited estimate for influenza mortality in the United States is about 675,000 deaths, but she said that this is almost certainly an underestimate. The 1918 pandemic has the well-known "W effect" in the epidemiologic curve of median excess mortality by age. Excess mortality for seasonal influenza is typically U-shaped, affecting the very young and very old. For pandemic influenza, however, excess mortality tends to be greatest among young adults, which added a middle peak to the usual U-shape (see Chapter 4 for further discussions on the "W effect"). Garrett noted that the pandemic also affected life expectancy rates in the United States and Europe; however, the paucity of available accurate information makes it difficult to quantify that impact.

Garrett outlined a set of lessons from the 1918 outbreak:

1. The 1918 H1N1 influenza virus developed from an avian influenza virus and spread worldwide;
2. H1N1 can cause human outbreaks if the virus jumps from birds to people in a form that can spread through human-to-human transmission;
3. All influenza A viruses in circulation among humans today are descendants of the 1918 H1N1 strain; and
4. All deaths related to influenza A viruses over the past century are at least partially attributable to the 1918 virus.

[9] Garrett said that among reported deaths in the United States, there were about 13,000 reported cases of influenza and about 124,000 deaths due to "respiratory" causes in 1917. In 1918, there were about 234,000 reported deaths due to influenza and about 245,000 deaths attributed to "respiratory" causes.

2009 H1N1 INFLUENZA PANDEMIC

Garrett shifted focus to the 2009 H1N1 pandemic and explored how the global response to pandemics has evolved since 1918. She explained that in 2009, the H1N1 influenza virus emerged in humans and was transmitted through swine. The first recorded human case was a young boy in Veracruz, Mexico, who survived and is sometimes called "Patient Zero" for the 2009 pandemic. However, she conjectured this pandemic probably originated in the Midwestern United States pork industry through isolated cases of pig-to-human transmission of the H1N1 strain when children were exposed directly to pigs at county fairs. In September 2008, for example, the Texas Department of Health Services reported that an individual had contracted a swine influenza A H1N1 triple reassortant virus from pigs, which appeared to be the same strain that passed from pigs to a teenage boy in Wisconsin in 2005 (Newman et al., 2008). In March 2009, health officials in Mexico noticed a spike in the number of reported influenza cases, and in the United States, two children in California contracted confirmed cases of H1N1 influenza (CDC, 2009). In April 2009, the virus infected several young people who returned to New York City from spring break vacation in Cancun, Mexico (CDC, 2009).

Response to the 2009 Influenza Pandemic

According to Garrett, the president of Mexico responded swiftly and contained the spread of the virus at the end of April 2009, announcing that many public services, government offices, private business, schools, churches, and mass transit modalities would be ordered to close. The military was deployed to distribute and enforce the use of face masks in public spaces and gatherings (Chowell et al., 2011). The Mexican government's level of transparency and its willingness to draw international attention to the outbreak was laudable, said Garrett. However, the government's response also gave a false impression that the virus was exclusively Mexico's problem. This notion was dispelled as the virus quickly spread across the world. By April 29, 2009, 9 countries had officially reported a total of 148 cases, including 91 laboratory-confirmed cases with 1 death in the United States and 26 confirmed cases with 7 deaths in Mexico (WHO, 2009b). According to data from the Mexican Health Department, 71 percent of the cases in Mexico occurred among people 29 years of age or younger (Charu et al., 2011). The similarity of this highly atypical pattern to the epidemiology of the 1918 virus was cause for great concern, she said.

In response to the epidemic, many countries issued travel alerts that recommended against travel to Mexico, and many commercial flights were canceled. According to Garrett, many travelers on airplanes that originated

in or passed through Mexico were required to pass through thermal sensors at destination airports, and were quarantined if they had a fever. Many airports mandated the use of face masks, although such masks were likely ineffective in limiting transmission (Khan et al., 2013). Airline and leisure company shares decreased due to people's fear that the outbreak would impact the global travel industry. On May 1, 2009, WHO issued a statement[10] declaring that there was no reasonable rationale for travel restrictions related to the virus since imposing travel restrictions would do little to stop the spread of the virus but would be highly disruptive to the global community. Nevertheless, many countries' travel sanctions and quarantine policies remained in place, and the Mexican tourist industry plummeted. Face mask production plants struggled to meet global demand for masks, and markets were flooded with fake antivirals because of the global medication shortage.

Mortality of the 2009 Influenza Pandemic

Garrett provided an overview of the mortality associated with the 2009 influenza pandemic. As of August 2010, WHO reported that more than 18,500 deaths were caused by laboratory-confirmed cases of H1N1 influenza (WHO, 2010). However, modeling studies have suggested that the actual mortality count could be as much as 10-fold greater. According to one study, the number of pandemic respiratory deaths worldwide may have exceeded 200,000 during the last 9 months of 2009 (Simonsen et al., 2013). Another study modeled global mortality during the first year of the 2009 pandemic, estimating more than 200,000 respiratory deaths and more than 80,000 cardiovascular deaths (Dawood et al., 2012).

As in the 1918 pandemic, younger adults were at greater risk of death during the 2009 pandemic; estimates have suggested that as many as 80 percent of respiratory and cardiovascular deaths occurred in people under 65 years of age (Dawood et al., 2012; Simonsen et al., 2013). Another similarity between the 1918 and 2009 pandemics is that mortality rates varied widely across the world, with more than half of the deaths occurring in Southeast Asia and Africa (Dawood et al., 2012). Figure 2-1 illustrates the global distribution of deaths associated with the 2009 pandemic during the first year. Garrett added that the global impact of the pandemic in terms of attack rates and mortality rates was relatively high, given that the 2009 H1N1 strain did not contain the known markers of pathogenicity (Mishra et al., 2010).

[10] *WHO | No Rationale for Travel Restrictions*. See https://www.who.int/csr/disease/swineflu/guidance/public_health/travel_advice/en (accessed December 18, 2018).

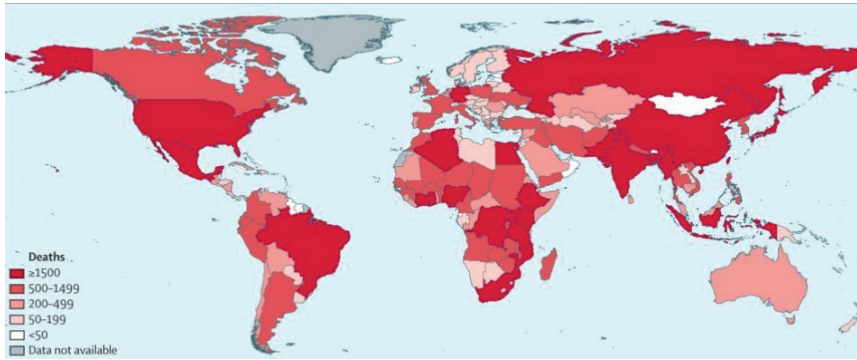

FIGURE 2-1 Global distribution of deaths associated with the first year of 2009 pandemic H1N1.
SOURCES: Garrett presentation, November 26, 2018; reprinted from *The Lancet*, Vol. 12, Fatimah S. Dawood et al., Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: A modelling study, 687–695, (2012), with permission from Elsevier.

POTENTIAL IMPACTS OF A MODERN PANDEMIC

Garrett considered the potential impacts a major influenza pandemic might have if it occurred today. According to an analysis that extrapolated the 1918–1920 mortality rates to the 2004 global population, between 50 and 80 million people could be killed by a modern influenza pandemic of similar severity to the one in 1918 (Murray et al., 2006).[11] A more recent analysis estimated that more than 720,000 pandemic-related deaths each year could be expected despite of the use of currently available medical technology (Fan et al., 2018).

In contemporary contexts, the economic impact of pandemic influenza would be profound both nationally and internationally. Globally, the expected annual losses from pandemic risk has been estimated to be around $500 billion per year (0.6 percent of the global gross domestic product [GDP]) (Fan et al., 2018). An analysis of the potential economic consequences for the United States alone suggested that an influenza pandemic could cause national GDP losses of between $35 and $45 billion, depending on whether a vaccine is available (Prager et al., 2017). A macroeconomic analysis suggested that countries could face GDP losses of up to 2 percent in the event of an influenza pandemic, but that school closures

[11] If this potential pandemic's mortality were concentrated in a single year, it would increase global mortality by 114 percent (Murray et al., 2006).

and prophylactic absenteeism from workplaces could increase the economic losses by more than three-fold (Keogh-Brown et al., 2010).

Could a Modern Pandemic Be Mitigated?

In light of the projected devastating impacts on mortality and economic and societal functions, Garrett explored potential ways to mitigate an influenza pandemic if it occurred today. The current global landscape differs significantly from the landscape in 1918, when no effective treatments for influenza existed. In addition to the availability of vaccines, antibiotics, and antiviral drugs, the modern context benefits from improved respiratory care and support therapy, a larger and more skilled health labor force, the absence of intense combat and world war, WHO and other international governance mechanisms, and the Global Health Security Agenda (GHSA). She assessed each dimension in turn for its potential and pitfalls in mitigating the impact of future influenza pandemics.

Medical Countermeasures and Respiratory Care

Garrett challenged the assumption that the availability of vaccines will necessarily counteract outbreak mortality. Peak mortality during the 1918 pandemic occurred over a period of just 6 weeks, which is too short to mobilize mass vaccine production. However, she added, the current global vaccine supply is insufficient to vaccinate everyone who might need it, even if the supply were boosted with an adjuvant (McLean et al., 2016).[12] She said that public misinformation about vaccination is another concern. A record number of children died from seasonal influenza during the 2017–2018 season, and 80 percent of those children had not been vaccinated (CDC, 2018a). According to a recent poll, one-third of all parents in the United States decline to vaccinate their children for influenza, and more than half believe that the vaccination itself can cause influenza (C.S. Mott Children's Hospital National Poll on Children's Health, 2018). Parents also rate the influenza vaccine as less important, less safe, and less effective than other childhood vaccines (C.S. Mott Children's Hospital National Poll on Children's Health, 2016).

Regarding the potential impact of antibiotics, Garrett noted that antibiotic resistance is increasing across all bacterial species relevant to respiratory infection treatments. However, only 12 new antibiotics have been licensed since 2000, and there are disparities in the global distribution of antibiotics (Kaufmann et al., 2017). Many pharmaceutical companies have

[12] An adjuvant is a substance added to a vaccine that increases the body's immune response to the vaccine.

now eliminated research and development for antibiotics, leaving only four major commercial companies in the antibiotic market—GlaxoSmithKline, Merck & Co., Inc., Pfizer Inc., and Roche. The efficacy of antivirals for treating influenza has also been compromised by rising drug resistance. Antivirals have never been widely available internationally, because of cost barriers and stockpiling of antivirals by wealthier countries. Domestically, in 2009, congressional funds only covered the cost for 31 million antiviral courses (Dimitrov, 2009).

The potential for improved respiratory care and support to mitigate a future pandemic is questionable, said Garrett. She noted that hospital bed capacity is lacking in many areas as a result of cost-cutting initiatives. Hospitals in the United States are largely operating at full capacity with no margin for surge capacity in personnel or facilities, she added, with limited capacity to use additional mechanical ventilators (Ajao et al., 2015).

Health Workforce

Garrett said with respect to the larger skilled health labor force, an adequately staffed health workforce cannot be depended on if an influenza pandemic occurs today. This is due to high absentee rates among the health workforce (driven by illness or fear), as well as the lack of day-to-day capacity—let alone surge capacity—to provide basic primary care. Furthermore, the number of health care personnel who reported receiving an influenza vaccine during the 2017–2018 season was suboptimal and varied among work settings, despite their regular exposure to infection (CDC, 2018b). Garrett also mentioned that while the absence of intense combat and world war is certainly a boon, attacks against health care workers are increasing around the world.[13]

International Governance and Global Health Security Agenda

Regarding the potential for international governance to mitigate the effects of a pandemic, Garrett commented that WHO is underfunded, and presumably, its existing funds continuously deplete with each new outbreak. Turning to the GHSA, Garrett said that only 39 countries have committed to contribute to the Action Packages.[14] The United States invested $1 billion

[13] For more on this, see WHO's surveillance system for attacks on health care workers: https://publicspace.who.int/sites/ssa/SitePages/PublicDashboard.aspx (accessed February 26, 2019).

[14] The Global Health Security Agenda was launched in 2014 to facilitate partnerships among countries, international organizations, and nongovernmental stakeholders to achieve core capacity targets outlined in 11 Action Packages. See https://www.ghsagenda.org (accessed February 25, 2019).

in health security under President Obama, but it is unclear whether support will continue under future administrations. No other country except Germany has so far matched this level of funding commitment, she said.

Garrett suggested that the brunt of a future pandemic will likely be borne by the poorest countries, which are more likely to have limited public health services, poor vaccine and antiviral availability, and inadequate disease management (Madhav et al., 2017). Without strong national- and global-level governance, she predicted, there will be vaccine hoarding, stockouts, travel restrictions, border closures, poor laboratory capacity, uncontrolled movement and spread of the virus, fear-mongering, and harsh military and police actions.

Impact of a Changing Planet

Garrett concluded by exploring how changes in the planet may be increasing the risk of a pandemic. Climate change is shifting the latitudes of the migration patterns, habitats, and movements of species that carry influenza. For example, migration patterns are shifting among marine species that are hunted by aquatic birds that carry influenza—as a species shifts, its predators also shift. Due to warming waters, more than 80 percent of global marine life is migrating north to escape the effects of climate change, with some marine species having migrated as many as 600 miles (Poloczanska et al., 2013). In response to climate change, ocean species are migrating 10 times faster than land species, and these shifts are expected to continue throughout the 21st century (Morley et al., 2018). The East Asian–Australasian Flyway is a key concern for influenza, said Garrett. Migratory aquatic birds on this flyway are the chief reservoirs of the influenza virus or family of viruses. The extent to which fish migratory patterns and other consequences of climate change are affecting the Asian flyway has not yet been quantified, she said, but it will likely affect influenza risk for both human and animal populations.

DISCUSSION

After the keynote presentation, the audience asked Garrett a couple of questions. Pia MacDonald, senior director of applied public health research at RTI International, asked whether the common belief that pandemic influenza strains originate in Asia is a misconception. Garrett explained that in every major pandemic H1N1 strain, some or all of its eight genes are descendants of the 1918 virus, which passed into Siberia from China. Although the second wave of the 1918 influenza pandemic appeared to emerge out of Haskell County, Kansas, it was based on the first-wave virus that had come from China. The descendant viruses do not disappear when

an outbreak or epidemic is quelled, Garrett added. The viruses continue to circulate before they are transmitted to humans from avian or swine species, particularly among concentrated livestock, as appears to have happened in the U.S. midwest pork industry in 2009.

Christopher Eddy, president of All1Health Systems, LLC, asked Garrett about the potential significance of future alternate transmission pathways for influenza, such as fecal-oral contaminated surfaces and fomites. Garrett replied that if a pandemic emerged with a highly virulent strain and efficient human-to-human transmission, the general population would immediately want to know how to protect themselves in practical ways. This would trigger evaluations of the virus and assessments of how to protect against it—for example, the effectiveness of handwashing, the distinction between risks of sneezing versus coughing, and clarifying the effectiveness of different types of masks. Much is still unknown about the relative impact of different interventions because very few large-scale studies have been conducted on this topic, said Garrett. She said that this area of research is underexplored and underfunded because it may not seem lucrative for product development, but the area warrants much more attention.

3

Global Progress to Prepare for the Next Influenza Pandemic

Following the keynote, the pre-workshop event featured a series of presentations that highlighted global progress in driving science, public health, and global governance to prepare for pandemic influenza. Suzet McKinney, chief executive officer of the Illinois Medical District, moderated the panel. In the first presentation, Yoshihiro Kawaoka, professor of virology at the University of Wisconsin–Madison, focused on scientific advances—particularly in virology—that can contribute to preparing for and countering the threat of an influenza pandemic. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID) at the U.S. National Institutes of Health (NIH), explored the challenges researchers have faced and the progress they have made on the path toward developing a universal influenza vaccine. David Fidler, professor of law at Indiana University Bloomington, examined how global governance has bolstered national and international preparedness for pandemic influenza. Finally, Jacqueline Katz, deputy director of the Influenza Division at the U.S. Centers for Disease Control and Prevention (CDC), described how the One Health approach can be applied to strengthen preparedness for influenza pandemics.

SCIENTIFIC ADVANCES IN COUNTERING PANDEMIC INFLUENZA

Yoshihiro Kawaoka, professor of virology at the University of Wisconsin–Madison, began the panel presentations by exploring how scientific advances have helped counter the threat of pandemic influenza

starting at the molecular level. In particular, he traced how the expanding frontiers of science and research techniques can be used to identify the pathogenicity of influenza viruses and assess their pandemic potential in nonhuman reservoirs.

Scientific Assessment of Influenza Viruses

Kawaoka described how modern research techniques have been applied to investigate the influenza A virus that caused the 1918 influenza pandemic. The influenza A virus contains two surface proteins, hemagglutinin (HA) and neuraminidase (NA). Specific influenza strains are named based on the properties of those two proteins and are classified as H1 through H18 and as N1 through N11—all of which reassort into subtypes (e.g., H1N1, H5N1, H7N9). In 1997, researchers sequenced the entire genome of the 1918 influenza virus, and in 1999, the development of the reverse-genetics technique allowed researchers to recreate influenza viruses from cloned cDNA with the goal of shedding light on the exceptional virulence of the 1918 virus. This may inform predictions of future influenza pandemics by helping to explain how these strains emerge and what genetic features contribute to virulence in humans (Taubenberger et al., 1997, 2005; Neumann et al., 1999; Reid et al., 1999, 2000, 2002, 2004; Basler et al., 2001).

Histopathology of the 1918 Virus

Kawaoka then described how these scientific advances have been used to investigate why the 1918 virus was deadlier that other pandemic influenza strains. For example, using macaques, one study compared the pathogenicity of the 1918 pandemic virus to that of the 2001 seasonal influenza virus (Cillóniz et al., 2009).[1] Within 8 days, every macaque infected with the 1918 virus had become so ill that it had to be euthanized. Histopathological studies revealed mild inflammation in the lung tissue of macaques infected with the 2001 seasonal influenza virus. However, the lungs of macaques infected with the 1918 influenza virus were filled with fluid and inflammatory cells—the same histopathology found in human victims of the 1918 strain. Kawaoka explained that the 1918 virus is unusually pathogenic because it replicates inside human lungs, and seasonal influenza viruses do not.

[1] Kawaoka noted the 1918 influenza virus is the only influenza virus that is lethal in nonhuman primates.

Airborne Transmissibility of Influenza Viruses

All influenza viruses originate from wild waterfowl, said Kawaoka, but the viruses can infect many different animal species. This makes it possible to assess the pandemic potential of influenza viruses in nonhuman reservoirs. Understanding the airborne transmissibility of influenza viruses in nonhuman animals helps to determine the potential for certain strains to cause pandemic influenza in humans. He noted that researchers are particularly interested in the H5N1 and H7N9 subtypes because of their pandemic potential.

In 1996, researchers first identified the H5N1 virus in geese in southern China. In 2005, a major H5N1 outbreak among wild waterfowl in that region spread the virus to Europe and Africa. The resulting influenza outbreak caused 450 deaths among more than 850 infected people (WHO, 2014). Kawaoka explained that, to date, humans have only sporadically been infected with H5N1 from bird species, and human-to-human transmission has been limited. However, the H5N1 virus could cause a pandemic if it mutated and developed effective human-to-human airborne transmission. Researchers have used ferret studies to test the airborne transmissibility of the H5N1 virus, and although airborne transmission did not occur among ferrets, four amino-acid mutations in one of the HA genes were transmitted via respiratory droplets (Herfst et al., 2012; Imai et al., 2012).

Kawaoka expressed that the H7N9 virus is another pathogen of concern. It was first identified in China in 2013, has since infected many humans each winter, and has reached a total of 1,567 confirmed cases as of 2018 (FAO, 2018). When the Chinese government began vaccinating poultry in September 2017, the number of human cases of H7N9 dropped dramatically. However, between 2013 and 2016, H7N9 viruses mutated from nonpathogenicity in chickens to high pathogenicity in chickens; humans have since become infected with the highly pathogenic form. Researchers have evaluated the airborne transmissibility of both the low-pathogenic and highly pathogenic forms of the H7N9 virus. One study used ferrets to compare the airborne transmissibility of the low-pathogenic H7N9 virus, the H5N1 virus, and the 2009 pandemic influenza virus. The 2009 virus was transmitted via respiratory droplets among all three animal pairs in the study, the H5N1 virus was not transmitted in any of the animal pairs without mutation, and the low-pathogenic H7N9 virus was transmitted via respiratory droplets in one of the three animal pairs (Watanabe et al., 2013). Growing concern among researchers emerged with the publication of results from another ferret study, which found that the highly pathogenic H7N9 virus was also highly transmissible among ferrets via respiratory droplets; the highly pathogenic H7N9 virus was transmitted

in three of four animal pairs in the study, and the virus was found in the brains of infected ferrets (Imai et al., 2017).

Scientific Advances in Influenza Control

Kawaoka continued his presentation by discussing how recent scientific advances have been made in attempts to develop anti-influenza drugs and more efficacious vaccines. For example, certain antiviral drugs for influenza called neuraminidase inhibitors (such as oseltamivir) have been created to target neuraminidase, the three-dimensional protein on the surface of the virus. Another new anti-influenza drug, a polymerase inhibitor named baloxivir morboxil and marketed as Xofluza, has also been approved by the U.S. Food and Drug Administration in October 2018. However, Kawaoka said, the need for better antiviral compounds was underscored by the emergence of the oseltamivir-resistant H1N1 virus during 2007 and 2008 and its global spread during 2008 and 2009. Kawaoka suggested prioritizing further scientific research into the biology of the influenza virus in order to develop more efficacious countermeasures.

PROGRESS TOWARD A UNIVERSAL INFLUENZA VACCINE

Anthony Fauci, director of NIAID at NIH, presented a case for the need to develop a universal influenza vaccine and sketched a pathway for making that vaccine a reality. To contextualize the need for a universal influenza vaccine, Fauci identified several challenges related to the current state of influenza vaccinology and explained how they would be ameliorated by the development of a universal influenza vaccine (see Box 3-1).

Challenges in Influenza Vaccinology

Fauci noted that current seasonal influenza vaccines are not consistently effective. According to estimates by CDC, the effectiveness of seasonal influenza vaccines peaked at 60 percent in 2010 and 2011 but dipped as low as 10 percent in 2004 and 2005 (see Figure 3-1) (CDC, 2018d). He said that the need to improve seasonal vaccines is illustrated by the 2017–2018 seasonal-influenza season, which was the worst on record in recent years: There were 80,000 reported deaths,[2] almost 1 million hospitalizations, and around 49 million symptomatic illnesses (CDC, 2018c). During this season, vaccine effectiveness reached only 40 percent overall and was as low as 25 percent for the circulating H3N2 strain.

[2] The typical number of influenza deaths in a season ranges between 12,000 and 56,000.

BOX 3-1
Influenza Vaccinology: Some Persistent Needs and Challenges

- Current seasonal influenza vaccines are not consistently effective.
- Post hoc pandemic vaccine development is often an ineffective response.
- Developing strain-specific vaccines for prepandemic viruses is both costly and ineffective.
- Traditional egg-based vaccine manufacturing techniques can be compromised by virus mutation and adaptation.
- Developing a universal influenza vaccine requires advanced manufacturing techniques.

SOURCE: Fauci presentation, November 26, 2018.

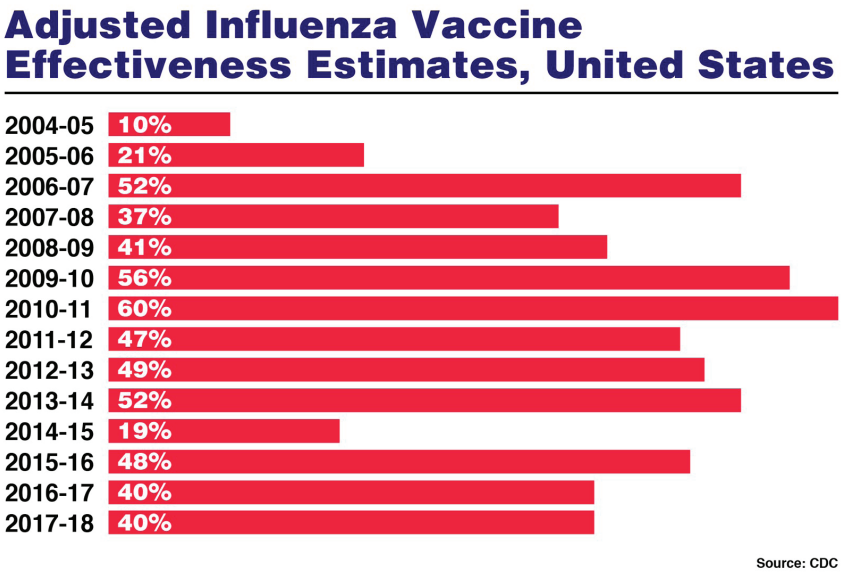

FIGURE 3-1 Adjusted influenza vaccine effectiveness estimates in the United States.
SOURCES: Fauci presentation, November 26, 2018; CDC, 2018d.

Fauci explained that when influenza pandemics occur, post hoc development of vaccines is often ineffective in response to the pandemic. During the 2009 H1N1 pandemic, for example, the first human outbreak occurred in March and began to spread worldwide by April. Egg-based vaccines take approximately 6 months to develop and produce, so public health officials presumed that the vaccine would be ready by the typical peak of influenza season in December and January. The vaccine was barely available when the pandemic peaked, and by the time vaccine doses were finally ready to administer, the pandemic had waned; only 90 million doses were used out of the 162 million doses that were produced.

Fauci said that the current vaccinology practice of "chasing after" prepandemic influenza is costly and ineffective. For example, influenza experts projected that the 2005 H5N1 outbreak would be a major event, and the United States president at that time requested $7.1 billion for pandemic preparedness, including the development of a vaccine; however, the outbreak never reached the pandemic level in humans (CDC, 1997; Lister, 2007). In 2013, significant investment was channeled into developing, producing, and stockpiling a vaccine for the H7N9 strain. However, the H7N9 virus circulating by 2017 had mutated, and the 2013 vaccine no longer provided adequate protection. This required developers to start chasing prepandemic influenza vaccines anew (Branswell, 2017). Fauci argued that the large investments would be better invested in efforts to develop a universal vaccine rather than strain-specific ones.

Furthermore, Fauci suggested that vaccine manufacturing techniques need to transition beyond traditional egg-based methods of vaccine production and toward cell-based technologies and cutting-edge platform technologies. Once a virus is selected, egg-based vaccine development and production take about 6 months before vaccinations can begin. Given the lead time required to have a vaccine ready for winter seasonal-influenza seasons, he explained, virus selection needs to occur in February or March. However, even if the appropriate virus were selected, the virus could change during that 6-month period—which would decrease the effectiveness of the vaccine being developed. This occurred from 2014 to 2015, and the seasonal vaccine's effectiveness only reached 19 percent (CDC, 2018b). Another challenge for egg-based vaccine-production methods is that viruses can adapt within the egg environment in ways that contribute to decreased effectiveness. For example, from 2016 to 2017, the H3N2 virus selected was a good match for the eventual seasonal virus. However, it mutated to grow more effectively in eggs, and the effectiveness of the produced vaccine was reduced.[3] That same year, similar mutations were not observed in vaccines produced using cell-based production techniques.

[3] The mutation occurred in an area of the protein that is the epitope for protection on the head of the HA; this compounded the effectiveness problem.

Fauci argued that a universal influenza vaccine would provide more effective protection when the next major influenza pandemic strikes (Paules and Fauci, 2018; Paules et al., 2018). However, he added that producing a universal vaccine would require advanced vaccine manufacturing techniques such as cell-based production and new platform technology. Fauci explained that researchers are currently pursuing new platforms to develop a universal influenza vaccine. These include recombinant proteins, viral vectors (e.g., cold virus/adenovirus), virus-like particles (i.e., non-infectious and devoid of genetic material), nanoparticles (with protein attached on the particle), and genetic immunization (DNA and RNA vaccines).

Pathway Toward a Universal Influenza Vaccine

Fauci sketched the pathway toward developing a universal influenza vaccine (Paules et al., 2017). The ideal universal influenza vaccine, he said, would cover all influenza strains in Group 1 and Group 2 of influenza A and potentially strains of influenza B—although this may be aspirational. He said the most practical path to a universal vaccine would be to iteratively broaden the vaccine coverage over time (see Figure 3-2).[4] The first step would be to develop strain-specific vaccines able to cover all circulating strains, to develop vaccines able to cover all strains within a single subtype, and to progressively develop vaccines able to cover multiple subtypes within a single group. The penultimate iterative step in developing a universal vaccine would be developing a pan-group vaccine able to cover all strains in Group 1 or in Group 2. He noted that a vaccine able to cover H3N2 strains and all of the H1N1 strains would be very good for seasonal influenza intervention. With the appropriate group specificity, it would also be useful against pandemic influenza.

NIAID has created a network, the Collaborative Influenza Vaccine Innovation Centers, to coordinate and attract expertise to universal vaccine development efforts.[5] A common research goal is a vaccine that induces a response to the part of the influenza virus that does not mutate frequently. He explained that the influenza A HA protein consists of a head region and a stem region. The target of current influenza vaccines is the head region, which is where mutations that can reduce a vaccine's effectiveness commonly occur. To address this problem, investigators have focused on the stem region of the HA as the target of universal influenza vaccines. The stem region is similar across different influenza strains, and it is the site of relatively few mutations each season. Approaches researchers have explored

[4] A recent strategic plan and research agenda for developing a universal influenza vaccine delineated the multiple approaches in detail (Erbelding et al., 2018).

[5] For more information on the Collaborative, see https://www.niaid.nih.gov/grants-contracts/influenza-vaccine-research-solicitation (accessed February 25, 2019).

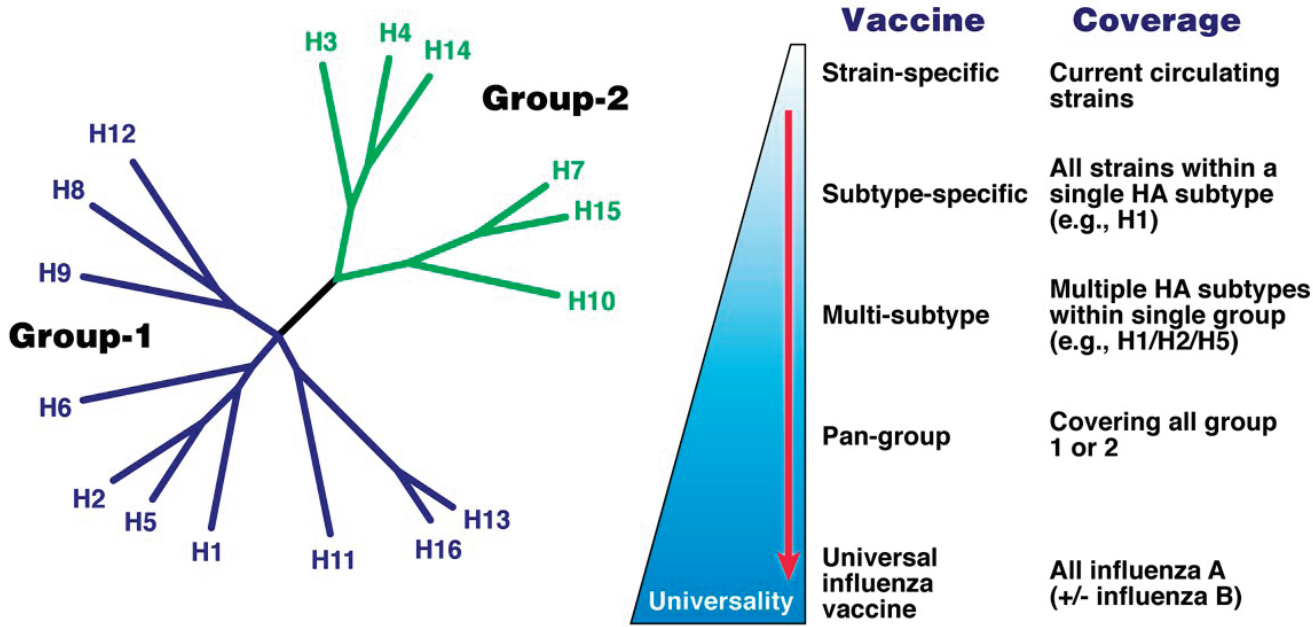

FIGURE 3-2 Iterative pathway to a universal influenza vaccine.
NOTE: HA = hemagglutinin.
SOURCES: Fauci presentation, November 26, 2018; Russell et al., 2008; Copyright (2008) National Academy of Sciences, U.S.A.; Paules et al., 2017; Reprinted from *Immunity*, Vol. 47/Issue 4, Catharine I. Paules, Hilary D. Marston, Robert W. Eisinger, David Baltimore, and Anthony S. Fauci, The pathway to a universal influenza vaccine, Pages 599–603, Copyright (2017), with permission from Elsevier.

include removing the HA head and then replacing it with an irrelevant head or placing the headless stem on a highly immunogenic nanoparticle.

A possible stumbling block to developing a universal influenza vaccine is the phenomenon of imprinting—or "original antigenic sin" (Francis, 1960). Fauci explained that a person's immune system preferentially reverts to and responds well against the first influenza strain it encounters through either viral exposure or vaccination. For example, a person born in an era when H1N1 circulated was probably exposed to that strain first, so subsequent exposure to any other strains would induce an immune system response to the H1N1 strain. Although this does not prevent the immune system from mounting a response against the current strain, it does distract the immune response. This phenomenon explains why different influenza pandemics seem to spare different age cohorts.

GLOBAL GOVERNANCE TO BOLSTER PANDEMIC PREPAREDNESS

David Fidler, professor of law at Indiana University Bloomington, gave the next presentation on the role of global governance in bolstering preparedness for pandemic influenza. He noted that the existing set of global governance mechanisms did not directly result from the 1918 pandemic. In fact, it took roughly another 90 years before the main international legal instrument for addressing infectious diseases specifically included provisions for influenza. As a consequence, contemporary global governance structures have yet to be tested by an event as catastrophic as the 1918 influenza pandemic.

Fidler described the existing global governance infrastructure for pandemic influenza as a *regime complex*: a set of interlinked and overlapping institutions, rules, processes, and practices. Overall, this regime complex forms and supports a web of influenza preparedness and response activities that work at both functional and strategic levels. Functionally, governance mechanisms enable surveillance, virus sharing, scientific research, and vaccine development. Strategically, this web of activities integrates national security, economic interests, human rights, and ethical values into pandemic influenza governance. This web of governance interweaves political calculations about threats of pandemic influenza with public health capabilities to mitigate those threats. However, he noted that because it was so recently developed, this web's sufficiency and resiliency need to be assessed in both political and public health terms.

International Health Regulations

Fidler explained that the World Health Organization (WHO) radically changed the global governance of serious health events when it revised the International Health Regulations (IHR) in 2005.[6] Before this revision, the IHR reflected a narrow approach that originated in the 19th century, centered on a limited number of infectious diseases, such as cholera and the plague, for case reporting and response measures justified on public health grounds. However, this regime never included influenza as a reportable disease. The revised IHR broke away from this approach by requiring countries to notify WHO about any disease events that could constitute a public health emergency of international concern. Specifically, the revised IHR

- mandate the reporting of any case of human influenza of a new subtype B;
- require states to develop surveillance and response capacities;
- empower WHO to gather surveillance from nongovernmental authorities;
- authorize the Director-General of WHO to declare a public health emergency of international concern and to issue temporary recommendations; and
- seek to ensure the necessity of any public health measures that adversely affect trade, travel, and human rights.

The revised IHR were quickly subjected to its first influenza challenge in 2006 when Indonesia withheld its virus samples from WHO after an outbreak of H5N1 and asserted that the influenza virus-sharing system produced benefits such as access to vaccines that were mainly reaped by countries deemed more developed (see Chapter 7 for further discussions on virus sharing and benefit sharing). The revised IHR were not yet in force, and the question of whether they required countries to share influenza virus samples was contentious.

According to Fidler, WHO began negotiations to address influenza virus sharing and benefit sharing once it determined the IHR did not specifically govern that issue. The negotiations ultimately produced the Pandemic Influenza Preparedness (PIP) Framework in 2011, which, unlike the IHR, is not binding under international law. However, this innovative governance framework facilitates influenza virus sharing while also creating benefits that flow back to countries that share viruses. Fidler said the PIP

[6] The International Health Regulations (2005) are a legal instrument binding all WHO member states that support the international community in the prevention of, control, and response to acute public health risks, including the spread of infectious diseases.

Framework has generally worked, but he has concerns about its future. In particular, he noted that virus sharing has declined since 2011 and that the PIP Framework has yet to be tested by a serious influenza pandemic (WHO, 2016a) (see Chapter 7 for a full list of concerns and challenges for the PIP Framework).

Fidler explained that the revised IHR were in full force in 2009 when the H1N1 pandemic provided its first real test. That pandemic was not as devastating as predicted, and the IHR generated overall benefits. However, a postpandemic review of the IHR revealed problems with country-level surveillance and response capacities and with questionable trade and travel measures (WHO, 2011). In contrast, Fidler described the 2014 Ebola outbreak in West Africa as a debacle for the IHR, and he suggested this outbreak was an example of the IHR's inability to operate successfully during a large-scale, virulent influenza event. He said various post-Ebola efforts to strengthen the IHR are under way, but governance issues during that outbreak illustrate that the current IHR have not adequately prepared the world for a dangerous strain of influenza.

Progress in Global Influenza Governance

Fidler concluded by reflecting on whether progress has been made in global influenza governance. Despite their problems, he suggested the IHR and the PIP Framework facilitate important contributions to existing webs of governance around influenza preparedness and response. Other governance efforts support this web, such as WHO's Global Strategic Plan to improve public health preparedness and response[7] and the global activities mentioned in the pre-workshop event's opening remarks (see Chapter 2). However, he said neither the political commitment nor the functional capacities starting at the international level currently exist to withstand a crisis. Fidler noted that the governance web for influenza preparedness and response "may turn out to be gossamer strands across the mouth of a cannon." Strategic interest in influenza appears to regularly wax and wane as crises happen and then threats eventually fade from headlines. He underscored this pattern in the West African Ebola outbreak and the development of the revised IHR. He also drew the audience's attention to ongoing uncertainty about the PIP Framework. He observed that the trend represents a political dynamic that handicaps functional work to build national and international preparedness and to increase response capacities. To transcend

[7] WHO's Global Strategic Plan was drafted in 2017 to meet the World Health Assembly's request for a 5-year plan that listed global deliverables and timelines for member states to improve public health preparedness and response—in line with the IHR requirements. See http://apps.who.int/gb/ebwha/pdf_files/EB142/B142_10-en.pdf (accessed February 25, 2019).

this pattern, he said, present and future influenza governance efforts should use lessons from the 1918 pandemic—a time when no international governance around influenza existed. He also said governance efforts should be relentless about ensuring that the next severe influenza pandemic does not cause similar devastation.

A ONE HEALTH APPROACH FOR PREPAREDNESS

Jacqueline Katz, deputy director of the Influenza Division at CDC, discussed the benefits of a One Health approach for pandemic influenza preparedness.[8] She explained that avian species and swine provide the reservoirs for the influenza viral genes that have contributed to past pandemics and will contribute to future ones. In the past century alone, four pandemics (those in 1918, 1957, 1968, and 2009) were caused by viruses with genes that originated from avian and/or swine species. The past three of these pandemics were caused by viruses created by reassortment—mixing genes within a common host. Katz reiterated that pandemics resulted when these viruses subsequently were able to infect humans and underwent sustained transmission in an immunologically naïve human population.

Increase in Novel Influenza A Viruses

According to Katz, the number of novel influenza A virus infections in humans has increased sharply over the past 20 years. These zoonotic infections are caused when an influenza A virus jumps from an animal source into humans; these viruses are antigenetically and genetically distinct from the seasonal influenza A viruses that circulate in humans. Ever-expanding virus subtypes have been derived either from avian or from swine species. The most recent influenza pandemic in 2009 was derived from a swine source, but that virus also contained genes of both human and avian origin. She explained that the 1997 H5N1 outbreak in Hong Kong was the first time researchers realized that a wholly avian influenza virus could infect humans, and this catalyzed the development of a One Health approach, which was able to quell the outbreak (see Box 3-2). She noted that the increasing number of zoonotic influenza A virus infections in humans will require ongoing laboratory and epidemiologic investigations carried out jointly by researchers from human- and animal-health sectors.

[8] One Health is a collaborative, multisectoral, and transdisciplinary approach—working at local, regional, national, and global levels—that seeks to achieve optimal health outcomes by recognizing the interconnection among people, animals, plants, and their shared environments (CDC, 2019b).

BOX 3-2
Development of a One Health Approach for H5N1 in Hong Kong

During the 1997 H5N1 outbreak in Hong Kong, surveillance and molecular epidemiology work carried out in poultry markets and in wild bird populations provided the evidence base for identifying the origin of the H5N1 virus, understanding its evolution, and grasping its ability to transmit from a bird to a human source. Surveillance at the animal–human interface provided serologic evidence of additional human infections with H5N1 among the poultry cullers and market workers, which suggested that exposure to poultry was the main risk factor for H5-subtype human infections (this is also true of the H7N9 virus). Ultimately, the human disease outbreak was curtailed by culling all poultry at the end of 1997, which halted the transmission of the virus to humans. In the years since, Hong Kong has been proactively developing and sustaining long-term strategies to protect human health through safer practices around purchasing and processing live birds at poultry markets—while simultaneously safeguarding the economics of the poultry industry. Such One Health approaches were beneficial during the emergence of subsequent diseases, including severe acute respiratory syndrome.

SOURCE: Katz presentation, November 26, 2018.

Influenza Viruses with Pandemic Risk

Katz said the H7N9 influenza A virus poses the greatest risk for a human pandemic. The number of H7N9 cases currently far exceeds the number of H5N1 cases worldwide (see Figure 3-3). This is likely due to a confluence of factors, including a two-fold increase in the global population of poultry, a steady increase in the number of pigs farmed globally, and a steep increase in the number of people who travel globally (UNWTO, 2018). She added that increased and improved surveillance contributes to the increasing number of cases detected. The emergence of highly pathogenic avian-influenza H7N9 viruses in 2017—not seen in previous H7N9 waves—prompted the Chinese government to introduce poultry vaccination for H7 strains (Shi et al., 2018). By controlling the virus in the poultry population, the government essentially controlled the disease in humans. Another developing concern Katz identified was the emergence of variant swine influenza viruses, which have infected humans. The largest wave thus far occurred in 2012 when 300 people were infected with H3N2 variant viruses; researchers identified a close association between these infections and children who showed swine at agricultural fairs or participated in swine events at seasonal state fairs (Bowman et al., 2014). This pattern has continued, although specific numbers vary by year. She emphasized that

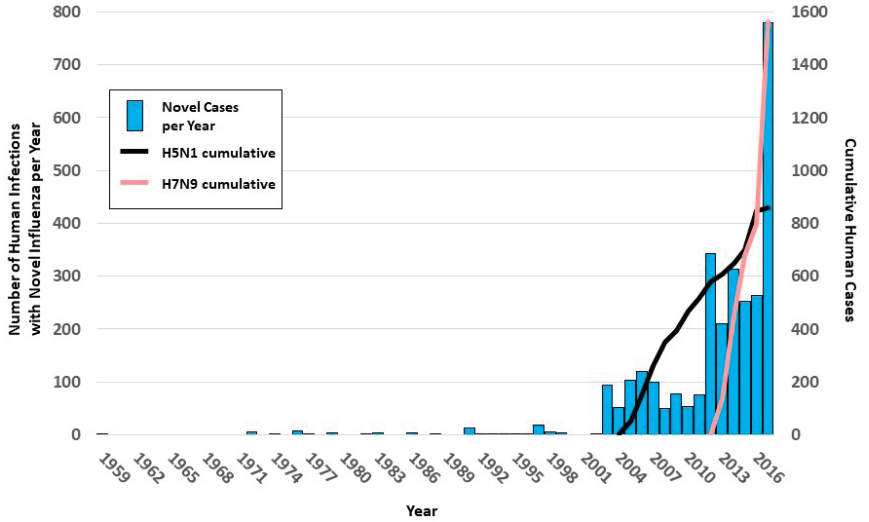

FIGURE 3-3 Increasing number of human cases of novel influenza A infections, 1959–2017.
SOURCES: Katz presentation, November 26, 2018; data from Freidl et al., 2014.

strong collaboration between human- and animal-health technical groups will be needed to ensure pandemic readiness and to carry out pandemic risk assessment for H3N2 variant viruses.

World Health Organization's Role in Tracking Viruses

Katz explained that the WHO Global Influenza Surveillance and Response System (GISRS) carries out year-round surveillance for seasonal viruses and for novel influenza A viruses that cause zoonotic infections (see Chapter 6 for more on GISRS). GISRS collaborates closely with OFFLU,[9] a joint animal-influenza expert group formed by the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE). WHO Collaboration Centers provide support for the antigenic and genetic characterization of animal viruses. This intersectoral collaboration creates the capacity to track viruses in animals and the emergence of zoonotic infections in humans. She noted that certain genetic markers are associated with enhanced mammal adaptation and greater transmission potential. Researchers follow these genetic markers

[9] For more information on the OFFLU network, see http://www.offlu.net (accessed January 31, 2019).

in emerging viruses to determine whether they acquire additional adaptive changes.

The collaborating groups meet twice per year to analyze data about the human epidemiology of zoonotic infections, virus distribution and ecology in animals, and the joint genetic and antigenic characterization of viruses from both human and animal sources. Katz explained that these biannual analyses provide the scientific rationale for developing new candidate vaccine viruses (CVVs) against emerging and re-emerging influenza viruses that have pandemic potential. WHO Collaborating Centers and Essential Regulatory Laboratories have so far generated more than 60 CVVs against H5, H7, and H9 avian subtypes and H1 and H3 variant viruses (WHO, 2018a). Most CVVs are egg-based, inactivated vaccines that are ready for use if needed. Many have been used to produce pilot lots for human clinical vaccine trials, which have provided information about how the vaccines work in humans, including what doses would be needed and whether adjuvants would be required. She added that some of the CVVs have also been used by veterinary vaccine producers.

Approach to One Health in the United States

Katz described how the One Health approach has been applied specifically to influenza in the United States. Since 2007, human infection with novel influenza A viruses has been a nationally notifiable disease; such cases trigger an investigation by CDC and/or state health officials. Samples of any associated animal infections are sent to the U.S. Department of Agriculture (USDA) National Veterinary Services Laboratories for characterization. CDC and USDA collaborate by exchanging gene sequencing data and epidemiologic information about both human and animal viruses; they have also co-developed protocols for notification of and response to potential zoonotic events detected in either sector. Finally, CDC and USDA have jointly developed educational and guidance materials about variant influenza viruses and the outbreak-investigation process for both animal-sector producers and the public, including targeted materials for 4-H youth development and mentoring groups.

According to Katz, the expansion of next-generation sequencing capacity has strengthened One Health surveillance and readiness in the United States. Field tests of new mobile technology for influenza sequence analysis (e.g., the Oxford Nanopore MinION) were conducted at the World Pork Expo, a major hub for influenza virus transmission among swine. Real-time genetic sequencing indicated that swine viruses from the Expo were similar to human viruses detected at state fairs months later. Katz suggested that this technology could potentially allow CVVs to be prepared in advance from genetic sequences found in swine earlier in the season; it

could also be used to carry out real-time sequencing in a human outbreak setting.

Global Challenges for the One Health Approach

Katz considered some global challenges for the One Health approach to influenza preparedness and response. Because of trade and export implications, surveillance and/or reporting of influenza in animals is insufficient in many regions of the world. Sharing influenza specimens and viruses with pandemic potential is a complex process that involves different regulations across multiple sectors and countries, and this sometimes delays risk assessment and response timeliness. Katz also noted that the PIP Framework does not include animal influenza viruses, which adds to the list of concerns Fidler outlined earlier about the PIP Framework.

Finally, Katz characterized CDC's Influenza Risk Assessment Tool (IRAT) as a global health evaluation tool to prioritize pandemic preparedness activities. It is used to assess potential pandemics for the risk of novel influenza-virus emergence in humans, including human-to-human transmission, and of public health impact and its severity.[10] Furthermore, it can enhance readiness activities related to the development, stockpiling, and deployment of diagnostics, reagents, vaccines, and antivirals. The tool employs a One Health approach in which CDC experts work closely with USDA agricultural experts.[11] Of the risk assessments conducted in recent years, H7N9 continues to pose the highest risk both for emergence and for impact, Katz reiterated. It is followed closely by H5 subtype viruses.

DISCUSSION

Suzet McKinney, executive director and chief executive officer of the Illinois Medical District, summarized her key points from the panelists' presentations:

- Kawaoka built a case not only for science to provide insight into the biology of influenza viruses but also for research and response communities to focus on lessons learned from prior pandemics and the threats posed by viruses such as H5N1 and H7N9.

[10] IRAT evaluates 10 elements to develop a risk assessment score. Virus-related elements are genomic variation, receptor binding, transmission in laboratory animals, and antivirals and other treatment options. Population-related elements are existing population immunity, disease severity and pathogenesis, and antigenic relationship to vaccine candidates. Ecology-related elements are global geographic distribution, infection in animals, human risk of infection, and human infections and transmission.

[11] For more information on IRAT, see https://www.cdc.gov/flu/pandemic-resources/national-strategy/risk-assessment.htm (accessed January 31, 2019).

- Fauci emphasized that existing seasonal influenza vaccines are not consistently effective because they are often based on predictions about which prominent strains should be included. Difficulties around this process are compounded by an additional challenge: rapid virus mutation. He underscored the necessity of a shift toward new technologies for vaccine production—ones that enable vaccines to anticipate rapid mutations and that engender a more proactive approach to preparedness.
- Fidler explained that the IHR and the PIP Framework are situated within webs of activities that integrate public health capability, economics, and pandemic influenza preparedness, but these activities should also be viewed through a political lens to optimize their effectiveness in a crisis.
- From the One Health perspective, Katz described several ongoing global health challenges associated with preparedness, including insufficient surveillance and complexities around virus sharing, and explained ongoing efforts to assess those global risks and to move preparedness forward.

To start the discussion, McKinney asked Kawaoka about the current state of global readiness to identify new viruses with severe pathogenicity prior to an outbreak. Kawaoka replied that influenza pathogenicity is driven by the specific traits of each virus, but immunity in each affected population affects the size of the outbreak. For instance, the impact of the 2009 H1N1 pandemic is often considered to be relatively low, but the virus affected children more than it affected older people, who tended to have preexisting immunity. Kawaoka said that experimental settings can help researchers identify or predict the pathogenicity of a virus, but they cannot be used to predict the magnitude of an outbreak, which is shaped by this population-immunity factor.

Keiji Fukuda, director and clinical professor, School of Public Health, The University of Hong Kong, then asked the panel about ethical and safety concerns related to research that involves dangerous viruses. Fauci replied that oversight systems have improved during recent years. In the United States, the federal government exercises oversight only on federally funded work, but it has no control over research funded elsewhere. He suggested that difficult decisions about certain types of research—those related to naturally occurring virus mutations, for example—must be formally assessed to determine risks versus benefits to society. Fauci asserted that creating something that would never occur in nature is the only type of experiment that should be completely disallowed. Katz added that federally funded scientific research is subjected to careful and thorough risk–benefit analyses to ensure that the benefits of public health research outweigh the

risks. Ed You, supervisory special agent at the Weapons of Mass Destruction Directorate at the Federal Bureau of Investigation (FBI), commented that the government's response to biological threats is multi-pronged: FBI works with partners, including CDC, USDA, state and local law enforcement, public health representatives, and state veterinary programs, to assess any unusual outbreaks and to determine if they are naturally occurring or intentionally released. At the same time, FBI is charged with protecting sensitive research and ensuring its security, as well as with protecting the people who conduct that work and their related institutions.

William Buchta, president of the American College of Occupational and Environmental Medicine, asked panelists how to preemptively create a geopolitical framework for equitably distributing the universal vaccine (when it becomes available) in a way that prevents hoarding. From a governance point of view, said Fidler, ensuring universal access would require a lengthy and complicated process that would probably not eliminate concerns about hoarding or guarantee that political promises will be fulfilled during a crisis event. Fauci added his prediction that hoarding would not be an issue if a truly universal influenza vaccine became available because mass influenza-vaccination campaigns would become as standard as mass campaigns for polio, measles, and smallpox. He noted that hoarding only occurs when there is an outbreak during which resources are limited.

Pia MacDonald, senior director of applied public health research at RTI International, asked the panelists where geographically animal surveillance should be prioritized in order for it to improve as a whole. Fauci remarked that animal surveillance needs to improve across the world, including in the United States. He noted that more robust animal surveillance would have detected swine influenza in the United States several months before the first human cases occurred. Katz said that resources for animal surveillance are far more limited than for public health surveillance in many countries, including the United States, because it is not a priority. She said, "If no one is looking for it, no one will know whether it is there." She noted that if a virus is discovered in a country, that discovery may have negative implications for trade and export. She maintained that governments worldwide need to recognize the importance of animal surveillance in pandemic preparedness and to fund it commensurately.

Laurie Garrett, science journalist and founder of the Anthropos Initiative, asked the panelists about a notable tension between the potential for live-poultry sales in Asian markets to potentiate outbreaks and the negative environmental consequences of introducing a cultural shift toward selling processed, refrigerated poultry. She added that carbon dioxide emissions would likely skyrocket if every person in Asia had a personal refrigerator. Katz noted that people in many parts of China express strong cultural preferences for fresh poultry, which would make this type of

cultural shift difficult in the short term, but she added that changes in mitigation practices are occurring slowly in Mainland China. She was less optimistic about the prospect of introducing such cultural measures in other parts of Asia. Kawaoka said that culture is very difficult to change, so it is more feasible to introduce risk-mitigation strategies in order to change the system incrementally over a longer period of time. For example, officials in Hong Kong have implemented measures to increase surveillance for influenza viruses, to limit the saturation of viruses in wild poultry markets, and to eliminate more virus-prone bird species from the system than they currently do. Katz added that multiple layers of mitigations can be put into place, such as the measures taken in Hong Kong's live-poultry markets to separate the general public from people who are involved in the slaughter process and who are therefore more likely to be exposed to viruses. From a political standpoint, Fidler said that influencing cultural behavior change is better suited to a regional rather than a global approach. Efforts to cooperate within Asian organizations initiated at the regional level tend to be more effective in creating functional, nonbinding approaches and for sharing best practices.

Regarding the topic of global collaboration and governance, Jerri Husch, a sociologist formerly with WHO, asked how stakeholders could move from talking about implementing interagency collaboration to making it a reality through dealing with its practical complexities. Fauci replied that the Global Health Security Network and the Global Health Security Agenda both represent progress in that regard. They are broadly aimed at improving surveillance and communication but also at facilitating real-time data sharing during a disease outbreak. Fidler said that international governance mechanisms are currently focused on the implications for genetic sequencing data, which are already being shared globally in real time through the IHR and the PIP Framework. He suggested that governance regimes should build information sharing into the design of rules and institutions so that collaboration would be integrated into the machinery of bureaucracy. Katz added that this work would require persistence and engagement from multiple sectors.

To conclude, Fukuda asked Fidler which area of global governance should be prioritized for improvement. Fidler suggested that instead of creating new global frameworks or initiatives, efforts should focus on existing components of the regime complex to improve and integrate governance operations. He said, "The concentration of political capital and economic capital should be put forward in ways that allow the incremental ratcheting up of resilience in the key pieces of the governance that are already in place—IHR, PIP Framework, and Nagoya." He added that these governance mechanisms need to be integrated in a way that does not resurrect the viral-sovereignty controversy each time a dangerous outbreak occurs.

4

Reflections on a Century of Infectious Disease Outbreaks and Pandemics

Building on discussions about pandemic influenza from the pre-workshop event, the 1.5-day workshop that followed delved into the world's current state of readiness to prevent, detect, and respond to not only pandemic influenza but also other novel and emerging diseases. Rick Bright, director of the Biomedical Advanced Research and Development Authority (BARDA) in the Office of the Assistant Secretary for Preparedness and Response (ASPR) at the U.S. Department of Health and Human Services (HHS), delivered a keynote address on the impact of infectious disease outbreaks and pandemics on people, communities, and economies across the world. Arnold Monto, professor of public health in the Department of Epidemiology at the University of Michigan, followed with a plenary presentation in which he reflected on a century of evolving pandemic and emerging infectious disease challenges.

IMPACT OF OUTBREAKS AND PANDEMICS ON PEOPLE, COMMUNITIES, AND ECONOMIES

Rick Bright, director of BARDA, began by explaining the role of ASPR: Its mission is to save lives and to protect Americans from health security threats in the 21st century. ASPR tracks a wide range of microbial threats, which span emerging natural threats, scientific accidents, and threats imposed intentionally by individuals or state actors. In 2018, the U.S. Executive Office of the President released the first National Biodefense Strategy of the United States, which is aligned with the ethos of ASPR's mission (USG, 2018) (see Box 4-1 for more details about the strategy).

BOX 4-1
The U.S. National Biodefense Strategy (2018)

The first National Biodefense Strategy in the United States was released in 2018 by the U.S. Executive Office of the President. The strategy contains five main goals for strengthening the biodefense enterprise, and it uses a layered risk-management approach to counter biological threats and incidents. The goals are to

1. enable risk awareness to inform decision making across the biodefense enterprise;
2. ensure biodefense enterprise capabilities in order to prevent bioincidents;
3. ensure biodefense enterprise preparedness in order to reduce the impacts of bioincidents;
4. rapidly respond to bioincidents to limit their impacts; and
5. facilitate recovery to restore the community, economy, and environment after a bioincident.

The strategy's end-to-end goals encompass preparing for emerging threats from nature, enabling early awareness and risk assessment, developing countermeasures to mitigate or to reduce the impact of microbial threats, and facilitating response to and recovery from the impact of microbial threats.

SOURCES: Bright presentation, November 27, 2018; USG, 2018.

ASPR's goal for pandemic influenza—as it is for any microbial threat—is to ensure that vaccine and countermeasure responses are in front of the epidemic curve. In 2006, ASPR conducted a national assessment that illustrated that the best national efforts to generate enough influenza vaccine to cover everyone in the country at two doses per person would be insufficient to curb the threat. Figure 4-1 illustrates ASPR's pandemic vaccine response targets. By 2009, the country's capacity to make more vaccines had improved but not quickly enough to get in front of the curve. In 2018, Bright reported that national capacity had improved to the extent that around 800 million doses of pandemic influenza vaccine could be produced if needed. The challenge now, he said, is to understand when to use the vaccine, where to use it, how to distribute it, and how to administer it as quickly as it can currently be produced.

Impact of Recent Outbreaks and Pandemics

Bright remarked that infectious disease outbreaks and pandemics continually emerge and evolve over time, but there are lessons that remain

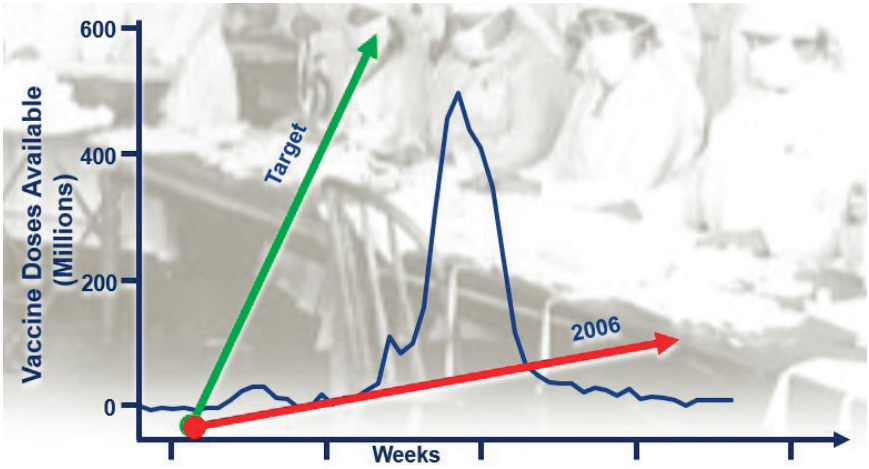

FIGURE 4-1 Pandemic vaccine response targets.
SOURCE: Bright presentation, November 27, 2018.

to be gleaned from threats that have been encountered in the past—and from those that people face today. He advised that aggregating and applying those lessons in a cohesive way would strengthen preparedness for future threats. Since the 1918 influenza A H1N1 pandemic, Bright said, many impactful outbreaks and pandemic events have occurred over time:

- The U.S. Centers for Disease Control and Prevention (CDC) first reported HIV in 1981, and as of 2017, almost 37 million people were living with HIV worldwide and 35 million people have died of HIV/AIDS since the beginning of the epidemic (WHO, 2018d).
- Between 2002 and 2004, severe acute respiratory syndrome (SARS) emerged in China and caused almost 800 deaths worldwide (CDC, 2013b).
- Between 2009 and 2010, the influenza A H1N1 pandemic caused more than 200,000 deaths worldwide.[1]
- In 2012, Middle East respiratory syndrome (MERS) was first identified in Saudi Arabia and has since caused more than 800 deaths (Hajjar et al., 2018).

[1] As noted in Chapter 2, the number of estimated deaths is unclear. CDC estimates that the pandemic caused 151,700 to 575,400 deaths, and this estimate is based on limited data and on untested cases that resulted in deaths from influenza-like illnesses (CDC, 2012).

- Between 2014 and 2016, the Ebola virus epidemic in West Africa caused more than 11,000 deaths (CDC, 2019a).
- In 2015, the Zika epidemic emerged and resulted in considerably fewer deaths but notably led to Congenital Zika Syndrome and Guillain-Barré syndrome (a rare neurological disorder) (WHO, 2016c).

Bright noted that those outbreaks and pandemics varied widely in mortality and morbidity, and in several cases, their overall economic impacts were more devastating in relative terms than their impacts on mortality and morbidity. For example, while the number of deaths from the 2003 SARS epidemic was relatively low, its global macroeconomic impact—estimated at between $30 billion and $100 billion—was severe (Smith, 2006). The Ebola epidemic was associated with $2.2 billion in lost gross domestic product (GDP) in 2015 across Guinea, Liberia, and Sierra Leone (CDC, 2018a); $3.6 billion was spent by Germany, the United Kingdom, the United States, and the World Bank to support the response to the epidemic (CDC, 2018a). Furthermore, the U.S. Congressional Budget Office has estimated that a modern moderate-to-severe influenza pandemic could have a macroeconomic impact in the United States of around 1 to 4.25 percent of the national GDP (CBO, 2005). Bright cautioned that even a severe outbreak of seasonal influenza—not necessarily a pandemic—could have a significant macroeconomic impact on the global economy. In 2016, the Commission on a Global Health Risk Framework projected the average expected economic losses from infectious disease crises in the future would be around $60 billion per year (GHRF Commission, 2016). A World Bank report on the emergence of antimicrobial resistance estimated that if resistance is unmitigated by 2050, the global economic losses could reach $100 trillion (World Bank, 2017).

Common Elements of an Outbreak Response

According to the World Health Organization (WHO), "Disease X represents the knowledge that a serious international epidemic could be caused by a pathogen currently unknown to cause human disease."[2] Bright explained that as many as 631,000 to 827,000 undiscovered viral species exist with zoonotic potential in mammal or bird hosts (Carroll et al., 2018). Furthermore, any one of the hundreds of thousands of additional organisms that are already known to circulate could emerge and cause total devastation in terms of morbidity, mortality, and economic loss. Bright

[2] More information about Disease X is available at https://www.who.int/blueprint/priority-diseases/en (accessed December 30, 2018).

added that this underscores the urgency of identifying common elements of effective outbreak response.

Bright offered a breakdown of the essential elements of an effective response: early detection, vaccination, behavioral countermeasures, and addressing gaps in host-based treatment. According to Bright, early detection of organisms that spread locally, regionally, nationally, or globally is a high priority because "we don't know what's coming our way until it's too late . . . every day counts." Knowledge about when and where to use vaccination and behavioral countermeasures is also critical, he added. Significant gaps remain in host-based treatment options, he said, and such gaps need to be addressed through a better understanding of immune modulation, cytokine storms,[3] and common processes triggered in the body upon exposure to bacteria or viral organisms.

Potential Impact of Pandemic Influenza

To demonstrate the speed at which the death toll mounts during a pandemic similar to the one in 1918, Bright presented an animated simulation, the "Shattuck Flu Map," developed by the Institute for Disease Modeling. Three months into the simulated pandemic, more than 10 million people had died around the world. After 4 months—the point at which factories would be able to start producing a pandemic influenza vaccine, given the world's current best efforts—the death toll had increased to 22 million people.[4] Six months into the simulated pandemic, when maximum vaccine production would be available, an estimated 33 million people had died. The simulation starkly illustrated the importance of early detection and timely warning systems, Bright said, and of the desperate need for new technologies to address this type of potential outbreak.

BARDA has developed an agent-based model to represent an unmitigated pandemic of comparable transmissibility to that of Shattuck Flu Map's global simulation. The model covers a specific area in the United States—Washington, DC, and the states of Maryland and Virginia—and simulates the transmission of pandemic influenza among people in these areas. Every person is represented by a unique agent in the simulation, and each agent mixes among multiple interaction groups in which transmission could occur—at home, work, school, and general context settings. As a result, the specific risk of transmission across settings varies by age group, and transmission risks are calibrated to the results of influenza-transmission

[3] A cytokine storm is an overproduction of immune cell cytokines, their activating compounds.

[4] The animated simulation is available at http://www.idmod.org/news/node/296 (accessed December 27, 2018).

context studies. This agent-based model is specifically designed to simulate real-world pandemic conditions, Bright said. It simulates the interactions among individuals as they become aware of the pandemic or infection outbreak, which allows people to act in ways that impact transmission.

Layering Interventions to Change the Epidemic Curve

BARDA's goal is to identify the most effective strategies for flattening the epidemic curve that underpins the vaccine-production targets modeled in Figure 4-1; such actions would push the curve outward and thus gain enough time to create vaccines. Bright outlined a set of factors that would contribute to changing the curve by 2030. He said that global collaboration is essential for early outbreak detection and for sharing data, knowledge, and virus samples—all of which are critical for getting ahead of the outbreak curve. He added that individuals also need to be empowered with actionable information so that people have adequate tools to intervene for themselves, take responsible action, and access treatment more quickly. He highlighted that investment in rapid, nimble production platforms for vaccines and for other medical countermeasures will also be critical for changing the curve by 2030.

Bright explained that BARDA considers its agent-based model to be a layered mitigation that uses future technologies to explore the impact of various interventions on the epidemic curve. In particular, it has simulated the impact of three interventions: (1) early detection, which enables earlier treatment initiation, (2) targeted implementation of nonpharmaceutical intervention (NPI) measures, and (3) rapid vaccine and vaccination systems.

Specifically, the first step was to model the impact of early virus detection through at-home diagnostics and wearable devices, which enable earlier disease detection and treatment and may encourage people to take faster action and to seek faster treatment. He explained that at-home technology could send alerts to people who are still pre-symptomatic and notify them if they are exposed to influenza, for example; this alert could be augmented by messaging from local public health entities if there were an outbreak or pandemic in the community. Exposure information could then be shared with people's health care providers through current telemedicine capabilities, and those providers could subsequently prescribe an influenza antiviral that would be delivered via curbside drop-off or drone delivery. He noted that these technologies are not futuristic; they are already in place, and they can enable people to receive faster treatment and to stay home, which may reduce further transmission of the virus. When BARDA modeled those interventions, Bright said, the impact of early antiviral use substantially flattened the epidemic curve by roughly 75,000 new infections per day and shifted the apex of the curve outward to about Day 80.

The next step was to model the targeted implementation of NPI measures. Various studies conducted in isolation have shown reduced transmission from hand hygiene, respiratory protection, confinement at home, school closures, and other interventions. However, because the relative impact levels of those interventions have not yet been established, BARDA combined those interventions in its model. Bright noted that the model assumed that individual agents will have a number of NPI options and that regardless of the specific option(s) they choose, individuals will act responsibly to try to reduce further transmission of the organism. Bright emphasized that the model suggested the synergistic impact of NPIs: When combined with early antiviral treatment, models of NPI implementation significantly flattened the epidemic curve to around 60,000 new infections per day and pushed out the apex of the curve by roughly an additional 50 days. Given the best current efforts at vaccine delivery, he said, this change in the epidemic curve effectively "buys time" for vaccines to become widely available and to begin affecting individuals' exposures.

Vaccines and future vaccination technologies were then applied to the model. Bright noted that significant effort is currently being devoted to developing vaccine technologies, such as using recombinant-based technologies to increase the speed of vaccine production and exploring new ways to distribute those vaccines. He highlighted the importance of investing in technologies that make vaccines available and of investing in the creation of community-level distribution channels that allow vaccines to be administered easily and rapidly—which, in turn, elicits the necessary immune response during an outbreak. When new vaccines and vaccination technologies were added to the model, their synergistic interaction with early antiviral treatment based on early detection and notification and with NPIs dramatically flattened the epidemic curve (see Figure 4-2).

Bright reiterated that a vaccine's impact depends on intervention synergy; in the context of current technologies, a vaccine intervention alone would only slightly—and insufficiently—shift the epidemic curve. The *combined* effects of multiple interventions are what effectively suppress the epidemic curve. Because of this, he explained, it is crucial to create a layered effect in a controlled, coordinated way in order to illustrate the true impact of early antiviral use, combined with NPI, then combined with an effective vaccine.

Potential Areas for Greatest Impact on Building Readiness for 21st-Century Threats

Bright concluded by delineating areas with the potential for the greatest impact on building readiness for threats in the 21st century (see Box 4-2). He noted that addressing end-to-end solutions in pandemic response is an

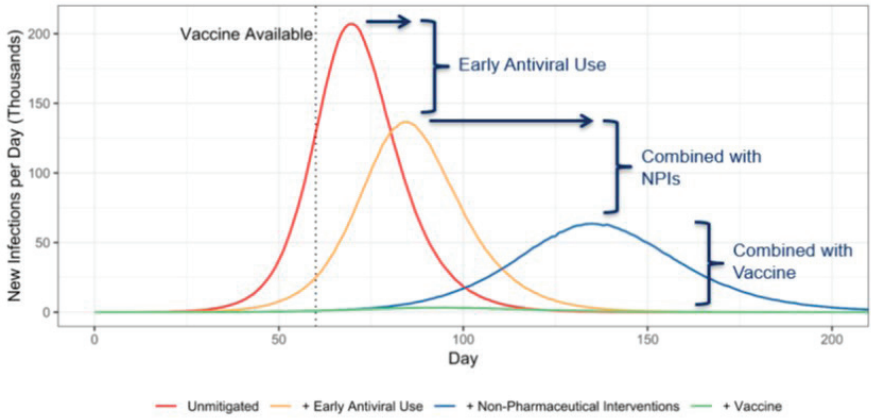

FIGURE 4-2 Combined interventions suppress the epidemic curve.
NOTE: NPI = nonpharmaceutical intervention.
SOURCE: Bright presentation, November 27, 2018.

BOX 4-2
Potential Areas for Greatest Impact on Building Readiness Against Infectious Disease Threats in the 21st Century

- Address end-to-end solutions in pandemic response.
- Cultivate strong leadership structures at the local, community, national, regional, and global levels.
- Foster global collaboration, alignment, and knowledge sharing.
- Simplify and regionalize the production of medical countermeasures.
- Engage in preparedness exercises at local, community, and hospital levels.
- Empower individuals with tools and information, such as at-home diagnostics.

SOURCE: Bright presentation, November 27, 2018.

important area of consideration, and researchers are conducting efforts on multiple fronts. These include cultivating better situational awareness and detection through new technologies; identifying and characterizing the most effective drugs and vaccines; and improving the design, validation, production, distribution, and administration of medical countermeasures. He noted that although each area is ripe for technological innovation, much of the current research is being carried out in isolation, which limits its potential benefit. For example, he explained that faster vaccine production needs to be tied to a faster early-notification system, incorporated into better

distribution channels, and streamlined through improved administration systems. He said, "We have to incorporate every single component of technology into an end-to-end solution, from early situational awareness all the way to the administration of the medical countermeasure."

Bright emphasized that technology alone will not solve a pandemic crisis; response efforts need to be governed by strong leadership structures at the local, national, and global levels. He added that technology needs to be developed and made available in the context of local and national health care systems that are prepared for responses and have the support needed to implement them. Bright surmised that global collaboration and knowledge sharing is likely to be the most important factor in the success of any pandemic outbreak response.

Bright suggested that the production of medical countermeasures needs to be simplified and regionalized, shifting focus from scaling-up to scaling-out. He said it is critical for all countries around the world to have access to vaccines since the efforts of only one country cannot stop a pandemic. It is also important to routinely consider the impact of local-, community-, and hospital-level preparedness and of how such preparedness ties into global mechanisms, he added, because each country cannot have a unique national preparedness-response posture in an effective global effort. He added that this again underscores the importance of ensuring the functionality of global coordination, alignment, and collaboration mechanisms prior to a bioincident through implementing robust national planning and through testing to failure of countries' pandemic response capabilities.

Finally, Bright noted that empowering individuals with tools and information is an important priority for both BARDA and ASPR. He said citizens should no longer need to wait passively for their governments to inform them about or rescue them from pandemics; rather, they should be given response tools that are already available, such as at-home diagnostics or indicators, technology that allows them to tether to a health care system from home, and actionable information in advance of an outbreak around how to reduce personal risk. According to Bright, this type of tool—which empowers the individual—may have the greatest impact on slowing, flattening, and pushing out the epidemic curve. He said:

> As we invest in the large-scale infrastructure and invest in meetings and collaboration around the world at the highest levels of government and down to states and communities, we have to invest just as much in making sure each individual knows their role in a pandemic or emerging disease outbreak.

A CENTURY OF EVOLVING PANDEMICS AND EMERGING INFECTIOUS DISEASE CHALLENGES

Arnold Monto, professor of public health in the Department of Epidemiology at the University of Michigan, presented on a century of challenges created by evolving pandemics and emerging infectious diseases. In order to strengthen responses to future incidents, he highlighted some of the issues around and myths about influenza that have occurred over the years. He also noted that researchers have only recently re-identified important findings about pandemics (i.e., those that have emerged through analysis of past incidents) and remarked, "We keep reinventing influenza . . . if we had a better idea of what went on in the past, we might be better prepared for some of the things that should not be surprises as we go forward."

Responses to Coronaviruses

Monto's presentation focused primarily on pandemic influenza but began with a brief overview of global responses to SARS and MERS outbreaks. He noted that the SARS response in 2003 exemplified how response efforts should be—but often are not—successful. Partly because health teams that were focused on influenza were already in place and primed to respond to a pandemic, SARS coronavirus and its transmission sites were identified relatively quickly (Fouchier et al., 2003; Kuiken et al., 2003). He mentioned that at the initial stage, NPIs were the only available response approaches. SARS differs from influenza in a notable way: Its viral load is lower in the first 5 days of illness. This predicts that transmission is less likely early in the illness, which is supported by epidemiologic data (Lipsitch et al., 2003). Consequently, SARS transmission was mainly nosocomial because patients tended to be hospitalized and to receive invasive procedures during their peak viral load. Researchers determined that transmission could be interrupted if patients were detected early and then isolated.

Because patients flocked to hospitals at the time they posed the greatest transmission risk, community-level transmission of SARS was comparatively rare. This is reflected in the age distribution of SARS cases, which Monto noted was "peculiar" because it skewed so heavily toward young adults—many of whom worked at hospitals or in nursing homes where SARS patients arrived and then transmitted the disease—while sparing the elderly (Xu et al., 2014). People between 20 and 29 years of age were the most frequently affected population, followed by people between 30 and 50 years of age. People younger than 20 and older than 50 years of age were affected in much smaller numbers (Dawood et al., 2012; Simonsen et al., 2013). Monto added that it was difficult to show with serologic studies that young

children were being infected at all. He emphasized the importance of quickly determining the age distribution of an epidemic since that will inform how interventions will be distributed. Regarding the SARS transmission chain, he said it quickly became clear that airline travel was involved in the wide and rapid spread of SARS. The outbreak of SARS in 2003 differed from influenza outbreaks in another way: so-called "superspreaders" were clearly identified and they presented another opportunity for effective use of NPIs. Overall, Monto said, the response to SARS contained the epidemic within one calendar year.

Like SARS, MERS has been associated with nosocomial transmission and with superspreaders. In contrast, the majority of MERS cases occurred among patients who sought care in the same facilities as the index case, but SARS affected a larger proportion of health care workers (Chowell et al., 2015). Furthermore, Monto added that SARS was contained relatively quickly, but MERS is ongoing and that the 2015 MERS outbreak in Korea was particularly devastating. Monto attributed this to a lack of national preparedness capacity to recognize the threat quickly and to contain it early. He observed that the MERS outbreak exemplified how transmission is one of many factors that can complicate effective responses to pandemic and epidemic threats.

Influenza Pandemics of the Past Century

Monto discussed several influenza outbreaks and pandemics over the past century in order to highlight specific lessons that can productively inform future preparedness efforts. He drew lessons from the H1N1 pandemic in 1918, H2N2 pandemic in 1957, H1N1 nonpandemic in 1976, and the H1N1 pandemic in 2009.

1918 H1N1 Influenza Pandemic

Monto noted that the global mortality estimates for the 1918 H1N1 influenza pandemic have changed substantially over the years because the entire developing world was excluded from the initial estimate (around 20 million deaths). However, estimates about the pandemic's devastating impact in developing countries were reported as early as 1927 (Jordan, 1927). For example, Monto said there were more than 12 million deaths in India—more than the bubonic plague—which illustrates how the devastating effect of any pandemic tends to be felt keenly in the world's most highly populated areas and in places where people tend to reside in close proximity.

Monto presented Figure 4-3 to exemplify the famous W-shaped curve of pneumonia and influenza mortality in influenza pandemics. In this type of curve, mortality is high among three age groups: very young children,

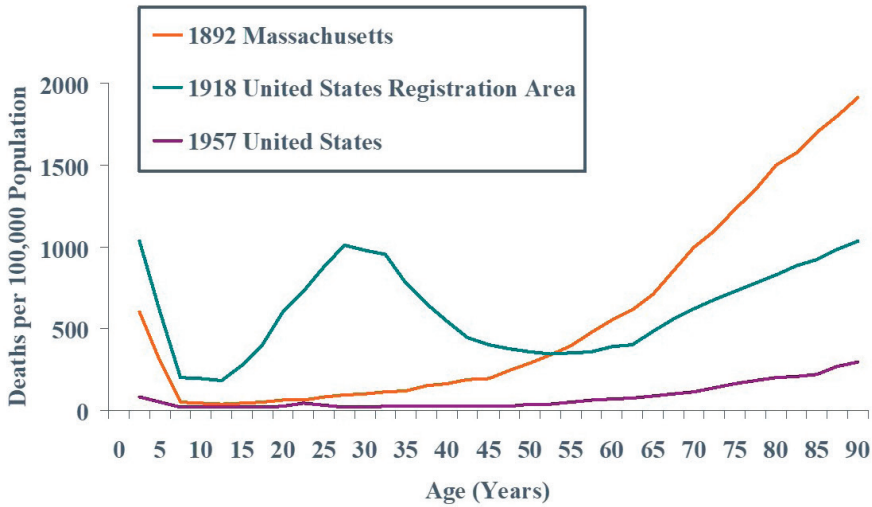

FIGURE 4-3 Pneumonia and influenza mortality in influenza pandemics.
SOURCES: Monto presentation, November 27, 2018; reprinted with permission from the American Thoracic Society. Copyright © 2019 American Thoracic Society. C. C. Dauer and R. E. Serfling/1961/American review of respiratory disease/83/15-28. The *American Review of Respiratory Disease* is an official journal of the American Thoracic Society.

young adults, and very old people (Dauer and Serfling, 1961). A more recent analysis of annualized 1918 data examined age-specific influenza death rates among females in England and Wales during a first-quarter wave of regular seasonal influenza and a fourth-quarter wave of pandemic influenza. This study showed that older individuals were spared, but young children were not (Nguyen-Van-Tam and Hampson, 2003). Monto said that a constant in every pandemic is that young children are at high risk, but this is often overlooked.[5]

Monto described how contemporary literature from the period also reflected that older individuals had been spared. A study among working-class persons covered by industrial policies at the Metropolitan Life Insurance Company (1917 versus 1918) revealed that age-specific excess total mortality rates were greatest among very young children and among people between 20 and 40 years of age (Craig and Dublin, 1919). Monto said the W-shaped curve, which represents what happens when older individuals are spared, was also evident in sex- and age-specific mortality rates for influenza and pneumonia during the Philadelphia outbreak in late

[5] Monto noted that the impact of influenza on very young children is the reason why oseltamivir is now licensed for children as young as 2 weeks of age (Çiftçi et al., 2016).

1918—a time when the death rate was exceedingly high across a 2-week period after a Liberty Bond march.[6] He remarked that these data are providing the foundation for new research. For example, virologists are investigating whether the population was sensitized during the 1889–1892 outbreak. If so, this may be linked to the higher mortality among young adults during the 1918 pandemic. He discussed the myth that the 1918 pandemic caused people to die within 1 or 2 days, and noted that in reality most people died between 9 and 11 days after the onset of illness as patients filled hospitals and strained surge capacity (Roberts, 1919). Pregnant women also experienced high risk during the 1918 pandemic (Jordan, 1927), but Monto added that this trend had to be "rediscovered" during the most recent influenza pandemic.

1957 H2N2 Influenza Pandemic

Monto used data from the 1957–1958 H2N2 influenza pandemic to illustrate how major outbreaks can occur at any time of the year when schools are open. For example, data from the U.S. pandemic that originated in Asia have shown that the incidence first peaked at 6,000 per 100,000 population in October and November 1957, dropped to 2,000 per 100,000 population during the winter school break, and then increased to a smaller peak of 3,000 per 100,000 population in February and March 1958 (Langmuir, 1961).

Analysis of data from the 1957 pandemic revealed the characteristic pattern of morbidity and mortality from influenza (Monto, 1987). A vaccine was eventually available, but it was delayed for 6 months because developers had to adjust its formulation (Murray, 1961). Monto added that this clearly illustrates the need for universal or next-generation vaccines in order to improve response efforts. He said that another observation made shortly after the 1957 pandemic was that ultraviolet lights can reduce the occurrence of an outbreak (Jordan, 1961), but this knowledge was only recently rediscovered by contemporary researchers. In addition, it has become increasingly evident, Monto noted, that some degree of airborne transmission occurs with influenza, which had not previously been supported by available data (McDevitt et al., 2012).

[6] Source: U.S. Bureau of the Census, Special Tables for Mortality from Influenza and Pneumonia, September 1 to December 31, 1918. Available at https://www.cdc.gov/nchs/data/vsushistorical/morttable_1918.pdf (accessed March 22, 2019).

1976 H1N1 Influenza Nonpandemic

Monto also traced the course of the 1976 H1N1 influenza nonpandemic and sought to weigh the risks and benefits of inaction and to illustrate how an outbreak response may be viewed as an overreaction in retrospect. In January 1976, H1N1 influenza was first detected in the United States, and the national response was keen and swift; a program to vaccinate the entire population was announced in March, and vaccinations began in October. However, within weeks after initial vaccinations, it became clear that the influenza vaccine had caused Guillain-Barré syndrome in roughly 1 in every 100,000 people who received it (Escher, 2017). About 450 people developed the disorder before the vaccination program was suspended in December, and the repercussions of this mass vaccination campaign may still affect public sentiment about vaccines to this day (Escher, 2017).[7] Monto stressed that this type of insight was only possible with the benefit of hindsight, and he asked, "If you didn't react and something had happened, what then?"

Reflecting on the prepandemic use of pandemic vaccines, especially when adjuvants are available, Monto noted that vaccines are approved based on which induction of antibody titer researchers consider protective; antigen sparing is not an issue, and manufacturing capacity is generally available. He explained that vaccines can be given alone or combined with other antigens, which is similar to the strategy once used experimentally in the U.S. military. Monto noted that this strategy is currently under serious consideration by governments based on the premise that delivering vaccines to people directly is a better alternative to stockpiling. He said this holds particularly true when they are delivered prior to a pandemic scenario, in which it would be difficult to administer stockpiled vaccines to people in the midst of an incident.

2009 H1N1 Influenza Pandemic

Before examining the 2009 H1N1 influenza pandemic, Monto explained that WHO proposed phases of epidemic and pandemic alert and response in 2008 (see Figure 4-4). Six phases were identified to illustrate the progression of an infectious disease through the peak of an outbreak. The

[7] In a related aside, Monto discussed another example of resistant public sentiment about vaccines. He said some people view any appropriate pandemic planning as a marketing ploy, and often cite a particular publication as a peer-reviewed defense of this position (Doshi, 2013). In fact, the publication is an op-ed piece to argue for the existence of a plot to market antivirals and, to a lesser extent, vaccines. In response, a meta-analysis of oseltamivir data—which Monto deemed unnecessary work—was conducted to show that the already-licensed drug was as good as the clinical trials had shown (Dobson et al., 2015). This type of resistance needs to be considered, he cautioned, in order to prepare researchers to counter "bad science with good science."

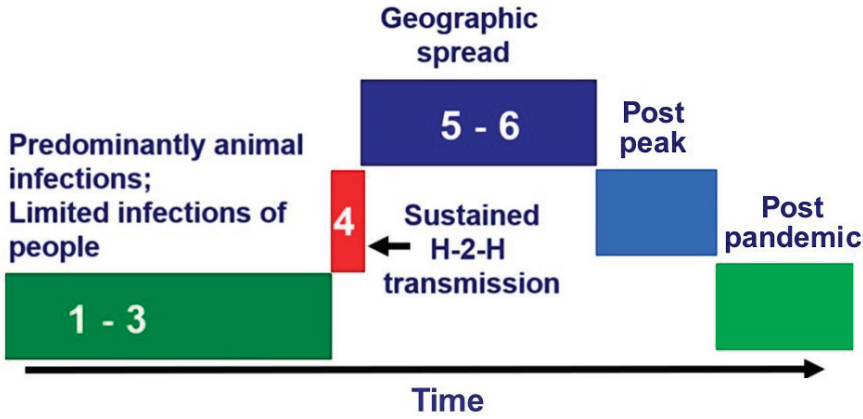

FIGURE 4-4 Proposed phases of epidemic and pandemic alert and response developed in 2008.
NOTE: H-2-H = human-to-human.
SOURCES: Monto presentation, November 27, 2018; adapted from WHO, 2009a. Reprinted from Current WHO phase of pandemic alert for pandemic (H1N1) 2009, Copyright (2009).

first three phases account for the period before sustained human-to-human transmission occurs in the fourth phase. Monto said the International Health Regulations were tested by a pandemic influenza epidemic in 2009, and this shifted the emphasis of response efforts toward the fourth phase. He noted that the fourth phase should be recognized as a key time; it is the point at which the virus becomes transmissible to humans, and health care professionals transition to pandemic preparedness as a result. Monto said current efforts have been situated in an interim scenario between the third and fourth phases for a number of years, and the primary threats of concern have been avian strains from Asia that have not yet exhibited sustained transmission in humans. He explained that sustained transmission is a bellwether: If a community-level outbreak were detected, and sustained human-to-human transmission were to occur, it would trigger urgent decisions about particular considerations (e.g., rapid containment and use of a pandemic vaccine). Monto explained that it remains impossible to predict when transmission is most likely, even when molecular work shows that resistance and transmission are possible. Consequently, he added, it will be necessary to prepare every time a potential threat arises, at great labor and expense, until the advent of a universal vaccine.

Monto explained that the 2009 H1N1 influenza pandemic occurred in two waves and that the second was a resurgence when schools opened in the autumn (Jhung et al., 2011). Similar to the 1918 pandemic, older people

were spared, and younger populations were hit hardest. Unlike the 1918 pandemic, he noted, some otherwise healthy young adults were at greater risk of a severe reaction or cytokine storm, but the mechanisms underlying that risk have not been identified. He added that pregnant women were discovered to be at higher risk during the 2009 pandemic—the same as in the 1918 pandemic—and that the entire program of antiviral distribution had to be adjusted (Louie et al., 2010). Indigenous populations in Canada were also found to have greater susceptibility for reasons that may include their living conditions, nutrition, genetics, or a combination of these (Kumar et al., 2009). Monto said that specific at-risk populations were identified in parallel all over the world and that this poses an important consideration for response elements (e.g., prioritizing the distribution of interventions).

Observations on a Century of Facing Evolving Pandemic and Emerging Infectious Disease Challenges

Monto concluded his presentation with a set of observations gleaned from a century of facing evolving pandemic and emerging infectious disease challenges. First, he said that although the clear virologic definition to describe what is a pandemic is no longer certain, the defining element should be that the virus is novel for much of the population. He noted that some people have questioned whether the 2009 H1N1 incident was a pandemic because it was not characterized by a new subtype of influenza. However, he noted that pandemics clearly occur through other mechanisms, such as when an avian segment enters the human population. The real matters of importance, he argued, are the antibody prevalence within a population and the likelihood that the virus will spread and cause a severe impact.

Second, he observed that the 1918 influenza pandemic remains an outlier in terms of morbidity and mortality. Although certain elements were repeated in the 2009 H1N1 incident, they were greatly reduced. Despite this, Monto cautioned that preparing for devastating epidemics remains a critical policy consideration. He also observed that each pandemic has unique characteristics, which makes complete generalization impossible and highlights the importance of early disease characterization. CDC has developed early assessment strategies to predict how a pandemic will progress and which populations it will affect. However, he added, these strategies are not infallible, and being nimble and being able to adjust to response efforts is critical. Finally, Monto observed that all modalities for intervention are imperative. If prior surveillance is sufficiently good, he said, some vaccines may even be made available in advance. NPIs are also crucial and warrant further evaluation, but Monto warned that high scientific standards for study designs have been set for this type of research, and they can be difficult to meet.

DISCUSSION

During the discussion, Peter Daszak, president of EcoHealth Alliance, asked Bright about progress toward high-tech solutions that promise to radically change the way diseases are diagnosed, such as new rapid and remote technologies. Bright responded that progress in this realm has been made in stages over the years and has included efforts to build centralized laboratories, large public health centers, and hospital laboratories; diagnostic technology has now filtered down to regional laboratories and to smaller units in "minute clinics" and mobile pharmacies. He said the next step is to push new diagnostics into people's homes, but this raises concerns related to specific organisms, diseases, and outbreaks. With influenza, for example, there are concerns about how an individual might deal with a false-positive or a false-negative result. He said that risk–benefit analyses will be necessary to examine the consequences of starting unnecessary antiviral treatment based on false-positive tests. A concern, he explained, might be whether that outcome would promote antiviral resistance or squander limited supplies of a therapeutic resource in a pandemic context. Bright said that his agency's broad aim is to encourage individuals to take responsible action to reduce transmission and to seek earlier antiviral treatment.

Furthermore, Bright noted that the capacity to miniaturize molecular technology to an affordable home-based system already exists, and the next step for at-home technologies is wearable devices. However, introducing such technology into homes creates another challenge: tethering the technology to a health care provider. He said tethering is important for individuals who receive a signal from an at-home device that instructs them to seek health care intervention. A notification pathway should be in place so that information from the indicator is coupled with a larger community database of health care. He said the current challenge is to identify appropriate biometrics within the regulatory pathway that can be coupled with an at-home test or with another type of intervention that occurs between an individual's home and a doctor's office. According to Bright, a plethora of wearables (e.g., tattoos, bandages, stamps, watches, rings, earrings, ear plugs) are already available and are being used to measure things that are "interesting but often useless." The key is that these wearables motivate people to change their behaviors. He posited that similar technologies on the horizon will have huge potential during an outbreak, by indicating and motivating people to change their behaviors and to help create barriers to transmission.

Suerie Moon, director of research at the Global Health Centre of The Graduate Institute of International and Development Studies, remarked that layering mitigations—that is, implementing four or five different strategies at once—is feasible for a pathogen like influenza, which is well

understood, and in the context of a country such as the United States, which has relatively high technological development. However, she noted that pathogens and outbreaks also occur in countries where layering is not practical. Moon asked how response planners should prioritize interventions that are especially synergistic in settings where layering is not feasible.

Bright noted that although the United States appears to have the capacity and knowledge to do so, interventions in the country remain unlayered because layering requires extensive coordination and preparation from individual to federal levels. He explained that the concept of community-level mitigation, coupled with individual-level mitigation, is not commonly accepted, and efforts are generally not well coordinated—even in highly developed countries. He suggested prioritizing NPIs, especially in situations in which a novel organism emerges. Bright cautioned that the dataset for NPIs is not strong, but public messaging still needs to be supported by data; people must trust that the advice they receive will have an impact. The simple act of hand washing tremendously reduces virus transmission. He also noted that efforts are under way to reimagine respiratory protection technology (e.g., masks and respirators), which has remained largely unchanged for the past 50 or more years. He added that the best improvement in respiratory protection might actually be hand sanitation since people who wear masks take them on and off repeatedly, and this action can spread a virus or organism from a person's hands to the person's face and therefore transmit an infection. He advised that layering strategies for NPIs should be prioritized as well as better understanding the context of actions and behaviors related to NPIs.

5

Building Local and National Capacities for Outbreak Preparedness

After the opening presentations, the workshop's first session covered major lessons learned from a century of major outbreaks and pandemics, examining the advances that have been made and lessons that still need to be applied from the local to national to global levels. Specifically, session 1 part A focused on the panelists' experiences with strengthening local- and national-level capacities after different types of outbreaks in diverse country contexts. Moderator Suerie Moon, director of research at the Global Health Centre, The Graduate Institute of International and Development Studies, emphasized that community- and national-level preparedness serve as the first line of defense against any infectious disease outbreak, a concept that was codified in the 2005 revision of the International Health Regulations (IHR) in the aftermath of the severe acute respiratory syndrome (SARS) outbreak. National-level preparedness is important not only for particular countries, she said, but also for the global community at large; building an adequate minimum level of capacity to prevent, detect, and respond to public health risks has become an international obligation. After the Ebola crisis of 2014, efforts to strengthen accountability among countries with respect to national-level preparedness gathered momentum through the World Health Organization (WHO) Joint External Evaluation (JEE) process (WHO, 2016a). She explained that this voluntary, collaborative peer-review process that assesses national capacities to prevent, detect, and respond to public health risks has contributed to strengthening political will and encouraging investment in national preparedness capacities. Moon called this one of the most significant reforms that occurred in the wake of the Ebola epidemic, but noted that sustaining

the necessary funding, political attention, and leadership for investing in those capacities remains a challenge and looked forward to the panelists' perspectives on this matter.

The first panelist, Abdullah Assiri, assistant deputy for preventive health at the Ministry of Health, Saudi Arabia, discussed lessons learned from the emergence of Middle East respiratory syndrome (MERS) in Saudi Arabia in 2012 and changes that have been made in the country's public health systems in the past few years. Mosoka Fallah, deputy director general for technical services of the National Public Health Institute, Liberia, described the lessons learned from the Ebola outbreak of 2014 and progress made in developing core capacities to respond to future outbreaks in Liberia. Gabriel Leung, dean of medicine at The University of Hong Kong, reflected on how Hong Kong's public health capacity-building efforts have strengthened since the SARS outbreak in Hong Kong in 2003. Finally, Amanda McClelland, senior vice president of Prevent Epidemics at Resolve to Save Lives, offered insight about her experiences working on the frontlines with international organizations and local communities during outbreaks and about her perspective on how to build local and national preparedness capacities.

LESSONS FROM THE MIDDLE EAST RESPIRATORY SYNDROME OUTBREAK IN SAUDI ARABIA

Abdullah Assiri, assistant deputy for preventive health at the Ministry of Health of Saudi Arabia, described the MERS outbreak in the Kingdom of Saudi Arabia. MERS, a viral respiratory illness caused by a novel coronavirus (CoV), was first reported in Saudi Arabia in 2012, and by the end of 2018, more than 2,200 laboratory-confirmed cases of MERS were reported, around 85 percent of the cases issued from Saudi Arabia.[1] MERS has not been eliminated, but infection prevention practices have brought the outbreak under control, and currently the case fatality rate is stable at around 35 percent.

Although the toll of MERS has been difficult for Saudi Arabia, Assiri said the outbreak has positively transformed the country's public health system. A public health emergency operations center initially established to respond to MERS-CoV has since expanded its function and scope to include all infectious disease hazards, with 20 regional incident command systems across the country, reported Assiri. In addition, the laboratory system has been upgraded to improve detection of MERS, and a nationwide system to transport biological samples is now in place. Most MERS outbreaks in Saudi Arabia were associated with health care facilities, he noted. Although

[1] WHO's current MERS surveillance information is available at https://www.who.int/emergencies/mers-cov/en (accessed January 29, 2019).

human-to-human transmission of MERS is typically limited, it is more common in health facilities because patients with MERS-CoV are typically admitted when they are at the peak of their infections and are more likely to transmit the disease to other people in the facilities (WHO, 2016b). In response, the government has invested in upgrading the infection control infrastructure. Assiri reported that tens of thousands of health care workers have been retrained on basic infection control skills, including respiratory protection and environmental contamination procedures. Health care facilities are externally audited four times per year to ensure compliance with basic infection control standards, he added.

Leadership in Saudi Arabia is committed to advancing emergency preparedness in its public health agenda, said Assiri. High-ranking officials have been repositioned to better respond to MERS, and on multiple occasions, leaders have participated in public health emergency drills related to antimicrobial resistance and respiratory outbreaks. To address MERS, he explained that the government has also created a high-level, multidisciplinary One Health team comprising experts from three ministries directly related to zoonotic diseases.

While the scientific community in Saudi Arabia has learned from the experiences of MERS-CoV and has moved into a stronger position to prepare for, detect, and respond to infectious disease threats, they have continued to struggle with two country-specific challenges related to infectious disease transmission and outbreaks. One challenge is the risk of transmission in mass gatherings (see Box 5-1), and the other is the prevalence of coronaviruses among camels in the country. Assiri reported that Saudi Arabia has more than 2 million camels, but many are hyperinfected with MERS. The animals do not appear to have long-lasting immunity to coronaviruses and therefore can become reinfected multiple times. Camel-to-human transmission of MERS-CoV is a major concern (Alshukairi et al., 2018). Assiri said health professionals are exploring camel vaccination and are conducting trials of potential therapeutic options, but this is challenging because of the complexity of the camel immune system and the technical difficulties related to dealing with such large animals.

LESSONS FROM THE EBOLA VIRUS DISEASE EPIDEMIC IN LIBERIA

Mosoka Fallah, deputy director general for technical services of the National Public Health Institute, Liberia, reflected on his country's experience during and after the Ebola outbreak of 2014–2016. By September 2014, Liberia accounted for more than half of Ebola cases in West Africa (CDC, 2014). Fallah described Liberia as a prime example of a country with a weak health system that was unprepared to deal with a crisis. When

BOX 5-1
Risk of Influenza Transmission in Mass Gatherings

The heightened risk of influenza transmission during mass gatherings is a specific health risk in Saudi Arabia (Ahmed et al., 2006). Saudi Arabia is the site of Hajj, an annual religious mass gathering that attracts around 3 million people from more than 180 countries to congregate in a crowded setting for 3 to 5 days. The Hajj follows the lunar calendar, so every 33 years, it shifts completely from summer to winter, during which time there is an additional risk to transmission control efforts. People come for the Hajj from both the northern and southern hemispheres, so regardless of when the Hajj occurs, many people visit from areas where influenza activity is at its peak (Ahmed et al., 2006). Because of the size of this mass gathering, it can be challenging to implement certain public health interventions, such as offering the influenza vaccine to all attendees. The government has mandated vaccination for Saudi Arabians who participate in the Hajj—a group that represents around 20 percent of attendees—but it is difficult to mandate vaccination for attendees from outside the country (WHO, 2017a). Challenges to be addressed include the logistics of developing the vaccine in time, having enough vaccine available, and controlling the cost of the vaccine.

SOURCE: Assiri presentation, November 27, 2018.

the Ebola outbreak struck, the country's poor health infrastructure and limited laboratory capacity delayed detection of the disease and precipitated its transmission. The nearest laboratory with diagnostic capabilities was in Guinea, requiring staff to make a 2-week journey to transport samples back and forth. Because Liberia lacked trained epidemiologists and surveillance officers at the time, the spread of the outbreak from rural areas into populous, urban centers was unmitigated, and transmission escalated quickly. High rates of nosocomial infection also accelerated transmission of the disease. A large proportion of health care providers in the country became infected, and many became superspreaders (Lau et al., 2017).

According to Fallah, Liberia took bold and innovative steps to respond to the outbreak that helped Liberia become the first country in the region to be declared Ebola free. For example, a lack of national protocol regarding risk communications led to initial mistakes in public messaging, but these were modified to provide a positive effect. At the beginning of the outbreak, the public was told that they would die if they contracted Ebola, which discouraged patients from seeking treatment and facilitated disease transmission. When public messaging changed to encourage patients to seek treatment early to increase their chances of survival—coupled with positive stories of people who survived the disease—people were more willing to seek care in treatment units (Schwerdtle et al., 2017). Liberia also

invested in creating comfortable care environments for people who were being treated for Ebola. In addition, a point-of-care diagnosis innovation enabled health workers to draw blood in the field, which helped end the outbreak in Liberia; it reduced the turnaround time for diagnostic testing to 2 hours versus the 6 hours required for polymerase chain reaction testing (Nouvellet et al., 2015).

Liberia's progress around developing core capacities to respond to future outbreaks is the silver lining of the country's Ebola outbreak, said Fallah. He described some of the lessons learned during the Ebola outbreak, and practices that have since been introduced. To alleviate the burden on the Ministry of Health, Liberia created an independent National Public Health Institute in 2017 to carry out surveillance and develop laboratory capacities. The institute now has the ability to test for seven pathogens and has responded to 39 outbreaks thus far. Its response turnaround times to non-Ebola outbreaks are of less than 1 week (NPHIL, 2017). Liberia had two resurgences of Ebola in 2017, both of which were contained within 3 weeks and provided an opportunity to carry out trials of new vaccination strategies (NIAID, 2017). Because of improved early detection capabilities, survival rates for Ebola have increased dramatically, and Liberia is now able to deploy the ZMapp[2] vaccine as a complementary countermeasure (Nyenswah et al., 2016). Fallah added that the development of sensitive surveillance systems and robust laboratory capacity have enabled the country to quickly and effectively contain recent cases and outbreaks of yellow fever, Lassa fever, and monkeypox. Strategies to further institutionalize preparedness include testing the system at least once per year and convening weekly meetings with partners across relevant sectors from logistics to coordination. Liberia is now ready to shift immediately from preparedness to incident management when an outbreak occurs, Fallah said. However, the country's reliance on foreign donors for logistics and reagents is a challenge that remains to be addressed.

LESSONS FROM THE SEVERE ACUTE RESPIRATORY SYNDROME OUTBREAK IN HONG KONG

Gabriel Leung, dean of medicine at The University of Hong Kong, presented on the lessons drawn from the 2003 outbreak of SARS in Hong Kong. Like other affected areas—including Canada, Mainland China, Singapore, and Taiwan—Hong Kong did not have the necessary capacities

[2] ZMapp is a vaccine made of three different monoclonal antibodies, designed to prevent the progression of Ebola virus disease in the body by targeting the main surface protein of the Ebola virus (NIAID, 2016).

in place to respond to the outbreak.[3] In the aftermath of SARS, Hong Kong established a new national health agency, the Center for Health Protection, and created new regional- and national-level liaisons with Mainland China to facilitate communication and coordination among their regulatory sectors for health, food, and commerce. Subsequent changes have included supply-chain management through farm registration, pre-import testing, and quota controls for farm animals that are integral to the influenza transmission cycle, such as poultry and swine.

Leung described some of the capacity-building efforts that have been implemented in Hong Kong since the 2003 SARS outbreak in order to reduce infectious disease transmission, improve public messaging, strengthen early detection, and build laboratory capacity. A set of progressive interventions was implemented in local farm wholesale and retail poultry markets to reduce influenza transmission. The first intervention introduced a rest day once per month to allow retail markets to be cleaned, but this was not sufficiently effective, so the rest-day frequency increased to every 2 weeks. This generally reduced transmission to acceptable levels, but outbreaks were still occurring. However, the transmission rate dropped to almost zero when Hong Kong introduced a policy that prohibited live poultry from being kept in markets overnight (Peiris et al., 2016). Figure 5-1 illustrates the impact of the progressive introduction of these measures targeting poultry markets on the tracer influenza virus isolation rate. Other efforts in Hong Kong have included proactive health communication regarding messaging, behavior surveillance, and engagement with the public. Since public hospitals account for more than 90 percent of all admissions in Hong Kong, seasonal influenza surges are addressed through a universal policy of screening all febrile respiratory admissions in public hospitals. In terms of laboratory capacity building, Leung said that Hong Kong has a high density of biological safety level-three laboratories, as well as a WHO Collaborating Center and two WHO-designated H5 reference laboratories with a mandate to provide WHO with data and risk assessments on H5 and other animal influenza viruses (HKU, 2019).

Leung then described Hong Kong's response to two infectious disease events that have occurred since the 2003 SARS outbreak. During the pandemic H1N1 outbreak in 2009, an entire hotel was quarantined for 1 week, schools were closed early, and a proactive public communication strategy was tested; these efforts helped to delay local transmission by 40 days (Wu et al., 2010). Subsequent evaluation has shown that school closure reduced transmissibility by 12–25 percent (Jackson et al., 2014).

[3] Leung noted that all of those affected countries subsequently replaced their top echelons of health officials, and they either established post hoc national health agencies or transformed their existing national health agencies.

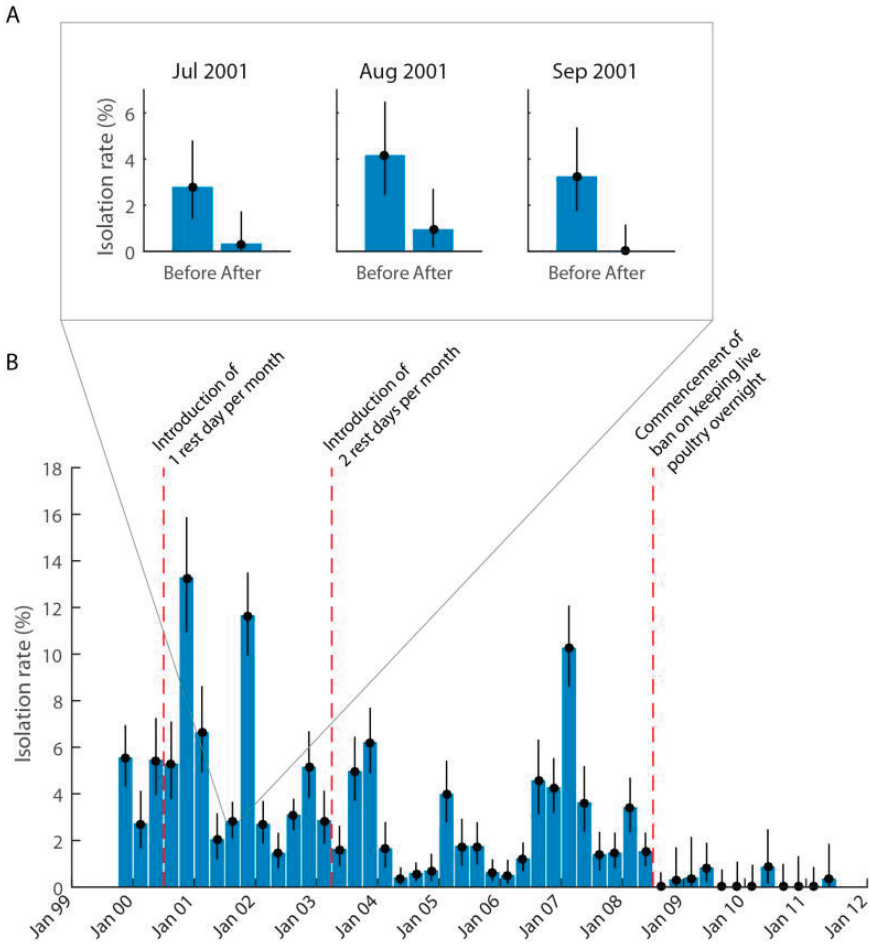

FIGURE 5-1 Progressive introduction of market-based interventions in Hong Kong to help reduce influenza transmission.
SOURCES: Leung presentation, November 27, 2018; reprinted from *The Lancet*, Vol. 16, Malik Perkis et al., Interventions to reduce zoonotic and pandemic risks from avian influenza in Asia, 252–258, (2016), with permission from Elsevier.

However, he noted that only during the H1N1 pandemic did school closures substantially reduce transmission. When schools were closed on two other occasions in 2008 and 2018, this intervention was associated with only modest reductions in transmission of 4 percent or less (Cowling et al., 2008; Ali et al., 2018). Vaccination efforts were carried out during the 2009 H1N1 pandemic response, he added, but it was "too little too late," and

most of the vaccines the government purchased were not used. Although the 2013 H7N9 outbreak did not reach Hong Kong, Leung and his colleagues contributed to the regional outbreak response in and around Shanghai. Leung and his colleagues helped to report on the first series of clinical cases, to determine the pathogenesis of the H7 subtype, to characterize the epidemiology of H7, and to examine the potential impact of closing poultry markets (Chen et al., 2013; Cowling et al., 2013; Hu et al., 2013; Yu et al., 2013, 2014). Reflecting on the progress made in Hong Kong over the past 15 years in terms of building the capacity to respond to infectious disease outbreaks, Leung believed it could be achieved in other countries and could lead to improved pandemic preparedness on a global level.

LESSONS FROM WORKING IN THE FRONTLINES WITH LOCAL COMMUNITIES AND INTERNATIONAL ORGANIZATIONS

Amanda McClelland, senior vice president of Prevent Epidemics at Resolve to Save Lives, reflected on her global experience working at the interface of communities and health systems. After years focused on engaging community and health care workers, she has come to realize that capacity building and shifting the course of an epidemic ultimately sits with politicians. McClelland said national governments and public health professionals tend to wait until a crisis occurs to build capacity, creating a cycle of panic and neglect in which public health workers are sidelined during periods when the necessary capacity building could be achieved. Shifting the conversation to engage politicians and communities would help break this cycle, she suggested (see Chapter 8 for more on breaking this cycle of panic and neglect). However, the preparedness enterprise is complex and difficult to explain to politicians and decision makers. For example, the JEE contains 19 technical areas and 54 indicators; national preparedness action plans may have more than 400 priority actions for the first year alone.[4] A program manager in a low-resource country may be tasked with coordinating six ministries over 200 or 300 priority preparedness actions. McClelland noted that countries furthest away from a sufficient level of preparedness are even less likely to have political buy-in and financial resources needed to build and support complex systems that are IHR-ready.

McClelland mentioned that Resolve to Save Lives would like to see a reduction of the number of requisite capacities and to prioritize core activities for preparedness. Ideally, this process would engage with communities in under-resourced countries to help them detect, prevent, and respond to outbreaks. For example, Resolve to Save Lives has been working to reduce

[4] For more information on the JEE components, see https://www.who.int/ihr/procedures/joint-external-evaluations/en (accessed February 8, 2019).

the 400 priority actions to an essential set of 50 actions that are focused on seven of the 19 technical areas within the JEE (Vital Strategies, 2018).[5] The main focus has been on building response, surveillance, laboratory, and health workforce capacities, then using legal and financial preparedness and risk communications to lever those capacities. McClelland said the legal and finance indicators within the JEE have posed barriers to moving forward because if countries do not have the mandate to declare emergencies, it is difficult to generate financing and gain political buy-in for preparedness. She added that improved capacities can potentially be problematic to explain to politicians. For example, if improved detection increases the frequency with which high-profile infectious disease outbreaks are declared, then political leadership may question the effectiveness of preparedness efforts. Capacities to report evidence and support politicians and policy advisors should be built in conjunction with the capacity to detect outbreaks, she suggested.

McClelland remarked that some capacities related to prevention, early detection, and response components are missing or not prominent enough in the JEE and IHR frameworks, even though these frameworks are helpful tools. For instance, the JEE is designed to ensure that countries can be IHR-compliant, but IHR compliance is not necessarily analogous to epidemic preparedness. With respect to the JEE, she noted that infection prevention and control components are not prominent, nor are capacities for frontline health care workers to detect, respond, and engage with communities during an outbreak. The Ebola outbreak in the Democratic Republic of the Congo is an example of the importance of empowering frontline health workers to deliver epidemic care, she highlighted, especially in conflict or hard-to-reach areas that should be accessible without depending on a regional or an international response. Furthermore, the JEE does not emphasize the role of civil society or how governments can engage with non-traditional partners. She suggested that these core capacities should be built by working within the JEE structure while still bearing in mind the lessons learned from past responses.

DISCUSSION

Remarking on the presentations, Suerie Moon, director of research at the Global Health Centre, The Graduate Institute of International and Development Studies, observed that the improvements in capacity building and knowledge gathering described by panel participants are grounds for optimism, but a number of challenges persist. Realistically, it is unlikely

[5] The Resolve to Save Lives platform with resources and JEE country data can be found at https://www.preventpandemics.org (accessed February 26, 2019).

that outbreak preparedness will remain high on the political agenda, so any short window of opportunity should be exploited in order to institutionalize change (e.g., new funding commitments, procedures such as the JEE, or national public health agencies). Although such windows of opportunity usually occur after a crisis, she was hopeful that a recent reform aimed at strengthening international accountability through the Global Preparedness Monitoring Board, organized by WHO and the World Bank, would help to institutionalize attention on existing weaknesses (see Chapter 2 for more on this board). Moon also observed that national capacity building warrants improved international support. For instance, accountability for preparedness varies widely across countries, with fewer than half of member states having participated in the JEE process. She highlighted the risk posed by harmful competition among different health agendas. For investments in preparedness to be politically sustainable, they should deliver tangible benefits for populations in the form of better health care today, not only during a crisis. Resource-constrained communities should not have to choose between day-to-day health care delivery and preparedness, she said, so investments should serve to strengthen both capacities.

Current National Challenges to Manage a Potential Major Disease Outbreak

Moon asked Fallah, Assiri, and Leung about the current state of preparedness at the national level, including challenges they continue to face. Specifically, she asked Fallah how national public health institutes in resource-constrained settings might encourage investment in preparedness, despite competing priorities related to the day-to-day provision of health care services. Fallah explained that Liberia's National Public Health Institute was created when the Ebola crisis demonstrated that public health threats could cripple the entire health system. The institute was developed to focus specifically on developing an early warning and surveillance system, and its initially committed budget has already faced potential cuts. Liberia's preparedness is fragile, he said, because the system is heavily dependent on donor funding, and any funding change can severely hamper its preparedness. Long-term funding mechanisms are needed to improve stability, he said. Liberia's preparedness is also skewed toward public health response to infectious disease outbreaks while multi-hazard response preparedness remains weak. Although diagnostic capacity has improved, he noted response is generally initiated only after multiple patients have died, rather than detecting patients at an early stage. Fallah agreed with Moon's earlier comment that a balance needs to be struck between investment in preparedness and investment in day-to-day health systems that are critical for the population's health and for reducing the transmission of infectious diseases.

Given the measures in place to reduce the level of infections from MERS, Moon asked Assiri about the extent to which MERS has become normalized as a semi-permanent fixture in the health landscape of Saudi Arabia. Assiri said that MERS continues to be a public health threat because of the continuous spillover of the virus from camels to humans. Although Saudi Arabia's investment in improved infection control within health care facilities has strengthened its preparedness to control future outbreaks, improvements in preparedness have not yet expanded to other infectious diseases or hazards, because efforts have focused primarily on MERS. For example, Saudi Arabia has largely reduced the risk of animal-to-human transmission of MERS by enacting laws to prevent the importation of camels into the Hajj area; as a result, he said influenza transmission is a greater concern during Hajj than MERS-CoV.

Moon asked about Hong Kong's overall state of preparedness for a major infectious disease outbreak. Leung responded that Hong Kong is not actually as prepared for a large-scale event as it would seem. A country is only as safe and secure as the weakest link in its entire area, he noted, and Hong Kong's population represents just 10 percent of the roughly 80 million people who live in the network of interconnected cities and villages in the Pearl River Delta (Cooper, 2014). Furthermore, Hong Kong imports about 95 percent of its food, which compromises its security from a One Health perspective (USDA Foreign Agricultural Service, 2017). In addition to directly transmissible respiratory pathogens, vector-borne diseases are also a major concern in the region.

Engaging and Motivating Communities and Politicians for Preparedness

Moving on to the topic of motivating communities and decision makers for preparedness, Moon asked McClelland about challenges related to engaging, mobilizing, and communicating with communities in settings with weak social cohesion, such as conflict or post-conflict areas. McClelland replied that communities with weak social cohesion tend to unify around a common cause when a natural disaster occurs, but such collaboration does not often occur in an epidemic response. In fact, existing social cohesion can easily be compromised by mistrust and poor messaging during a major epidemic. She noted that the social science component of epidemic response—which is often relegated to risk communications—should be centralized in emergency operations as part of incident management and should be leveraged in every pillar of a response. Because of the constant flux in social cohesion and the relevance of social science to both pharmaceutical and non-pharmaceutical interventions (e.g., vaccination, school closures, and handwashing campaigns), she suggested

that social science should be integrated into behavioral measures and used to monitor social cohesion in relation to the dynamics of transmission.

Jonna Mazet, executive director of the One Health Institute and professor of epidemiology and disease ecology at the University of California, Davis, added that politicizing diseases can lead—and has led—to misinformation, divisiveness, and mistrust that negatively impact future interventions. She asked how the global health community could empower communities to embrace prevention and preparedness while also limiting that political posturing. Following up, Keiji Fukuda, director and clinical professor, School of Public Health, The University of Hong Kong, asked panelists about the factors that can drive decision making and progress in capacity building for preparedness, without relying on a crisis as the catalyst.

Leung said it is easier to persuade countries to invest in preparedness if they have experienced multiple major outbreaks, particularly those with severe economic and political impacts. For countries that have not experienced such catastrophes, he said, it could be helpful to highlight the experiences of countries that have, in order to motivate precautionary investment in preparedness. Local governments can take action through three levels of engagement, Leung explained. One level is to communicate through media, especially social media, to directly and proactively engage with the population so that they will lobby politicians about the importance of pandemic preparedness. The second level is to forge relationships and exchange information with the global health community at the technocratic level. These crucial relationships may lead to building capacity during interim periods or may emerge as a result of simultaneously having experienced a major epidemic. The third level is to use supranational or multilateral agencies to promote the importance of preparedness in international fora. Although this approach may not result in much change on the ground or at the technocratic level, he said, the political significance of raising the issue is a kernel that can be followed up.

Assiri commented that advocacy for preparedness requires keeping decision makers on their toes—for example, seven ministers were replaced in Saudi Arabia due to the MERS outbreak. This directly led to a sevenfold increase in the public health budget between 2012 and 2018, he stated, and it also changed the way that other diseases are addressed. He suggested that momentum can be maintained by media engagement and by keeping public health at the top of the government's agenda. Assiri added that the JEE process has also been helpful in fostering political leadership's interest in public health. McClelland noted that the JEE was not designed to pit countries against each other, but competitiveness in preparedness has emerged as a motivating factor that will help to compare progress among countries as the JEE process enters its second round. Fallah remarked

that politicians' tendencies to focus on the economic impact of diseases could be leveraged to encourage preparedness. However, now that more sensitive surveillance systems are enabling more diseases to be detected, some countries have become concerned about sharing outbreak-related information that may have economic and security-related implications. This has posed a challenge to regional efforts to build capacity in Africa, he said, and there is a delicate balance to strike between countries' rights to protect sensitive information and the global community's need for information about outbreaks.

McClelland observed that the perception of risk—of an epidemic or of potential economic loss—is the biggest entry point for mobilizing governments and communities and for motivating change. Thus, as Leung indicated, it is difficult to mobilize effectively unless there has recently been a major risk, she said. At the community and government levels, people tend to focus on balancing risks and prioritizing behavior change. In terms of public health, it is difficult for a politician to prioritize investing in an emergency operations center that is activated only once per year over investing in maternal and child health; similarly, she added, it is easier to mobilize a community to demand better maternal and child health care than to demand better infectious disease outbreak preparedness. She underscored that motivating investment in preparedness needs to be country- and community-specific, and suggested taking a strategic view—country by country and community by community—to assess the risks, risk perceptions, and choices that communities and governments make to prioritize preparedness above other health risks or other economic or safety risks.

Finally, Dennis Carroll, director of the Global Health Security and Development Unit of the U.S. Agency for International Development, added that the private sector could be leveraged more effectively to boost preparedness efforts. He remarked that the SARS outbreak had a large impact on the global supply chain and that the Ebola outbreak motivated collaborative action from the extractive industry and agribusiness sector, which recognized the risk and self-mobilized to try to mitigate it. He suggested the power of the business sector could be harnessed in its own self-interest for risk mitigation, for example, through business continuity plans and the sector's influence on politicians and communities.

6

A Spectrum of Considerations for Pandemic Vaccines

Session 1, part B of the workshop explored major lessons related to a spectrum of challenges for pandemic vaccines based on the 2009 H1N1 influenza pandemic. Moderator Jacqueline Katz, deputy director of the Influenza Division of the U.S. Centers for Disease Control and Prevention (CDC), explained that vaccination is the most effective method for preventing influenza-related complications. However, the development and delivery of vaccines is challenging, particularly during a pandemic, because vaccines need to be available in a timely manner to mitigate the height of illness. The 2009 H1N1 influenza pandemic, as an example, illustrates the complexities and challenges related to pandemic vaccines. In the United States and in Hong Kong, the first vaccines became available at the peak of the major pandemic wave, when it was largely too late for vaccines to provide protection. Closing this timing gap, Katz said, will require improvements in vaccine development, production, and distribution. During the 2009 pandemic, for example, challenges arose at almost every step of the vaccine process: strain selection, manufacturing, potency testing, regulatory approval, and clinical trials to determine dosing. After the vaccine became available, further challenges hampered the logistics of vaccine distribution and administration; post-vaccination safety issues also arose in some countries. Many countries entirely lacked access to vaccines, and vaccine donation programs that attempted to bridge this gap in equity also faced challenges from the lack of local-level infrastructure to accept, deliver, and administer vaccines (Broadbent and Subbaro, 2011; HHS, 2012). Panelists who had experience working with the World Health Organization (WHO), private-sector companies, nonprofit organizations,

and governments shared their perspectives on progress made over the past decade and remaining challenges and opportunities for pandemic vaccines.

The first panelist, Wenqing Zhang, manager of the Global Influenza Programme at WHO, described the role of global coordination in vaccine development and focused on the Global Influenza Surveillance Response System (GISRS). Karen Midthun, senior advisor of the Center for Vaccine Innovation and Access at PATH, illustrated the regulatory considerations of vaccine development. A perspective from the pharmaceutical industry on pandemic vaccine manufacturing was provided by Clement Lewin, associate vice president of research and development strategy at Sanofi Pasteur. Bruce Gellin, president of global immunization at Sabin Vaccine Institute, focused on the importance of vaccine timing in response to a pandemic. Finally, Steven Solomon, principal legal officer at WHO, surveyed some legal considerations related to vaccine response.

GLOBAL COORDINATION IN VACCINE DEVELOPMENT: A SNAPSHOT OF THE GLOBAL INFLUENZA SURVEILLANCE AND RESPONSE SYSTEM

The past century of infectious disease outbreaks and pandemics has underscored how many population health problems, such as influenza, must include international collaboration and coordination, said Wenqing Zhang, manager of the Global Influenza Programme at WHO. The international community did not begin taking action on this front until 30 years after the 1918 pandemic, when the WHO Constitution entered into force and when WHO approved the establishment of the Global Influenza Programme in 1948. Another influenza-specific milestone was the establishment of the Global Influenza Surveillance Network in 1952, which became GISRS in 2011.

Research, innovation, and global coordination are major components of vaccine development, said Zhang. The global public health response to influenza is driven by the constant evolving nature of influenza viruses. The prevalence of the West Nile virus in birds makes the eradication of influenza impossible, and little is known about the potential for an animal influenza virus to acquire human-to-human transmissibility and to emerge as a pandemic strain. Given these barriers, Zhang said the global approach to influenza response requires an internationally coordinated, step-by-step approach that spans every stage from surveillance to preparedness and response.

WHO's role is to enable this global collaboration, she said, with the GISRS as an essential mechanism. The GISRS network, which includes institutions from 114 countries, tests around 4 million clinical specimens each year, including around 40,000 virus specimens shared by WHO

Collaborating Centers for advanced analysis (WHO, 2019b). For a vaccine to be effective, the viruses it contains must be updated regularly. She explained how this complicated updating process is facilitated by the GISRS system, with updates conducted twice per year for seasonal vaccines and occur on an ad hoc basis for pandemic and prepandemic vaccines. She described the seasonal influenza vaccine cycle as an effective public–private partnership. In other words, the vaccine cycle occurs across a very tight time frame that requires smooth, effective, and timely interaction among key players throughout the year in order for a seasonal vaccine to be market ready before influenza season, she explained. WHO assists in this process by facilitating communication and disseminating information among all stakeholders, including antigen manufacturers, regulatory agencies, and the GISRS.

Zhang highlighted three additional concepts that underpin effective influenza surveillance and control: timeliness, sharing, and partnership. Timeliness is important, she said, because the effectiveness of countermeasures depends on the extent to which their availability lags behind virus evolution. Sharing is relevant because an important virus strain could emerge anywhere in the world at any time, and the response to the virus must be global. Partnerships are necessary among the global teams working at every step in the process, from surveillance to preparedness and response. She said WHO works to foster collaboration among other sectors and initiatives in addition to vaccine manufacturers. GISRS plays a role in fostering trust and sharing, she added, and strengthening the GISRS system has the potential to save more lives when the next pandemic hits.

REGULATORY PATHWAYS

Karen Midthun, senior advisor of the Center for Vaccine Innovation and Access at PATH, described her experience in the United States during the 2009 pandemic as the director of the Center for Biologics Evaluation and Research (CBER) at the U.S. Food and Drug Administration (FDA). CBER has a long history of collaborating with WHO, both as a WHO Collaborating Center for biological standardization and as a WHO Essential Regulatory Laboratory for influenza vaccine. In vaccine-related matters, CBER works closely with the U.S. Department of Health and Human Services (HHS) and with HHS agencies including the Biomedical Advanced Research and Development Authority (BARDA), CDC, and the National Institutes of Health (NIH).

Midthun said that prior to the 2009 pandemic, much regulatory groundwork had already been laid: the Pandemic Influenza Plan (issued by HHS in 2005 and updated in 2017) (HHS, 2017); guidance on licensure of seasonal and pandemic influenza vaccines (issued by HHS/FDA/CBER

in 2007) (FDA, 2007a,b); and Guidelines on Regulatory Preparedness for Human Pandemic Influenza Vaccines (issued by WHO in 2007) (WHO, 2007a). After the seasonal influenza vaccine shortage in the United States in 2004, CBER used FDA's accelerated approval program to license three additional seasonal influenza vaccines between 2005 and 2007. This contributes to pandemic responsiveness, she noted, because pandemic vaccine manufacturing is built on the seasonal vaccine infrastructure (Weir and Gruber, 2016).

Regulatory Pathways for Development of the 2009 Pandemic Vaccine

Midthun explained that some of the issues that occurred during development of the 2009 pandemic vaccine—such as the need for vaccine reference strains, reagents, and biocontainment procedures—were already expected because of insights from WHO's pandemic preparedness planning. Other issues were not necessarily expected, such as initial low yields, difficulty making the vaccine from reassorted vaccine candidates, and difficulty making the antiserum needed for the vaccine's potency test.[1] From CBER's perspective, Midthun said, a critical regulatory issue was finding the most expeditious pathway to make the pandemic vaccine available, preferably as a licensed product, though possibly under emergency use authorization.[2] CBER determined it could license the monovalent 2009 H1N1 pandemic vaccine as a strain-change supplement to vaccine manufacturers' existing licenses for seasonal influenza vaccines, which speeds up approval by not requiring new clinical data.[3] Depending on their regulatory precedents, regulatory agencies in other countries and regions pursued different pathways. For example, the European Medicines Agency approved a core pandemic dossier and mockup for an adjuvanted H5N1 vaccine that switched the H5N1 antigen with the H1N1 antigen, as the most expeditious pathway to licensure (CHMP, 2008). Development of the 2009 pandemic vaccine involved extensive WHO-coordinated collaboration among regulatory agencies, manufacturers, and public and expert advisory

[1] Potency testing is performed on vaccine lots to demonstrate the capability of the product to confer protective immunity.

[2] An emergency use authorization allows for the use of an unapproved medical product or an unapproved use of an approved medical product under certain emergency circumstances declared by the HHS secretary, when there are no adequate, approved, and available alternatives.

[3] This regulatory process allows new strains to be incorporated into the vaccine based on nonclinical, chemistry, and manufacturing control data; it is used every year to change the composition of seasonal influenza vaccines that target H1N1, H3N2, and B-lineage influenza viruses.

committees, Midthun said. Postmarketing safety surveillance also had to be expanded for the pandemic vaccines. Ultimately, it took 6 months to make the pandemic vaccine available, and the bulk of the licensed vaccine did not become available until after the pandemic had peaked (Al-Muharrmi, 2010).

Challenges and Progress in Pandemic Vaccines

Midthun said that the experience during the 2009 H1N1 influenza pandemic underscored several gaps in vaccine development and production, such as the need for faster identification of higher-yield vaccine candidates and for alternative potency assays. In the decade since, she noted that significant progress has been made on both those fronts. The 2009 experience also highlighted the need to develop alternative vaccines through newer technologies for more rapid manufacturing, Midthun added, including (1) cell-based and recombinant hemagglutinin influenza vaccines, (2) adjuvanted vaccines that provide for antigen-sparing, and (3) a universal influenza vaccine that provides broad and durable protection against a swath of influenza strains. FDA has since licensed a cell-based seasonal influenza vaccine, a recombinant hemagglutinin seasonal vaccine, an adjuvanted influenza vaccine for seasonal use, and an adjuvanted H5N1 vaccine. In the longer term, she noted, a universal influenza vaccine would provide the best preparedness for both seasonal and pandemic influenza, but this vaccine remains a work in progress (see Chapter 3 for more on opportunities and challenges related to universal influenza vaccines).

Seasonal influenza vaccine manufacturing capacity has increased worldwide since 2009, Midthun commented, which in turn has strengthened global capacity to manufacture, evaluate, and regulate vaccines. WHO has a prequalification process for vaccines, medicines, and devices already licensed or approved by various national regulatory authorities. This process allows countries to introduce vaccines on a more streamlined basis if they choose to do so. In response to the 2014–2016 Ebola outbreak in West Africa, WHO established a procedure for an emergency use assessment and listing, and a revised version is currently under way (WHO, 2015). This procedure could be a useful mechanism for making unapproved products (including vaccines) widely available in a pandemic setting, she suggested. However, the ultimate decision to use an unapproved product is made at the national level, she said, which requires having adequate infrastructure to allow such decisions to be made and supported.

MANUFACTURING CAPACITY AND PRODUCTION

Clement Lewin, associate vice president of research and development strategy at Sanofi Pasteur, provided a perspective from the pharmaceutical industry on manufacturing pandemic vaccines. He said that for the pharmaceutical industry, a pandemic is not business as usual; the industry is committed to contributing to the response and preventing the consequences of disease. Sanofi Pasteur, as one of the largest manufacturers of influenza vaccines using both egg-based and recombinant manufacturing technologies, and other vaccine manufacturers view pandemic preparedness not as a business opportunity, but as a public health challenge to which they can contribute, he stated.

To prepare for potential pandemics, Sanofi Pasteur is ready to produce as many influenza vaccines as possible and then to collaborate with public and private partners to distribute those vaccines. During the 2009 pandemic, for example, Sanofi made a substantial effort to make the vaccine available in 6 months, said Lewin. Currently, the company is working to improve its manufacturing processes by collaborating closely with BARDA and with other organizations in pandemic preparedness efforts. He added that Sanofi Pasteur maintains a year-round supply of eggs to ensure that pandemic production capacity is available when needed. The company also has experience in producing pandemic vaccines that can be tested both with and without adjuvant. Lewin was hopeful that forthcoming clinical data for H7N9 and H5N1 vaccines would help ensure that pandemic production capacity is available.

Lewin said Sanofi Pasteur works closely with WHO and other public health authorities on pandemic influenza activities, including vaccine development, licensing, and distribution. The 2009 pandemic demonstrated the importance of a history of collaboration among the vaccine manufacturing industry and government sectors. In 2009, Sanofi Pasteur's prompt response was enabled by existing relationships with the government and by proactive investments made by both sectors. He explained that for vaccine manufacturers, the distribution process for pandemic vaccines is unusual because the distribution is determined by public health authorities based on their prioritization of certain populations. The pharmaceutical industry is partnering with national and supranational authorities on pandemic preparedness and response, he said, and the Pandemic Influenza Preparedness (PIP) Framework adopted in 2011 strengthens Sanofi Pasteur's ability to respond to a pandemic (see Chapter 7 for more on the PIP Framework).

Pandemic preparedness has improved since 2009, with increased capacities and new technologies; however, Lewin said that staying ahead of the epidemic curve will require continued vigilance and investment in new

technologies. From Sanofi Pasteur's standpoint, creating demand and uptake for seasonal influenza vaccines is the best way to ensure that pandemic vaccine capacity is available when it is needed. He predicted that increased coverage of seasonal vaccines will spur industry to build sustainable mechanisms that will benefit the delivery of pandemic vaccines. Across the pharmaceutical industry, it would be cost prohibitive and infeasible to create dedicated production facilities for pandemic vaccines that are only used once per decade or more. Thus, the development of platform-based technologies would enable standard manufacturing processes and facilities to be used for the production of nonpandemic vaccines as well. Creating an integrated fill-finish plan is another important consideration, he added. For U.S. manufacturers, current filling capacity is about 150 million doses, but around 600 million doses could be needed in the event of a pandemic (MacGregor, 2018; HHS, 2019). Finally, he suggested that optimizing regulatory pathways could help ensure that new vaccines are licensed as quickly as possible.

TIMING AND DEPLOYMENT OF VACCINES

Bruce Gellin, president of global immunization at Sabin Vaccine Institute, emphasized the importance of timing in vaccine response—both time to the first dose and time to the last dose. He reiterated that the process of developing and deploying vaccines is complex and also spans surveillance, research, development, licensing, recommendations, deployment, and impact measurement. He cautioned that because the current system relies on the same manufacturing infrastructure for both seasonal and pandemic influenza vaccines, this system in the event of a pandemic threat forces a difficult decision about when to halt a given year's seasonal vaccine production and switch over to pandemic vaccine production. This choice must be made with minimal knowledge about how the pandemic threat might unfold but with full knowledge that switching production will compromise the next year's seasonal vaccine supply.

Donation of Vaccines and Ancillary Products

Gellin explained that donation of vaccines and ancillary products is a complex endeavor, requiring financial support, coordinated bilateral support, and legal agreements covering vaccine donation and receipt (WHO, 2012). WHO can help coordinate the deployment of donated vaccines, which involves identifying countries that are eligible to receive the donations and ensuring that recipient countries have a deployment plan, so the vaccines do not go unused, particularly during a global shortage. Legal considerations and political concerns related to vaccine donation

can contribute to delays in vaccine timing, Gellin said. He described political discussions that took place in the United States in the summer of 2009 about donating H1N1 vaccines to other countries. One camp was concerned about donating vaccines when the U.S. population was not adequately covered; the other camp was concerned about the rest of the world not having enough vaccines and believed the United States should help. In September 2009, President Obama decided that the United States would donate 10 percent of its vaccines to WHO and would allow WHO to make decisions about distribution and deployment. Delegating WHO as the impartial distributor allowed the U.S. government to avoid a political problem in donating vaccines to one country but not another.

Pandemic Vaccine Timing in 2009

The 2009 H1N1 pandemic in the United States illustrated the importance of timing, said Gellin, because the vaccine did not reach most clinics until after the virus had peaked. By the time vaccine delivery had ramped up, some countries were only receiving the vaccine deliveries while other countries had vaccination programs fully under way or even completed. Figure 6-1 depicts global monthly vaccine deliveries made through the WHO Deployment Initiative in 2009 and 2010. Several delays in the system contributed to this overall timing problem, he said. Some delays were unpredictable, such as the volcanic eruption in Iceland that disrupted air shipment of vaccines at a critical stage. Other delays were caused by customs requirements, such as those for certificates of fumigation. The volume of vaccines needed overwhelmed many existing systems, such as the cold chain. The vaccine delays in 2009 highlighted the shortcomings of a deployment system developed "on the fly," said Gellin.

WORLD HEALTH ORGANIZATION'S ROLE AND LEGAL CONSIDERATIONS IN VACCINE RESPONSE

Steven Solomon, principal legal officer at WHO, explored legal considerations relevant to international vaccine response, including governance, equity, and vaccine donations. He began by explaining that from political and legal perspectives, ministers of health have the most power to respond and communicate during a pandemic; ministers of health also have the power to establish global norms through WHO. The touchstone for ministers of health is the WHO Constitution, which posits the definition of health but also establishes the principle of equity (WHO, 2006). From the broadest perspective, the fundamental objective of WHO is to ensure the highest possible level of health for all people. WHO's mandate is principally to respond and furnish aid in emergencies, but more importantly, he said

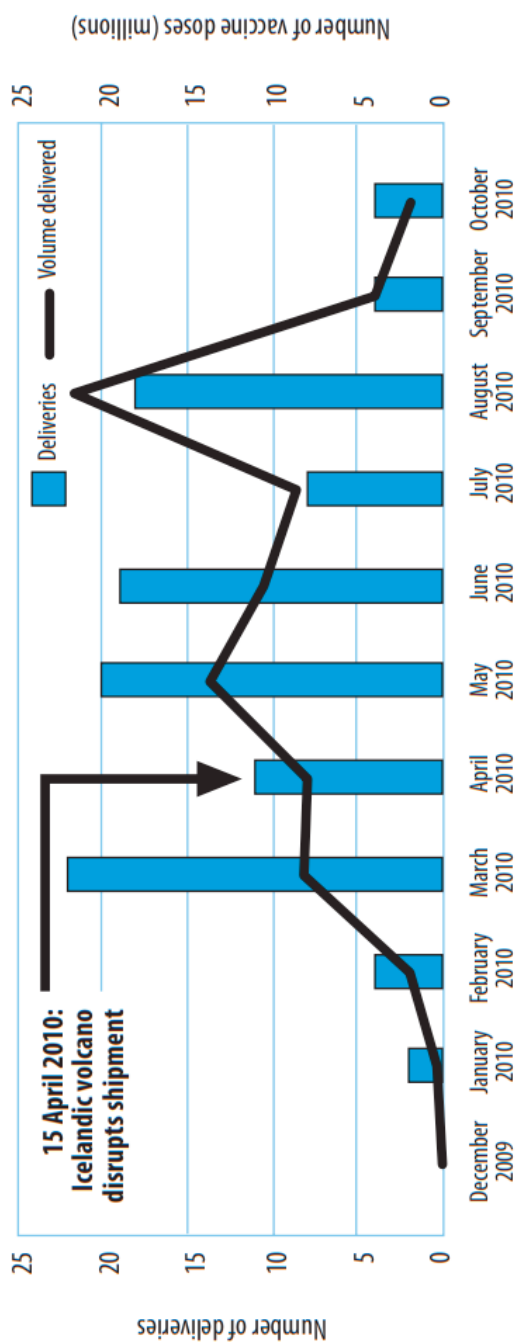

FIGURE 6-1 Global monthly vaccine deliveries made through the World Health Organization Deployment Initiative, 2009–2010. SOURCES: Gellin presentation, November 27, 2018; reprinted from Report on the WHO Pandemic A(H1N1) Vaccine Deployment Initiative, Page 20, Copyright (2012).

WHO can also assist governments in strengthening health services prior to a crisis. WHO executes this by working with all stakeholders through coordination, collaboration, and cooperation. The revised International Health Regulations (IHR) have driven some progress since coming into force in 2005; for example, improvements have been seen in core capacity building, emergency committee functioning, and providing information to WHO. However, more work is needed, he argued, to improve financing in order to support implementation, compliance, access to pathogens, benefit sharing, and awareness of the regulations.

Legal Context for Vaccine Donation

Solomon laid out a set of complex and time-consuming procedural steps between countries and WHO that may contribute to delays in vaccine timing during a pandemic. Despite the time-consuming nature of each step, they still must happen quickly during a crisis. First, WHO carries out its own mandatory prequalification review of new vaccines (WHO, 2019a). Then, WHO conducts an eligibility assessment to prioritize potential recipient countries by evaluating their domestic capacity to produce vaccines and their ability to purchase vaccines commercially. The WHO Director-General then sends letters containing complicated legal terms and conditions to ministers of health in potential recipient countries, Solomon described, to which the ministers must process and respond to confirm interest. Next, ministers must sign the terms and conditions and develop a national deployment plan to submit to WHO, which assesses the plan and assists in finalizing it. Contract law related to liability and indemnification can delay the process, said Solomon. The terms and conditions for recipient countries are couched in "legalese," but WHO provides support in navigating the language. According to Solomon, a more pressing issue is the indemnification clause, which requires recipient countries to pay the legal fees if the donor is sued. This clause needs to be addressed because it is not feasible for many under-resourced and vulnerable countries, he said.

In 2009, the legal complexities were dealt with relatively quickly with good uptake from potential recipients—95 countries were ultimately deemed eligible potential recipients, and 77 countries developed the national deployment plan and received vaccines. However, the major problem was that, in many cases, countries' national deployment plans were unable to accommodate the necessary speed of operation. Solomon suggested three approaches that could improve the speed and effectiveness of the process from WHO's perspective:

- Using clearer 'legalese' that is translated into a broader range of languages (beyond WHO's official languages);

- Prediscussing, preagreeing, and prepositioning the terms and conditions before a crisis; and
- Considering a global insurance mechanism for adverse events, particularly for vulnerable countries.

DISCUSSION

After the presentations, Jacqueline Katz, deputy director of the Influenza Division of CDC, remarked that the importance of timing in a pandemic and the importance of coordinating public–private partnerships were factors highlighted by all panelists. She noted that the latter already occurs annually for seasonal influenza through existing relationships and established expectations. However, because every strain is unique in a pandemic situation, a unique set of problems arises and needs to be addressed. Katz began the discussion with follow-up questions for the panelists and then opened the session for public audience engagement.

Successes and Challenges with GISRS in the 2009 Response

First, Katz asked Zhang to elaborate on the performance of GISRS during the 2009 H1N1 influenza pandemic. Zhang explained that many components were executed well. The capacity of GISRS had been built over previous decades, so virus detection went smoothly, surveillance was sufficient, and genetic sequence data were shared efficiently. Timing was fortuitous because the pandemic was detected and declared in early April, a period when annual seasonal vaccine production had already finished in the southern hemisphere and had not yet started in the northern hemisphere. This averted the dilemma about whether to stop seasonal vaccine production in order to start the production of a pandemic vaccine. The process of developing the candidate vaccine virus in WHO Collaborating Centers also went well, she added, and the H1N1 pandemic vaccine yield was better than the average yield of the seasonal vaccine. She said that in terms of surveillance, enough evidence was available to determine which at-risk groups should receive the vaccine in the first round.

However, GISRS also faced challenges in 2009. Zhang noted that the response was complicated by fixed pandemic phases based on pandemic preparedness planning. The phases called for action that needed to be triggered during each pandemic phase. Biocontainment recommendations were another challenge. At the time of the outbreak, the virus was already circulating in the community and causing mild disease. However, Biosafety Level 2 Plus was still required, but this level did not exist in most manufacturing plants at the time. In terms of regulatory capacity, many recipient countries did not have adequate mechanisms in place to receive donated

vaccines. Policy-related challenges to deployment also arose because other seasonal viruses were co-circulating toward the end of the pandemic, but people were still using the monovalent H1N1 vaccine.

Improved Potency Assays

Katz asked Midthun to describe the current state of development for improved potency assays, which can help with the timing issues related to pandemic vaccine development. Midthun replied that BARDA has established an influenza vaccine improvement plan in collaboration with CBER, CDC, and NIH. A consortium has also been established with WHO Essential Regulatory Laboratories and with manufacturers to test different potency assays. Progress has been made in finding assays with apparent potential, but questions remain about how quickly the necessary monoclonal antibodies can be developed. Further work is needed to find more suitable candidates that have rapid or preexisting reagents, she said, which would preclude the need to develop strain-specific antisera when the virus is being manufactured. Midthun noted that the current approach involves searching for new potency assays for traditional inactivated influenza vaccines; however, with new types of vaccines already in the development pipeline, it may not be feasible to assume that a single potency assay will be appropriate for all new vaccines.

Increasing Fill-Finish Capacity

Katz called on Lewin to discuss more about the gap in fill-finish capacity in the United States. Lewin said that installed manufacturing capacity will be key to providing surge capacity in pandemic response since the process of increasing vaccine development capacity is lengthy. For example, companies tend to fill vaccines in prefilled syringes, as demanded by the market using a fill-finish strategy based on what they currently sell—which is a capacity of about 150 million doses in the United States (although not all doses are filled in the United States). If a pandemic occurred, about 600 million doses (two for every American) would probably need to be filled in multi-dose vials, as determined by BARDA and other agencies (MacGregor, 2018). Finding the requisite capacity to fill and finish vaccines requires a technology transfer licensed by FDA, which in turn enables the available capacity to be used when it is needed. These issues need to be considered now, he said. Even if the bulk could be produced, it would need to be filled as quickly as possible to avoid creating a bottleneck, he added. This typically involves engaging contract manufacturing organizations that can fill-finish, he noted, and that requires a reservation fee as well as investment in the necessary technology. Katz said that syringes were a major gap identified

during a recent pandemic exercise carried out by CDC and BARDA—even with sufficient vaccine capacity, not enough syringes would be available to administer the vaccine. Lewin added that manufacturers plan their supply chains for seasonal vaccine production, but there are ongoing initiatives to improve pandemic manufacturing preparedness. Gellin remarked that it could be beneficial to involve logistics experts in planning.

WHO's Prequalification Process and Eligibility Requirements

Katz asked Solomon to elaborate on WHO's prequalification process and its eligibility requirements for potential recipients of donor vaccines. Solomon said prequalification is mandatory for all vaccines because many member states lack their own national regulatory authorities and rely exclusively on WHO's prequalification process (which could take as little as 1 day to as many as 20 days). Eligibility for donated vaccines is determined by domestic production capability—which so few countries have—and by a country's capacity to purchase vaccines on the commercial market. Most of the global vaccine supply is precontracted, so most countries do not meet the latter criteria, either. Solomon said that these eligibility criteria underscore the importance of the PIP Framework's benefit-sharing scheme and of the 10 percent commitment from countries.

Surveillance During Vaccination

Matt Zahn, medical director of the Division of Epidemiology and Assessment of the Orange County Health Care Agency in California, asked about gathering surveillance data after a decision is made to vaccinate. Midthun said that FDA licenses a vaccine based on clinical trials that show its effectiveness against a confirmed influenza disease; the vaccines are adjusted as new strains evolve. Katz added that clinical studies are used to monitor vaccines, and CDC monitors the effectiveness and safety of vaccines in real-world situations. From a domestic standpoint, Gellin emphasized the importance of a highly robust safety system coupled with transparency about safety concerns. When the 1976 vaccine was linked to Guillain-Barré syndrome, for example, the crisis was addressed by leveraging every available government system, by using immunization registries in new ways, and by convening monthly meetings of the National Vaccine Advisory Committee to assess data and to ensure transparency. Gellin said the aim was to put the best-possible system in place for surveillance while also being able to communicate effectively with the public to allay concerns. The system was eventually de-escalated, but it was built on existing government processes and infrastructure that could be ramped up again. Global surveillance is another matter, Gellin noted, because it requires

distinguishing between a causal and temporal event and determining the appropriate response or compensation.

Progress in Vaccine Preparedness Since 2009

Peter Daszak, president of EcoHealth Alliance, asked about the current prospects for beating the epidemic curve in the event of a pandemic that was similar to H1N1 but that involved a new, rapidly moving virus and a vaccine that must be started from scratch. Gellin replied that BARDA is looking at applying new technologies to compress the development and deployment time frame, but current technology is not sufficiently advanced to beat the first viral wave; he said this highlights the need for a universal influenza vaccine. Solomon remarked that the PIP Framework contributes to progress on the global level because it has precontracted almost 400 million pandemic vaccine doses with preagreements for the terms and conditions. Lewin said that the licensed adjuvants, recombinant vaccines, and cell-culture vaccines currently available would help to decrease the timeline slightly, but a 6-week response timeframe is not yet feasible. A substantial improvement, Lewin noted, would require significant investment in technological advancements that may take decades to develop. Zhang added that WHO introduced a Pandemic Influenza Severity Assessment after 2009, which enables more granular evaluation of a disease if an outbreak occurs. Information from that assessment could enable vaccine manufacturers to devote a proportion of their production process to the influenza monovalent vaccine while continuing to produce the seasonal vaccine. Since 2009, she noted, progress that includes regulatory, logistical, and deployment elements has been made in national pandemic-preparedness planning.

Keiji Fukuda, director and clinical professor, School of Public Health, The University of Hong Kong, commented that by the time the vaccine was available in 2009, it was already clear that the impact and mortality were relatively milder than people had feared; technical processes proceeded smoothly because the operation was an intensification of systems already in place. After that point, the process was more ad hoc and thus more difficult. If the pandemic had been more severe than it was, he said, it is unclear whether the system would have fragmented or would have collaborated effectively. Gellin said that the urgency of a severe outbreak may have curtailed some process timelines, but not significantly; many systems had already collapsed at that point. Gellin surmised that a more severe pandemic would have affected U.S. political decisions about donating vaccines to other countries; in that case, the government would have considered taking vaccines away from U.S. citizens to be problematic. Zhang noted that in the past decade, specific guidance related to some key decisions (e.g., whether to switch vaccine production from seasonal to pandemic) has been

developed, and it could be communicated to a population prior to a pandemic. She said such guidance might reassure the public that evidence-based decisions are being made to ensure the best possible public health outcomes.

WHO's Health Emergencies Programme

Finally, Gabrielle Fitzgerald, founder and chief executive officer of Panorama, asked how preparedness for pandemic influenza relates to WHO's Health Emergencies Programme, which was established after the Ebola outbreak. Zhang explained that WHO's seasonal influenza program is housed within the Health Emergencies Programme because it is a persistent, annual health threat. Because a country's entire health system is the platform for any response, building capacity to respond to seasonal influenza improves preparedness for pandemics of influenza or for any other disease. Solomon added that lessons from the 2009 pandemic have been applied to the Health Emergencies Programme, but the tools and resources to apply those lessons beyond influenza may not currently exist. For example, the IHR lack a financing mechanism, have compliance issues, and do not mandate access to pathogens and their genetic sequence data.

7

The Development of the PIP Framework: Global Lessons on Equity and Fairness for Pandemic Preparedness

Session 1, part C of the workshop highlighted global lessons on equity and fairness related to pandemic preparedness. Panelists focused on illustrating such lessons through discussions about the virus-sharing controversy that emerged during the 2006 H5N1 avian influenza outbreak and that catalyzed the development of the Pandemic Influenza Preparedness (PIP) Framework. Makarim Wibisono, professor at the Indonesian Defense University, offered his perspective on the Indonesian government's decision to withhold virus samples from the World Health Organization (WHO) based on issues about inequitable access to the benefits derived from those samples. John E. Lange, senior fellow for global health diplomacy at the United Nations (UN) Foundation discussed his experiences as part of the U.S. delegation in the virus-sharing controversy and contributed his perspectives on the events that led to the development of the PIP Framework. Steven Solomon, principal legal officer at WHO, described the technical process behind the PIP Framework's negotiations, and Anne Huvos, manager of the PIP Framework Secretariat at WHO, provided an overview of the challenges to and opportunities for the PIP Framework moving forward. The discussion was moderated by Keiji Fukuda, director and clinical professor, School of Public Health, The University of Hong Kong.

CONTEXT FOR THE DEVELOPMENT OF THE PIP FRAMEWORK: PERSPECTIVE FROM INDONESIA

Makarim Wibisono, professor at the Indonesian Defense University, provided insight into the Indonesian government's decision to withhold virus samples from WHO during the country's H5N1 outbreak. He explained that the first outbreaks of H5N1 occurred in China between 1996 and 2003; H5N1 then spread rapidly to Southeast Asia and was first detected in domestic poultry in Indonesia in 2003. It was not diagnosed in humans in the country until July 2005, at which point it spread swiftly from western Java (WHO, 2014). In addition to its devastating effect on domestic and wild bird populations, H5N1 caused 115 deaths among 141 confirmed human cases by April 2009 (WHO, 2014). A cluster of cases in Sumatra induced public panic because it was unclear if transmission had occurred among humans rather than from animals to humans. This incited Indonesian media outlets and politicians to begin questioning the ability of the Indonesian Ministry of Health to contain the virus.

During the outbreak, the Indonesian government initially complied with the Global Influenza Surveillance Network (GISN) regulations related to sharing the H5N1 virus. Established by WHO in 1952, the GISN requires affected countries to send samples of their virus to WHO Collaborating Center libraries and is the precursor to the current Global Influenza Surveillance and Response System (GISRS). The laboratory then identifies the candidate vaccine virus (CVV) and disseminates those findings to pharmaceutical companies for vaccine manufacturing. Wibisono said that despite Indonesia's willingness to share virus samples with the GISN, the country experienced great difficulty accessing the H5N1 vaccines that those samples helped produce. A delegation led by the minister of health in Indonesia traveled to WHO to seek a stockpile of the vaccine. The delegation was informed that WHO did not have processes in place to supply drugs directly to countries. Wibisono described that the delegation was advised to approach the manufacturer of the antiviral oseltamivir, but the manufacturer informed that the government of Indonesia would have to wait 2 years to receive the medication because the product was sold out based on advance purchase commitments. In response, the Indonesian minister of health announced in December 2006 that Indonesia would no longer share its H5N1 virus samples with WHO Collaborating Centers.[1] The minister of health said that the GISN process was inequitable because vaccines produced from samples shared by developing countries were less likely to be available to those countries' populations.

[1] Indonesia resumed sharing the H5N1 virus in March 2007 after a 2-day, high-level technical meeting organized by WHO that included representatives from approximately 20 countries. See https://www.who.int/mediacentre/news/releases/2007/pr09/en (accessed February 26, 2019).

CONTEXT FOR THE DEVELOPMENT OF THE PIP FRAMEWORK: PERSPECTIVE FROM THE UNITED STATES

John E. Lange, senior fellow for global health diplomacy at the UN Foundation, provided the U.S. perspective during the virus-sharing controversy and the events that led to the eventual development of the PIP Framework. He noted that high-level political engagement by the U.S. government was a boon to the H5N1 response, as illustrated by the creation of the International Partnership for Avian and Pandemic Influenza in September 2005. When Indonesia's minister of health announced Indonesia's refusal to share viruses with WHO Collaborating Centers in December 2006, high-level U.S. government officials expressed concern about the potential for that decision to precipitate a catastrophic influenza pandemic if additional countries stopped sharing viruses. Lange said that immediate sharing of samples is important because timing is critical in an emerging pandemic situation. Samples need to be delivered as quickly as possible to WHO Collaborating Centers and then to manufacturers to produce a vaccine, he explained.

In May 2007, WHO passed a resolution at the World Health Assembly to create a process for discussions that would lead to the PIP Framework 4 years later (WHO, 2007b). That process included bilateral discussions between the Indonesian government and the U.S. government, both of which had different perceptions about those discussions (Supari, 2008). Indonesian representatives were focused on ensuring equitable access to the vaccines produced by the virus samples they provide, while the U.S. representatives were focused on public health and the immediate need to share virus samples for global benefit. Lange reported that the subtext of the discussions from the U.S. perspective, however, was a tension between using the vaccine for domestic purposes or helping developing countries. These deliberations sparked critical U.S. media coverage of the Indonesian government's claim to "viral sovereignty"[2] (Holbrooke and Garrett, 2008). Lange noted that in response to such critique, Wibisono wrote an article on the Convention on Biological Diversity, arguing that countries have sovereignty over their biological materials—including pathogens found in their territories—and that countries could mandate benefit sharing in return for access to influenza virus samples (Wibisono, 2008). The negotiation process around this issue took years to resolve and was challenging, Lange remarked, but it was ultimately concluded successfully in May 2011 with the passage of the World Health Assembly Resolution 64.5 and the development of the PIP Framework.

[2] Viral sovereignty was described as the idea that "deadly viruses are the sovereign property of individual nations even though they cross borders and could pose a pandemic threat to all the peoples of the world" (Holbrooke and Garrett, 2008).

PROCESS OF DEVELOPING THE PIP FRAMEWORK

Steven Solomon, principal legal officer at WHO, explained that member states had collaboratively decided that a framework was needed to ensure rapid and robust virus sharing in a framework that equalized the value of sample sharing and of benefits sharing—resulting in the mandate in 2007 that Lange described earlier. Solomon said the process of developing the PIP Framework took 4 years, but such processes tend to be lengthier in order to ensure that the product of the process is reached by consensus. He also commented that 4 years is a relatively swift negotiation period considering that 194 member states are involved. WHO and the World Health Assembly both operate on the basis of consensus, which does not mean that no country has concerns, but he clarified that no country objects strongly enough to block the adoption of the framework. As a resolution of the World Health Assembly, the PIP Framework is not a legally binding document on the whole. However, it does have some legally binding elements under international and domestic law, such as contracts with vaccine manufacturers.

Solomon explained that in 2011 the World Health Assembly re-entered the process to consider the product of the work by the member states it had mandated. At that point, the issue blocking consensus was a debate over the Nagoya Protocol,[3] which was still being negotiated. The Nagoya Protocol's implications for pathogen sharing (including influenza) were beginning to be recognized, which led to disagreement about whether the PIP Framework should reference the Nagoya Protocol. Solomon noted that the issue continues to this day; the World Health Assembly will convene in 2019 to consider the implications of the Nagoya Protocol for the PIP Framework, and negotiations could continue for several more years.

POTENTIAL CHALLENGES AND OPPORTUNITIES FOR THE PIP FRAMEWORK

Anne Huvos, manager of the PIP Framework Secretariat at WHO, described how the PIP Framework contributes at an international level and what challenges remain for it. Ultimately, the PIP Framework was the product of a 4-year investment by WHO member states to resolve two critical issues for public health security: (1) ensuring that countries continue to share influenza viruses with pandemic potential for risk assessment and for developing pandemic vaccines, and (2) ensuring greater equitable access

[3] As described in Chapter 3, the Nagoya Protocol is a supplementary agreement to the Convention on Biological Diversity. It provides a transparent legal framework for the effective implementation of the fair and equitable sharing of benefits that arise from the use of genetic resources. For more information on the Nagoya Protocol, see https://www.cbd.int/abs/about/ (accessed February 11, 2019).

to future pandemic vaccines by all countries based on public health need, irrespective of development status or other financial considerations.

Huvos remarked that the idea for the PIP Framework originated in 2003 in response to fears that the reemergence of avian influenza would cause a devastating pandemic. However, the spark that drove the framework-creation process was developing countries' loss of trust in the global system for virus sharing and access to vaccines. The governments of developing countries felt that the WHO-coordinated system of virus sharing was inequitable and failed to provide reasonable protection for their people. The initiation of the PIP Framework discussions marked the start of the trust-rebuilding process among countries. Ultimately, the process facilitated the resumption of virus sharing in the years after the PIP Framework was adopted.

Huvos said that the PIP Framework also represents a successful approach to partnership with the private sector. More than $163 million in partnership contributions have been collected from individual manufacturers, and those funds have been used to strengthen pandemic preparedness capacities and to gradually build a response fund for the next pandemic (WHO, 2018e). WHO has also signed multiple contracts to secure approximately 10 percent of future pandemic vaccine production and therefore will be able to send vaccines to countries in need during the next pandemic. Currently, this represents about 400 million doses of vaccines, and this number will likely increase if manufacturing technologies continue to improve and the next pandemic does not occur soon (WHO, 2017b).

Several global challenges may threaten the success of the PIP Framework (see Box 7-1). One challenge, Huvos noted, is how to deal with sharing genetic sequence data under the framework. Given the nature of the contracts signed as a part of the PIP Framework, the increasing use of genetic sequence data could potentially impede WHO's access to vaccines and to other critical pandemic response products. Contracts must be signed by any entity that receives physical PIP biological materials from GISRS. However, if a product is manufactured only with genetic sequence data, WHO cannot require the manufacturer to sign a contract to share its product. This issue is currently hypothetical for vaccines because of the regulatory processes in place, but the PIP Framework could be compromised if those regulatory and manufacturing processes evolve.

The second challenge Huvos identified was the adoption of the Nagoya Protocol. The basic premise of this protocol is that anyone who wishes to access a country's genetic resources must provide agreed-upon benefits in return to that country. The treaty currently has nearly 110 parties that are in the process of developing their own national implementation laws, which can and do differ substantially by country. The Nagoya Protocol recognizes that some genetic resources are already covered by other access- and

BOX 7-1
Some Challenges and Concerns About the Pandemic Influenza Preparedness (PIP) Framework

Although the development of the PIP Framework has been a significant achievement, several concerns and challenges remain, according to David Fidler, professor of law at Indiana University Bloomington (see Chapter 3), and Anne Huvos, manager of the PIP Framework Secretariat at the World Health Organization (WHO):

- The PIP Framework covers influenza viruses with pandemic potential but not seasonal influenza viruses or other pathogens.
- The timely and adequate sharing of viruses has generally declined since 2013.
- The increasing use of genetic sequence data could potentially impede WHO's access to vaccines and to other critical pandemic-response products.
- The potential impact of the Nagoya Protocol on the balance of virus sharing and benefit sharing in the PIP Framework is unclear and could disrupt the global system, which relies on the timely, rapid, and broad sharing of viruses to develop effective seasonal influenza vaccines.
- The PIP Framework has not yet been tested in response to a serious influenza pandemic.

SOURCES: Fidler presentation, November 26, 2018; Huvos presentation, November 28, 2018.

benefit-sharing instruments, and this is considered acceptable if those instruments are consistent with the Nagoya Protocol. For instance, if the PIP Framework for influenza viruses with pandemic potential is deemed to be an access- and benefit-sharing instrument that is consistent with Nagoya standards, then the Nagoya Protocol will not apply to influenza viruses with pandemic potential. Huvos explained that the Nagoya Protocol would apply to sharing and to accessing seasonal influenza viruses because those viruses are not covered by the PIP Framework. Potential conflicts between the Nagoya Protocol and the PIP Framework might disrupt the global system, which relies on the timely, rapid, and broad sharing of viruses to develop effective seasonal influenza vaccines.

Huvos said that moving forward with the PIP Framework will require robust communication strategies that emphasize the public health importance of the framework for all countries and for their populations. In 2017, the World Health Assembly requested that WHO analyze the implications of genetic sequence data with regard to the Nagoya Protocol on the PIP Framework. The resulting analysis sketched several options for each of

those issues, such as adapting GISRS or developing one or more broader instruments to cover all pathogens. Huvos argued that WHO's most important task is to avoid repeating the mistakes of the past, which WHO could accomplish by acting transparently, inclusively, and iteratively to maintain the trust of all its partners.

DISCUSSION

Keiji Fukuda, director and clinical professor, School of Public Health, The University of Hong Kong, observed that the PIP Framework emerged as a solid solution to a difficult situation in a way that balanced two important and noncompeting values while satisfying the member states and other stakeholders who substantially contributed to the discussions. He said the PIP Framework is unique because "it goes beyond merely stating principles to actually *acting* on it. I think that is why, for so many people, the PIP Framework remains a touchstone about what we should be aspiring to." The importance of achieving a collective global benefit as well as fairness and equity for individual parties, he reflected, will need to be struck in order to facilitate future multilateral global cooperation related to pandemics and other global health issues. However, he cautioned that although developing the PIP Framework was a great achievement, time does not stand still; other global frameworks and technologies are being developed and therefore necessitate discussions to negotiate how they fit with each other and to identify how they impact day-to-day work on preparedness. The loss of the PIP Framework would be a major step backward, he argued, because its implementation has improved the availability of vaccines and antivirals, garnered some continuous funding, and helped countries develop needed structures to support surveillance and other public health necessities.

Applying the PIP Model to Future Negotiations

Fukuda asked panelists if the process used to negotiate the PIP Framework is an applicable model for the future. Wibisono said that the PIP process is a new and important model of international relations for addressing global challenges. The discussions were unique because they involved active participation from all stakeholders in order to achieve a difficult task: reaching consensus on adaptable solutions. Lange said that this new model may be useful for facilitating international cooperation without a cumbersome treaty process. He remarked, "The beauty of the PIP Framework is that it is not a treaty; it is a resolution that was passed by the World Health Assembly, which has ended up as a standard of materials transfer agreement and a contract . . . and it has worked."

Solomon said the model would be useful for ensuring legitimacy and credibility in discussions aimed at building trust and ensuring equity, which require long-term investments in transparency, inclusiveness, and broad understanding among all stakeholders. Huvos said that the PIP model may be useful for future discussions, but some aspects may be hard to replicate. She explained that preparedness for influenza is a unique microcosm of mutually supporting interests: Governments need vaccines to protect their people, countries need to share their viruses in order to have a good vaccine, and industries need to make vaccines and to derive some revenue. Unlike many emerging diseases, influenza is already recognized as an important concern in many countries' public health systems. Huvos suggested that the core principles of the PIP model—equity, fairness, partnership, and transparency—are replicable elements. Some of the platforms and mechanisms for seasonal influenza and for pandemic preparedness may also be replicable in other discussions.

Frameworks for Other Pathogens

Suerie Moon, director of the Global Health Centre of The Graduate Institute of International and Development Studies, asked if frameworks similar to PIP will be needed for pathogens other than influenza. If so, she asked how to gather the requisite political startup energy to develop that type of framework in the absence of a crisis such as the one that catalyzed the PIP Framework. Solomon responded that new frameworks that apply to all pathogens will be required. However, a crisis will probably be needed to instigate the process unless countries come to realize that the global health benefit of rapid sharing can only be gained through a multilateral regime like the PIP Framework. He added that, in his experience, many health ministers believe that the problem of pathogen sharing has been solved by the PIP Framework since failures to share other types of pathogens have not yet had a negative global impact. Huvos remarked that the PIP Framework's narrow scope only covers pandemic influenza vaccines, so the first priority should be to create a framework to share seasonal influenza viruses before moving on to non-influenza pathogens. A crisis is emerging in which seasonal influenza viruses are not being shared in time for consideration at seasonal vaccine composition meetings. As a result, she said the seasonal virus sharing system will likely deteriorate as the Nagoya Protocol is implemented in more countries. Wibisono noted that the PIP Framework has helped expand countries' capacities to produce the seasonal influenza vaccine. Arnold Monto, professor of public health in the Department of Epidemiology at the University of Michigan, added that member states will not advocate for a seasonal influenza framework until they recognize the importance of seasonal influenza vaccines. One example of this importance

is the fact that pandemic influenza vaccines cannot be produced without an existing system for producing seasonal influenza vaccines, he said.

Implications of Genetic Sequence Data and Emerging Technologies

Eva Harris, professor of infectious diseases and vaccinology at University of California, Berkeley, elaborated on earlier remarks that genetic sequence data can jeopardize the PIP Framework. For example, companies might be able to avoid signing the contract on the technicality that genome sequence data are not biological material per se because they are *derived* from biological material. Peter Daszak, president of EcoHealth Alliance, asked how the capability to reverse engineer an entire virus could be addressed from a legal perspective. A single base pair in a genetic sequence could be tweaked to make it an essentially different organism, which would create another series of legal and regulatory problems.

Fukuda remarked that this multiplicity of conceptual and legal issues people had raised about the Nagoya Protocol are complex because the protocol was developed with an environmental focus while the PIP Framework was developed with a public health focus. Trust and mistrust are still fundamental issues, he added, despite the years-long efforts during the negotiations to identify mistrust and find a solution for it. The PIP Framework was considered successful because all participants were instrumental in reaching a final agreement, but these emerging issues have exposed a lingering level of mistrust. He warned that mistrust needs to be confronted before it burgeons again because every time a potentially dangerous new pathogen is identified, the same issues arise—who owns the virus, what will happen to it, which agreements will need to be made, and whether consent will be needed. Fukuda predicted that another lengthy process of deliberations will be required to resolve issues raised by genetic sequence data and by other emerging technologies such as artificial intelligence and big data.

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Overcoming Impediments to Achieving Greater Preparedness

Session 2 of the workshop focused on identifying potential strategies to systematize and integrate outbreak and pandemic preparedness at the local, national, and global levels. This session was moderated by Kumanan Rasanathan, a board member of Health Systems Global. Panelists discussed how to end the cycle of panic and neglect that often occurs between major outbreaks and how to make a business case for sustained political and financial support for preparedness. To illustrate what this cycle entails, Rasanathan described the experience in New Zealand during the 1918 pandemic. Conservative estimates suggest that half as many New Zealanders died from influenza compared to those who died from World War I (Rice, 2005). Despite the significant number of deaths from the 1918 pandemic in the country, he said that New Zealand's outbreak experience receives little attention in the country today. While after-event analyses of the pandemic spurred important changes in the country, such as the 1920 Health Act, he noted that this type of action is often made from a position of panic right after outbreaks occur; once the panic is quelled, the issues recede from mainstream priorities. Some periods of action have served as opportunities to build institutions, but for Rasanathan, sufficient political and financial support has not yet been mobilized to make preparedness activities mainstream during all seasons. He suggested that breaking this cycle is the key to making pandemic preparedness a stable, integrated, and systematic activity, and he explained that the workshop panel would speak to the heart of these issues.

The first panelist, Julie Gerberding, executive vice president and chief patient officer at Merck & Co., Inc., discussed strategies for institutionalizing

the exercise and practice of preparedness as a way to break this cycle of panic and neglect. Jimmy Kolker, visiting scholar at the American Association for the Advancement of Science (AAAS), explored the role of U.S. leadership in international efforts to advance preparedness. Suzet McKinney, executive director and chief executive officer of the Illinois Medical District, described strategies for strengthening local-level preparedness capacities. Finally, Peter Sands, executive director of The Global Fund to Fight AIDS, Tuberculosis and Malaria, explored the need to broaden the concept of health security and to strengthen day-to-day health systems in order to bolster preparedness capacities. The session also featured small-group discussions that allowed the public audience to examine potential priorities for systematizing and integrating outbreak and pandemic preparedness.

INSTITUTIONALIZING PREPAREDNESS

Julie Gerberding, executive vice president and chief patient officer at Merck & Co., Inc., explored strategies for institutionalizing the exercise and practice of preparedness. She remarked that the preparedness cycle is not always characterized by panic and neglect per se, but the cycle generally features a period of intense focus and attention, investment, planning, collaboration, and coordination that eventually relaxes into a phase of inattention and dispersion. She noted that the after-action reviews that typically occur when the intense response period has settled tend to identify "left-brained" improvement areas for responses to threats, such as collaboration, coordination, capacity, and competency. In contrast, the response during a threat occurs in a "right-brained" environment associated with emotions. Efforts intensify and escalate during an event, but when the action ends, people relax into a state of inattention, and the focused conditions are not sustained. She suggested finding ways to take these left-brained ideas and tools—such as sustained investment, global leadership, and continuity of preparedness over time—and apply right-brained energy to translate them into an action agenda to strengthen preparedness between events.

The high water mark of domestic preparedness typically occurs when an entire country is galvanized around preparing for a pandemic, Gerberding said. The challenge is to find ways to encourage members of leadership to engage and invest in preparedness efforts even in the absence of an impending threat. One possible strategy is to institutionalize the exercise and practice of preparedness on an ongoing basis. However, she said, activities such as exercising response plans require resources and budgetary support that are not typically available during interim periods. She suggested communicating the urgent message, to all levels of decision makers, that a budget sustained beyond specific threats is required in order

to restore the abilities to exercise and to strengthen preparedness both nationally and globally. She added that leaders should use such budgets to establish routine opportunities to plan and to exercise the scenarios that are most likely to threaten the population.

Participating in preparedness for response exercises can impress upon leadership and the general public that current preparedness efforts are insufficient to deal with a crisis. Gerberding said, "Even though the threat may not be imminent, they can imagine what it would be like, and they recognize the gap between what they are able to do now and what they need to be able to do." A stronger coalition of people committed to preparedness would also help to coordinate work that is currently being conducted in silos. Finally, she suggested that one way to support the role of the World Health Organization (WHO) as a strong global leader in preparedness would be through greater investment and greater engagement from national governments, many of which rely on WHO's coordinating function during a global event.

U.S. LEADERSHIP IN ADVANCING GLOBAL PREPAREDNESS

In his presentation, Jimmy Kolker, visiting scholar at AAAS, focused on the role of U.S. leadership in overcoming national and global impediments to preparedness. Drawing on his experiences as a former ambassador and as an assistant secretary for global affairs in the United States, he said that people often talk about political will as if it were a switch to be flipped by diplomats or by policy makers who are skilled at inserting their priorities into political agendas. However, a more effective way to build political will and to garner attention for an issue is to publicize data and evidence tailored to local contexts; this makes theoretical problems more relatable and attractive to the people who make decisions. For example, this type of tailoring might involve breaking down disease burden statistics by country, providing comparison data, and employing personal narratives.

Kolker explored the role of the United States as a leader in corralling global political and financial support. He noted that the United States is often viewed as a reference point for international discussions about preparedness, despite the fact that its system is far from perfect. However, he added that the experience with The President's Emergency Plan for AIDS Relief illustrated that presidential leadership, interagency buy-in, sustained financial commitment, and global reach are crucial for the U.S. leadership to affect global-level change. Kolker used the global efforts to combat antimicrobial resistance to illustrate how the United States can play a leadership role in preparedness for pandemic threats and how those efforts can be hampered by a lack of global reach and sustained financial commitment (see Box 8-1).

BOX 8-1
U.S. Leadership in Global Efforts to Combat Antimicrobial Resistance

The U.S. government disseminated data and evidence on antimicrobial resistance in a 2013 report that laid the groundwork for the 2014 U.S. National Strategy for Combating Antibiotic-Resistant Bacteria (National Strategy) (CDC, 2013a). The National Strategy set forth specific requirements for U.S. government agencies to help gain interagency buy-in, but it did not have sustained financial commitment or enough global reach to communicate to other countries the importance of addressing antimicrobial resistance. In 2015, the U.S. Congress appropriated funds for the accompanying U.S. National Action Plan for Combating Antibiotic-Resistant Bacteria, which outlined milestones to implement the National Strategy.

The World Health Assembly passed the Global Action Plan on Antimicrobial Resistance (Resolution 68/20) in 2015, for which every country was to develop a national antimicrobial resistance plan; however, the Global Action Plan had no attached funding. In 2018, 52 countries (mostly high-income) enrolled in the World Health Organization's Global Antimicrobial Surveillance System. Since then, some progress has been made. Forty countries have provided information about national surveillance systems. In addition, 22 countries have provided data on levels of antibiotic resistance, but a much larger number of countries have not provided any information (WHO, 2018c).

The United States has maintained the National Strategy under the current presidential administration. Progress against antimicrobial resistance in the United States is evident in the U.S. Food and Drug Administration's ban on the use of antibiotics to promote growth in livestock. However, U.S. policy has lagged behind Europe in other areas such as failing to prohibit the distribution of antibiotics to healthy animals in a herd with no sick animals. Experiences in Europe suggests that such policy changes could help control antimicrobial resistance.

SOURCE: Kolker presentation, November 28, 2018.

Kolker said despite the current vacuum of U.S. engagement in many multilateral forums, the U.S. role in combating antimicrobial resistance remains important because efforts made at the local, state, and national levels are scrutinized by other countries as a model of sufficient health and scientific standards. He outlined a set of additional areas in which the United States could play a leadership role on the international front. For example, antibiotic stewardship could be a condition of health cooperation with respect to prescription practices, over-the-counter restrictions, and manufacturing practice (particularly related to waste management). Market failures driven by the lack of economic incentives for research cause concerns with specific relevance to outbreaks and epidemics (Heymann et al., 2015). He suggested that better incentive models are needed that

do not place the onus on the U.S. government or on WHO to finance the development of new antibiotics through an advance market commitment to assume responsibility for the stewardship of those new drugs. Kolker observed there is a similar sense of uncertainty about the responsibility for leadership in ensuring that medical countermeasures will be available for future outbreaks of global significance.

Kolker explored the extent to which the Global Health Security Agenda (GHSA) and Joint External Evaluation (JEE) efforts may help end this cycle of panic and neglect in preparedness. He noted that considerations of antibiotic resistance are not explicitly part of the International Health Regulations (IHR) but are part of the GHSA action packages and that the JEE does assess capacity and needs related to combating antimicrobial resistance. He explained that prior to the JEE process, the IHR did not provide assistance in outbreak preparedness and response, but the Ebola outbreak underscored the need for such support. He described the GHSA and JEE efforts as "game changers" that provide a necessary but not sufficient condition to halt the cycle of panic and neglect. However, many countries or partners still fail to fully recognize the programmatic advantages of addressing antimicrobial resistance as part of health security.

Kolker concluded by suggesting that the most important action that the U.S. government should take is to increase its investment in global health research and preparedness. Such investment would provide support for global institutions to take a normative, leadership role within an international multilateral system. This would alleviate some of the burden on the United States with respect to both financing and responsibility, he noted. Also, such investment would directly benefit the United States because the alternative ad hoc scenario would place a disproportionate burden on the country to prepare for future crises.

MAKING THE CASE FOR LOCAL PREPAREDNESS

Suzet McKinney, executive director and chief executive officer of the Illinois Medical District, provided a local-level perspective on preparedness. She said a business case needs to be made for sustainable investment in outbreak preparedness, but this is difficult because of the competing priorities and limited resources at the local and state levels. Although the local level is where the "rubber meets the road" in terms of science, policy, and operational guidance, complacency remains a problem. She noted that the impact of previous outbreaks is quickly forgotten, and during pre-outbreak periods, members of leadership do not have tangible evidence of impending threats. She suggested finding more compelling ways to convey the significance of outbreaks to leaders and stakeholders in terms they can understand and to which they can relate. For example, workshops

could convene local and state officials and stakeholders from the health care, government, and business sectors. Stories and narratives from actual emergencies and outbreak situations could also be leveraged to emphasize the importance of outbreak preparedness. Champions from industry and philanthropy could also be helpful, especially when they could provide additional financial support. Sustained federal investment in preparedness is important, she added, because it is difficult to make the case that local and state officials should invest in preparedness in the absence of sustained federal investment.

McKinney explored strategies to gain political and financial support from high-level stakeholders at the local and state levels. The overarching strategy she recommended was to educate local leaders and stakeholders about how outbreaks in their jurisdictions could affect their abilities to govern and about how investment in preparedness could protect against those challenges. For instance, outbreaks and pandemics could affect the political prospects of elected officials by impacting local economies, disrupting educational systems, and causing civil unrest. Educating local business leaders about the potential effects of outbreaks and pandemics on their bottom lines might also encourage protective investment in preparedness.

People who live and work in local communities can help contribute to ending cycles of panic and neglect. However, McKinney said, they need to be equipped with information and knowledge to empower them and to enable them to act. This is a challenge because many communities, especially those with underrepresented or vulnerable groups, continue to mistrust the government. Moving beyond this mistrust will require being more inclusive of communities in preparedness efforts, she remarked. Community engagement is a powerful tool that can help quell panic and chaos during a crisis by increasing compliance with preparedness efforts, such as vaccination, and by helping public health officials understand the unique vulnerabilities within specific communities. McKinney noted that community health workers, faith-based organizations, and community-based organizations are often considered trusted agents that can also play a role in helping communities understand the importance of preparedness.

BROADENING THE CONCEPT OF HEALTH SECURITY

Peter Sands, executive director of The Global Fund to Fight AIDS, Tuberculosis and Malaria, said the cycle of panic and neglect is unsurprising from an economic standpoint. Behavioral economics has shown that when faced with low-probability, high-impact risks, people tend to overreact or to massively underreact; people also tend to be susceptible to the availability heuristic and to over-optimism. In the context of an infectious disease

outbreak, this combination of factors drives the cycle of panic and neglect. He suggested breaking that cycle will require structural and institutional efforts to make the risks and the degrees of preparedness more transparent.

There have been a fair number of economic analyses of the risk of infectious disease outbreaks, Sands said, but the situation is not ideal in terms of institutionalizing these analyses. Ad hoc economic analyses of the cost of a large-scale influenza epidemic, for example, are not useful unless they are incorporated into the mainstream macroeconomic analyses that drive policy decisions. This tends to happen only after an incident has occurred. He suggested that in order to converge different decision maker perspectives on investment in preparedness, the risk of outbreaks needs to be successfully factored into economic policy making in the same way that other kinds of risks are factored into the economy.

Sands remarked that the global health community is currently focused on collaboration to achieve multiple objectives through different institutions with individual mandates (e.g., the Global Action Plan for Healthy Lives and Well-Being for All[1]). Such collaboration would also benefit global preparedness efforts because response efforts are shaped by context—outbreaks do not occur in isolation. For example, the response to the current Ebola outbreak in the Democratic Republic of the Congo is being impeded not by technical limitations but by violence in the area, which prevents health workers from intervening effectively. He suggested that adopting this broader perspective would also help strengthen local capacity because encouraging local officials and communities to invest in preparedness requires communicating the concept of health security in a way that makes practical sense to them. Sands argued that the concept of health security often promulgated is counterintuitive—from a political perspective or, arguably, from an ethical perspective—because it asks national governments to invest money in diseases that *might* kill their people instead of asking them to invest sufficiently in diseases that *are* killing their people in large numbers every day. For example, the current Ebola outbreak in the Democratic Republic of the Congo has killed more than 500 people and has mobilized much effort and attention, but during the same period, 20,000 people died of malaria in the country (WHO, 2018b). He said that given this disparity, convincing officials to prioritize Ebola over malaria is difficult.

Sands maintained that a new concept of health security should be developed to directly address the diseases that are currently killing people in

[1] Coordinated by WHO, this Global Action Plan unites 12 health and development international organizations to commit to finding new ways of working together to accelerate progress toward achieving the Sustainable Development Goals. For more information, see https://www.who.int/sdg/global-action-plan (accessed February 26, 2019).

vulnerable countries. This involves building day-to-day capacities—such as disease surveillance, frontline health workers, and diagnostic laboratories—that simultaneously build the contingency and resiliency capabilities necessary to handle outbreaks. He said institutions should focus more keenly on how efforts to fight diseases such as malaria can be used to achieve broader health security objectives. Catalyzing action, Sands reiterated, will require conceptualizing health security in a way that makes sense to people working on the ground. He added that businesses are an under-leveraged point of action because many are unaware of their vulnerabilities to infectious disease risk and of the net impact of outbreaks. Engaging business owners and encouraging them to think more systematically about the nature of their exposures can encourage them to advocate for better preparedness.

DISCUSSION

Reflecting on the panel presentations, Kumanan Rasanathan, board member of Health Systems Global, highlighted the importance of identifying and connecting with people's specific interests and incentives to ensure adequate preparedness. He said the broad realities of people's lives need to be considered—at the global level, with the Sustainable Development Goals as a unifying framework—and at the individual level, by identifying the health threats of greatest concern. In 2013, 40,000 children under 5 years of age died in Sierra Leone, but this tragedy was not considered a global health emergency; in contrast, an outbreak that people fear is a global risk can suddenly become a global health priority (UNICEF, 2013). Rasanathan observed that the cycle of panic and neglect is difficult to escape because, in many ways, the habitual framing of outbreaks lends itself to this cycle. He suggested that trying to understand and to address these challenges in particular ways—such as by communicating evidence and risks through narrative strategies that personalize the potential impact of outbreaks—may lead to improvements. Furthermore, the cycle itself could be exploited by capitalizing on any opportunities that arise from the focused attention during crises in order to build lasting capacities and institutions. He noted that people who participate in exercises on preparedness for response exercises, for example, develop a sense of the potential impact of outbreaks on their lives and their core businesses, which incentivizes their continued focus.

In addition, Rasanathan underscored that preparedness work needs to be bridged with other health concerns and with other sectors. Global health has often encouraged "single issue fundamentalists" who focus exclusively on a given issue, in many cases very successfully, but he urged that pandemic preparedness needs to be situated in the broader context. As Sands suggested, to gain credibility, preparedness should be linked to existing infectious threats (such as malaria), to day-to-day health concerns (such

as diabetes and cardiovascular disease), and to individuals' concerns about their personal security in conflict areas. Rasanathan reminded the audience that communities are heterogeneous and diverse, so one-size programs do not, in fact, fit all. To be equitable, he said, more attention must be paid to vulnerable populations that have high levels of risk and that often miss out from government and private-sector interventions. The heterogeneity of society at large should also be recognized, he added, because preparedness is often a government enterprise that does not sufficiently reflect the inputs of communities or of the private sector, which has many resources and capacities to contribute. He added that although investment cases are useful, there are so many of them in global health—which tend to be based on models with a large number of assumptions—that they can be difficult for policy makers to bring together. There is rarely a sense of relative prioritization that examines the tradeoffs involved in different investment strategies.

Transcending the Cycle of Panic and Neglect

Rasanathan asked panelists if they believed it was possible to transcend the cycle of panic and neglect or if periods of higher and lower priority were inevitable. Gerberding said pandemics and outbreaks are increasingly probable events, but because their geographic spread and timing cannot be predicted, a national defense model is more apt than a probabilistic one. She noted that even the poorest countries seem to be able to find resources and to sustain investments in their defense capabilities, and this mentality should be shifted to the fight against microbial enemies. Kolker remarked that in the near future, the economic impact of infectious diseases will be of similar magnitude to those of terrorism and of climate change; yet, spending on infectious disease preparedness is orders of magnitude lower than spending on other areas. An episodic approach is not appropriate for infectious disease preparedness or any other systemic problems, Kolker said. McKinney maintained that the status quo is unacceptable because outbreaks have become more frequent and severe over time. She suggested a whole-community approach to preparedness, which balances top-down approaches to engage high-level local leaders with bottom-up approaches to engage community members, stakeholders, and faith-based leaders.

Sands agreed that outbreaks are increasing and are not the type of events that occur only once in 100 years. Although efforts to deal with the morbidity and mortality impacts of infectious disease outbreaks have improved, complacency is unacceptable because today's interconnected global economy is more vulnerable to the swift and powerful knock-on economic impacts of events that occur on the other side of the world. He said preparedness efforts need to improve through a holistic capacity-building approach, which will require building the components of the JEE to be able

to deliver on near-term health objectives for a specific community. This approach enables joint benefits: It solves immediate health problems and exercises and tests a system's capacities prior to a major event. Sands added that health security capacity building should be integrated with efforts to solve communities' immediate health needs; this type of effort would build trust within communities and would enhance the credibility of health authorities and frontline workers.

Peter Daszak, president of EcoHealth Alliance, asked for examples of how the cycle of panic and neglect has been transcended for infectious diseases or other cyclical health threats, perhaps strategies that were institutionalized during one crisis but were designed to last through the next. Kolker reflected on some of the strengths and weakness of the anthrax and Ebola responses. Both were emergency appropriations and did not create a continuum of funding. However, the Biomedical Advanced Research Development Authority (BARDA) and the Assistant Secretary for Preparedness and Response (ASPR) within the U.S. Department of Health and Human Services were created in response to the anthrax event, which has institutionalized business–government cooperation. He noted that the Ebola outbreak helped catalyze the GHSA, which, in turn, led to developing the JEE and placing WHO at its lead. Kolker added that after its 2015 reforms, WHO approached the Zika and Ebola outbreaks in the Democratic Republic of the Congo in a more coherent way. This included the creation of standing agreements to increase surge capacity with actors that did not previously have organic working relationships with WHO. However, he said, U.S. government agencies such as the U.S. Centers for Disease Control and Prevention (CDC) still tend to have a risk-avoidance mentality rather than a risk-management one, which precludes the agency's intervention in less secure settings such as Eastern Congo. This risk-avoidance mentality is self-defeating, Kolker said, because it undermines the new approaches to pandemic preparedness that the United States helped establish. He noted that CDC has specialist experts who could be dispatched to help other countries elevate their systems to first-world capacity, but the agency is not structured to do so.

Insurance for Preparedness and Response Efforts

Bruce Gellin, president of global immunization at Sabin Vaccine Institute, asked about the potential for insurance to mitigate downstream risk and to reduce payouts after an event. Sands responded that the role of insurance is both overstated with respect to countries and understated with respect to the private sector. Insurance related to outbreaks has two functions: (1) it provides cash to respond to an event after it has happened, and (2) it creates incentives for better preparedness if that investment is

reflected in lower premiums. Among more vulnerable countries in particular, however, money is relatively easier to obtain during a crisis response than during preparedness efforts. Insurance does not create the right type of incentives for this situation, Sands added, because vulnerable countries will not be able to obtain a sensible price for infectious disease risk; furthermore, any preparedness efforts that do exist are typically donor-funded. He argued that it is not advantageous to have low-resource countries pay expensive premiums for an insurance product—using money they could be spending on actual risk mitigation—because insurance, in and of itself, does not mitigate any risk.

Sands noted two factors about infectious disease outbreaks that make the economics of insurance more difficult. First, because the externalities are so large in relation to the risk borne by the payor, much of the cost and threat of an infectious disease outbreak is not borne by the country in which it first originates. Second, an outbreak is not a discrete event with immediate consequences, such as an earthquake or a flood; because it is an event that unfolds over time, its trigger is much more difficult to define. Sands noted that the only payout from World Bank's Pandemic Emergency Financing Facility to date was from a component of the mechanism that was not insurance-driven because the insurance component had not been triggered. Sands suggested that more insurance options related to infectious disease outbreaks could be useful in the corporate sector because they would establish the right incentives for businesses to better prepare for outbreaks, and that would be reflected in premiums. However, corporate insurance for outbreaks is not currently available in most places.

Building a Political Movement for Preparedness

Carolyn Reynolds, vice president of policy and advocacy at PATH, suggested that moving the preparedness agenda forward will require investing directly in building political will. She emphasized that politicians and funders need to be presented with a cogent political argument to garner interest and to convince them to act. Kolker said that obtaining predictable and sustainable funding for preparedness will require creating a political coalition. McKinney described an innovative local-level approach to building political will that was used in New York City: A one-page threat-response guide was created for local elected officials, which summarized the threat, the impact it could have on the city, and the actions necessary to avoid that impact. She suggested that this type of practice could be extrapolated to build political will among other elected officials. For example, guidance could be provided to the members of U.S. Congress who control appropriations, so they are aware of the importance of preparedness. Leveraging other existing systems that have already been developed

could also help to maintain the continuum of preparedness in the face of funding cuts, she added. For example, existing community coalitions could be incorporated into issues around outbreaks and pandemic preparedness. Gerberding noted an additional benefit of strengthening private-sector business participation in preparedness is that it is a component of building political will.

Bridging the Dichotomy Between Pandemic and Day-to-Day Preparedness

Rima Khabbaz, director of the National Center for Emerging and Zoonotic Infectious Diseases at CDC, pointed out the perceived dichotomy between investment in preparedness and investment in day-to-day threats. Pandemics receive large amounts of attention and resources in the short term, but these reactions do not build the type of awareness needed to encourage people to invest in capacities for both day-to-day threat response and surge capacity for preparedness. Gerberding said that focusing more attention on preparedness during the interim periods will require drawing on institutions and measures already in place. For example, businesses could integrate and institutionalize preparedness as part of their existing planning processes. Businesses are often required to conduct risk assessment, risk mitigation, and risk planning, so many companies already have approaches that could be expanded to include outbreak risk. Bringing preparedness planning into existing risk assessment structures would highlight the potential impact of an outbreak on the continuity of business and the potential for mitigation. In a health-related business, planning for a health threat becomes even more germane, she added. Not only must the business be protected, she said, but the people who depend on vaccines and medicines must also be protected. Pia MacDonald, senior director of applied public health research at RTI International, said that the business community needs to be better educated about the risk of pandemics. She noted that a recent risk evaluation study of Fortune 500 companies found that many firms that had disclosed significant levels of international sales had not disclosed any risks around disease outbreaks or other public health issues in their 10-K filings.

Sands reiterated that much ongoing work could have practical benefits for outbreak preparedness. For example, creating emergency operation centers focused on malaria also builds emergency management capability that can be multipurposed for an outbreak. Some of the JEE's components may map onto current work, such as Gavi, the Vaccine Alliance's cold chain distribution systems for vaccines and the Global Fund's disease surveillance system for tuberculosis, HIV, and malaria. He suggested that systems and capabilities should be implemented in a deliberate, systematic, and forward-thinking way to serve specific purposes while also having the

potential to strengthen preparedness efforts. If the more general elements of preparedness are achieved through multipurpose programs in pursuit of the broader health systems development agenda, he added, then efforts specific to health security will become narrower in scope and easier to achieve.

Integrating Health Security Capabilities into the Health Agenda

Rafael Obregon, chief of communication for development at the United Nations Children's Fund, asked about practical entry points for integrating health security capabilities into the broader health agenda, given that the donor community and ministries of health tend to be issue-driven and to support vertical programming. Sands said one point of integration could be one of the indicators (3d) of Sustainable Development Goal 3 (SDG3), which states the importance of strengthening the capacities of all countries, in particular developing countries, for early warning risk reduction and for management of national and global health risks.[2] The significance of the Global Action Plan for Healthy Lives and Well-Being for All is that the participants will not only pursue their individual mandates but also work together to help other countries deliver on the SDG3 agenda.

Kolker noted that the SDGs, while important, have encroached somewhat on the integrated global health agenda because they do not directly address health security. As a result, health security is not being prioritized in spending decisions or being measured to the extent that it should. Sands said though they are far from perfect, the SDGs reflect the frame through which major donors and health multilaterals think. He argued that a broader concept of health security with greater political and ethical legitimacy is needed. The current narrative around health security is that "poor, vulnerable countries should invest in things that might kill them, rather than the things that are killing them . . . this has not worked, and it is not going to work," Sands said.

Shifting from Threat Protection to Health Promotion

Keiji Fukuda, director and clinical professor, School of Public Health, The University of Hong Kong, observed that public health focus has expanded to include noncommunicable diseases as well as infectious diseases, which has driven a fundamental shift toward promoting wellness in addition to reducing health threats and fighting diseases. He wondered if the traditional threat-reduction approach will be abandoned because many people perceive infectious disease outbreaks as irrelevant, distant events.

[2] For more information on the other SDG3 indicators, see https://sustainabledevelopment.un.org/sdg3 (accessed February 11, 2019).

Similar concerns apply to the current focus on catalytic funding rather than sustainable funding for capacity building. Fukuda asked if the message should be changed or if shifting the narrative would undermine the effort. Gerberding remarked that local and state tools have been updated to include measures of how many people are optimally well in a given population. Such updates could allow health to be reconceptualized as a community good that warrants investment, like any other natural resource, through the "health in all policies" approach. McKinney suggested communicating how the lack of appropriate pandemic preparedness may undo advancements in health and wellness and create even greater disparities and inequities in health.

Potential Technological Advances and Considerations

Avital Percher, AAAS fellow at the National Science Foundation, asked about technological advancements that may enhance response to an outbreak or pandemic. Kolker replied with an example from the Ebola and H1N1 outbreaks. Before surveillance systems were implemented, Internet search terms about symptoms were predictors of where outbreaks would occur. He suggested finding ways to systematize social media to help identify problems and to respond to them.

Sands highlighted several types of technologies that he believed would be impactful, including

- inexpensive, point-of-care diagnostic technologies that can be used by relatively unskilled workers to support response to any disease;
- advanced geospatial mapping tools that could be used in resource-poor environments as a basis for contact tracing and incidence mapping, which would allow interventions to be targeted effectively; and
- modern communication technologies that could be used to build rather than to undermine trust, which would allow governments to maintain a voice of authority and credibility.

Monique Mansoura, executive director for global health security and biotechnology of MITRE, asked panelists about the sustainability of the business model for companies that make vaccines or other medical countermeasures. Gerberding reported that Merck's experimental Ebola vaccine, which is currently being used in the Democratic Republic of the Congo, was not developed as a commercial opportunity. Because it cost far more money to produce than the company would ever recover, Merck did not consider it to be a sustainable solution. She suggested that the Coalition for Epidemic Preparedness Innovations (CEPI), a global alliance that finances

and coordinates the development of vaccines against infectious diseases, is important because it facilitates the development of priority countermeasures to known threats. However, she added, CEPI will likely require partnership with existing companies because they are unlikely to have experience in the domain of approval and licensure. Vaccines and vaccine technology also remain a global concern; there are daily shortages due to difficulties with manufacturing and to the decreasing number of manufacturers. Gerberding predicted market failure will become increasingly inevitable and will require a change in strategy toward a biodefense mentality.

Reflections on Overcoming Impediments to Pandemic Preparedness

In summary, Rasanathan underscored the need to think about preparedness in a "big picture" way by reflecting on successes in past responses and on why the cycle of panic and neglect is difficult to escape. As Rudolf Virchow (2006) said in his report on the 1848 typhus epidemic in Upper Silesia, "medicine is a social science, and politics is nothing else but medicine on a large scale." Rasanathan noted that the same challenge persists today: integrating public health evidence and science with efforts to address psychology, behavioral economics, and personal incentives and emotions. According to Rasanathan, the panelists seemed to agree that the cycle of panic and neglect can be escaped, but it will be difficult. When approaches to outbreak preparedness and to non-disease threats, such as war or terrorism, are compared, stark differences in the investments and their sustainability emerge. However, given the advancements in outbreak preparedness over the past century, Rasanathan noted that today's scenario could be much better. He suggested that in order to motivate people—from a village in Liberia to high-level policy makers in Switzerland—to engage in the preparedness endeavor, stakeholders need to understand how preparedness relates to their daily lives and how it connects with other challenges and threats they encounter on a daily basis.

Additionally, the preparedness community needs to focus on attaining a continuum of funding, Rasanathan said. He noted that even the health sector does not appear to be convinced that preparedness warrants significant investment. Garnering investment in preparedness should be feasible, he said, given that $10 trillion is available in the global health sector within the broader frame of the integrated global health agenda. At the same time, other relatively low-probability, high-impact events, such as war or terrorism, have been able to garner continuous funding. He observed that one reason for this trend may be people's ability to relate to stories about war and terrorism. Similar stories are not typically told about outbreaks, but heroic stories abound during crises. For instance,

in a village in Liberia, Rasanathan heard tales of heroism, such as stories about people who decided to care for their fellow villagers and who did not touch their own children for 3 months. But these stories, he reiterated, are quickly forgotten and seem to disappear from the public consciousness in a way that stories of war and terrorism do not. Rasanathan suggested the public health community should be proud about some of the achievements in preparedness, but the community should also reflect on how to improve current efforts. Although the efforts might not always proceed in a straight line, he concluded, it is important to leverage the inflection points at which efforts might be intensified and institutions might be built.

SMALL-GROUP DISCUSSIONS: POTENTIAL STRATEGIES TO SYSTEMATIZE AND INTEGRATE PREPAREDNESS

For the second half of the session, the audience members assembled in small-table groups to reflect on specific actions and strategies that could be prioritized so outbreak preparedness could become a routine—and not extraordinary—part of governmental and other organizational activities at the local, national, global, and private-sector levels. To help spark these discussions, the moderator Jonna Mazet, professor of epidemiology and disease ecology and director of the One Health Institute at University of California, Davis, summarized some key points for ending the cycle of panic and neglect that she captured from the panelists during the first half of the session (see Box 8-2).

After the table-group discussions, members of the audience shared some of their reflections from the session. Audience members discussed issues that ranged from bolstering preparedness capacities of governments and communities to creating effective messaging and educational tools for relevant stakeholders.

First, David Fidler, professor of law at Indiana University Bloomington, highlighted the importance of accepting and embracing the window of panic as an inevitable component of preparedness. He added that every policy area experiences this cycle of panic and neglect; it is not exclusive to global health. Panic should be construed as a process to be studied in order to find ways to leverage the opportunities that a crisis provides and to work more effectively with decision makers in panic situations, he said. Approaching panic as a process can provide opportunities to reduce the political elasticity seen in global health and to make it more like other areas of policy, which are more inelastic with regard to the cycle of panic and neglect.

Jay Siegel, retired chief biotechnology officer and head of scientific strategy and policy for Johnson & Johnson, said that his group discussed whether adequate governmental organizational structure and leadership is

BOX 8-2
Potential Priorities for Ending the Cycle of Panic and Neglect

Jonna Mazet, executive director of the One Health Institute and professor of epidemiology and disease ecology at the University of California, Davis, presented some takeaways she captured from panel discussions about strategies at local, national, global, and private-sector levels that may help end the cycle of panic and neglect for pandemic preparedness:

- Conceptualize health security and preparedness in ways that make sense not only at global but also at local and national levels.
- Establish a sustained budget for preparedness efforts so that institutionalized capacities and systems can be built.
- Build local- and national-level political will for preparedness.
- Convene forums and workshops focused on preparedness at the local and state levels.
- Educate, equip, and empower local communities, using trusted community agents, with the information and knowledge to act.
- Fight day-to-day endemic diseases by building health system capacity and by engendering trust among communities so that systems are in place—and community members are willing to use them—when an emergency strikes.
- Publicize data, evidence, and narratives about preparedness in a more compelling way.
- Effectively leverage social media to coordinate preparedness efforts.
- Support the strengthening of the World Health Organization and other global institutions in order to facilitate preparedness efforts.

SOURCE: Mazet presentation, November 28, 2018.

in place for preparedness in the United States. He noted that government responses to disasters over the past few decades (e.g., the sulfanilamide and thalidomide disasters) have led to the creation of legislation and infrastructure that are able to deal with and prevent many problems. He reported that some members of the group wondered whether BARDA and ASPR are adequately resourced and staffed to drive behavioral changes throughout different levels of government and across society as a whole.

Julie Pavlin, director of the Board on Global Health at the National Academies of Sciences, Engineering, and Medicine, reported that her group discussed institutional capabilities to create a broad interagency organization in the United States. Ideally, this agency would have the authority and budget necessary to unify the different capabilities in a sustainable and expandable way in times of international disaster. A model like the U.S.

Federal Emergency Management Agency (FEMA) could be useful—one that delegates responsibility and decision making for preparedness and response but also has a complementary international focus. Pavlin also noted the importance of educating politicians, the public, and other governments about the risks of seasonal influenza, which are often poorly understood, and how to use seasonal influenza response capacity to build a platform of knowledge and capacity to respond during a pandemic event.

Other participants also proposed adopting a FEMA-like model. Elizabeth Hermsen, head of global antimicrobial stewardship at Merck & Co., Inc., reported that some of her group members discussed the need to develop a FEMA-style playbook for preparedness that clearly outlines leadership roles and actions for specific situations and that details back-up plans. This playbook should extend beyond the health-specific response components to include a more multisectoral and whole-community response, she said. In conjunction with the playbook, the group discussed the idea of creating a credit line on reserve to expedite access to funding and to avoid the lengthy negotiations typically required for appropriations. Ashley Grant, lead biotechnologist at MITRE, added that members of her group also discussed the potential of a FEMA-style model for preparedness.

In addition to strengthening government-level capacities for preparedness, Eva Harris, professor of infectious diseases and vaccinology at the University of California, Berkeley, commented on the need to embrace communities. The concept of community is heterogeneous. In some settings, communities are already unified, and in others, they are fragmented—but there is always some level of organization already in place. She said the task should be to recognize and strengthen existing elements and to create linkages to health and preparedness.

Similarly, Emily Erbelding, director of the Division of Microbiology and Infectious Diseases at the National Institute of Allergy and Infectious Diseases, reported that her group focused on the importance of strengthening local capacities, particularly the surge capacity of local health departments, because many departments lack sufficient capacity to conduct day-to-day work. She also noted that some participants in the group discussed day-to-day surveillance for infectious diseases, outbreak response, and outbreak prevention and debated whether health departments would be better prepared for a crisis if systems were in place to collect metrics from more typical outbreaks. These metrics could be monitored to identify deficits and to apply resources to address them. Furthermore, some group members also discussed the need for structural interventions, such as advance purchase agreements, to reduce the need to procure large quantities of vaccines and/or antivirals during a crisis.

Further highlighting the role of communities, Obregon also argued for the need to strengthen local capacities and community preparedness, with

an emphasis on preparedness exercises. He said that to build community resilience and the capacities necessary to prepare for and respond to outbreaks, a broad set of stakeholders and community actors should be included in the process. This process might include, for example, templates or approaches developed for influenza that would also cover a number of other critical elements for strengthening local capacities. A broader public health perspective should be adopted, he added, to ensure that the approach is flexible and adaptable to other kinds of outbreaks or situations that are priorities for the community on a day-to-day basis. He stressed that efforts should also focus on coalition building and on bringing actors from beyond the health sector to the table for discussions—for example, engaging with local politicians and decision makers to communicate the benefits of investing in preparedness for that particular community.

Finally, Obregon noted the need to use targeted messaging and communication strategies to raise awareness about the potential impact of outbreaks on local communities. Care should be taken to frame messages positively, he said, and to avoid negative framing that may be amplified by social media and other communication channels. For instance, in the event of a vaccine failure, it would be helpful to focus on the lives that were saved rather than on the failure itself. In a similar vein, Hermsen suggested focusing on education about pandemics and implementing non-pharmaceutical interventions at the local level—such as infection prevention in school-age children—to ensure that community-level preparedness functions are better engrained. Amanda McClelland, senior vice president of Prevent Epidemics at Resolve to Save Lives, added that work is needed to determine how strategies for risk communications should be put together for the community level, particularly in the United States where social media plays such a central role in public life.

9

Visions on Potential Priorities and Actions for Preparedness by 2030

Session 3 of the workshop culminated in discussions about top priorities and potential actions for strengthening preparedness by 2030—the target date for the Sustainable Development Goals (SDGs) to achieve a better and more sustainable future for all. The session was moderated by Rima Khabbaz, director of the National Center for Emerging and Zoonotic Infectious Diseases at the U.S. Centers for Disease Control and Prevention (CDC). It opened with visionary statements from four panelists about what they identified as the most pressing actions and priorities for improving preparedness and global health security by 2030. Panelists discussed how those efforts could synergize with other global efforts and investments, such as the SDGs, health systems strengthening, and the Coalition for Epidemic Preparedness Innovations (CEPI). Harvey Fineberg, president of the Gordon and Betty Moore Foundation, discussed ways to strengthen preparedness capacities by improving public understanding about influenza and by developing new vaccines, diagnostic technologies, and antiviral treatments. Gabrielle Fitzgerald, founder and chief executive officer of Panorama, explored the importance of using a strong advocacy agenda to make preparedness a political priority. Nicole Lurie, former Assistant Secretary for Preparedness and Response at the U.S. Department of Health and Human Services (HHS), emphasized the need to build preparedness capacities by strengthening day-to-day systems. Ciro Ugarte, director of the health emergencies department at the Pan American Health Organization (PAHO), discussed the importance of improving local, national, regional, and international capacities and of overcoming coordination challenges. Finally, to conclude the workshop, Keiji Fukuda, director and clinical

professor, School of Public Health, The University of Hong Kong, provided reflections and some takeaways on potential ways to move forward in order to achieve greater preparedness.

BOLSTERING PUBLIC UNDERSTANDING AND THE ORGANIZATIONAL, RESOURCE, AND TECHNOLOGICAL COMMITMENTS FOR PREPAREDNESS

Harvey Fineberg, president of the Gordon and Betty Moore Foundation, explored several ways to strengthen preparedness and response—with a focus on influenza—in the coming decades. He drew a distinction between panic and preparedness and highlighted the "paradox of indifference" against unknown threats and risks. Gaining political and policy support for preparedness, he said, ultimately depends on the understanding and support of the general public. To promote better understanding, he suggested, public health discussions about influenza pandemics should not use the term "the flu" in connection with preparedness. After decades of misuse in advertising for over-the-counter medications (e.g., for the "stomach flu" or "cold and flu symptoms"), the public perceives "the flu" as an ill-defined and relatively minor ailment. According to Fineberg, rather than trying to change these entrenched public misconceptions, the term influenza, rather than flu, should be always be used to discuss preparedness. This could help promote public understanding that influenza is a unique and serious disease—no other condition has such a severe burden on an annual basis and such a capacity for catastrophic burden on a periodic, non-occasional basis. Influenza should be addressed every year as a serious problem and occasionally as a potentially catastrophic problem, he added. Fineberg also suggested that the distinction between seasonal and pandemic influenza should be discarded in order to bolster public understanding. For example, CDC estimated 80,000 deaths from influenza in the United States in 2017, but on an annual basis, influenza probably causes at least 600,000 deaths worldwide (CDC, 2018). He said that periodically, that number could be 10-fold or even 100-fold greater.

Additionally, Fineberg focused on the need for better organization and greater resource commitments. He noted that the world is still ill prepared to respond to a severe influenza pandemic or to any sustained global public health emergency—this holds for Ebola, severe acute respiratory syndrome, or influenza. Although there have been successes and substantial improvements in organizational preparedness, such as the Pandemic Influenza Preparedness (PIP) Framework and pre-agreements with vaccine distributors, he said the shortfalls also need to be recognized. For example, the world currently does not have the capacity to produce 10 billion doses of vaccine in a given year. He said the pandemic preparedness community

"is constantly at risk of either being at fault because we've done too much when too little has happened, or at fault because we've done too little when too much has happened."

Finally, Fineberg suggested that adequate preparedness in the future will require progress in three technological domains: vaccines, diagnostics, and antiviral treatments. First, progress with influenza vaccines will require a "quadruple jump" across four main obstacles to attain sustained capacities to protect populations and to allow outbreak response to get ahead of the epidemic curve (see Chapter 3 for more on influenza vaccine challenges and the road to a universal influenza vaccine). He specified that influenza vaccines should be

- effective against all or most strains instead of against a selective, small number of strains;
- more efficacious and protective (ideally at least 90 percent);
- protective for decades rather than a few months; and
- producible on a shorter time scale.

Second, Fineberg remarked that diagnostics that allow people to test themselves at home would swiftly inform the community, caregivers, and public health authorities about influenza conditions that are currently prevalent (see Chapter 4 for more on at-home diagnostics). Finally, he added, better antivirals are also needed to stifle severe influenza and to transform it into a manageable disease—much as the cocktail of antivirals has done for HIV. He suggested that this could facilitate acute case management and potentially reduce the severity of influenza.

POLITICAL PRIORITIZATION AND STRATEGIES FOR PREPAREDNESS

In her presentation, Gabrielle Fitzgerald, founder and chief executive officer of Panorama, remarked that political prioritization of a health issue can create a sea of change in people's thoughts about how to solve problems. The significant changes effected by political strategies to address malaria, polio, and HIV/AIDS have inspired optimism that similar progress could be made through a concerted effort to develop a political strategy related to address microbial threats and outbreak preparedness. For example, The President's Emergency Plan for AIDS Relief initially received a funding commitment of $15 billion over its first 5 years because there was a concerted effort to prioritize HIV/AIDS on high-level political agendas (UNAIDS, 2018). Similarly, funding for malaria increased dramatically through the President's Malaria Initiative. Resource mobilization strategies by Gavi, the Vaccine Alliance, and CEPI have also resulted in billions of dollars in new funding.

"Major change can happen when the right political forces align," Fitzgerald reiterated. She explored how health diplomacy might elicit political action toward readiness for microbial threats. Public health is inherently political, and health diplomacy involves finding ways to incentivize governments to achieve health goals. She said that a sophisticated health diplomacy and advocacy strategy will be needed to promote preparedness issues on political and financing agendas, she said. Although the United States remains the largest funder of global preparedness capacity, other countries could also fill leadership roles if they were engaged and if they had the support to do so. She suggested that philanthropists could also be agents of change, as demonstrated by global foundations that have leveraged philanthropic dollars to encourage others to act. For example, an initial $540 million was raised for CEPI through a catalytic coalition led by Norway and the Wellcome Trust.[1] She also highlighted the potential to accelerate the pace of change through collective efforts driven by a unified coalition of entities working on preparedness.

Fitzgerald described some priority changes for which a political strategy around outbreak preparedness could advocate. In a recent publication, global health scholars reviewed progress that has been made in areas of needed improvement[2] that were identified by post-Ebola panels and commissions (Moon et al., 2017). Significant improvement was found in only two areas: WHO's preparedness and response capacity had improved with the creation of the Health Emergencies Programme, and progress toward developing new vaccines had improved with the creation of CEPI. Although many countries had completed the Joint External Evaluation (JEE) process, few had costed the plan, and little financing was available for countries to implement the JEE recommendations. In most other areas, progress was incremental or very limited. Fitzgerald maintained that a political strategy should highlight this general lack of progress in broader global health and national security conversations.

Fitzgerald was hopeful that investment in health diplomacy and advocacy would help break the cycle of panic and neglect in preparedness. Quoting Lawrence H. Summers, Charles W. Eliot Professor and president emeritus of Harvard University, Fitzgerald noted that pandemics and epidemics have the highest ratio of global seriousness to policy attention, but relative to their significance to humanity, no other issue receives less attention. To help shift this ratio, she suggested advocating for several

[1] For more information on CEPI investments, see https://cepi.net/news (accessed March 22, 2019).

[2] The eight areas of needed improvement were leadership and monitoring, financing, national health systems capacity, the role of WHO, the humanitarian aid system, research and development of health technologies, knowledge sharing, and trade and travel restrictions.

specific improvements: leadership, coordinated planning efforts, and increased and sustained funding. Although WHO has improved capacity to manage outbreaks, she noted, it is not positioned to respond to a global crisis or pandemic. She suggested that to improve leadership, the United Nations (UN) Secretary-General needs a standing mechanism to prepare for and to coordinate across all areas of a pandemic response. A coordinated planning effort would involve an overarching global plan that articulates all of the needed areas for improvement and that regularly measures and tracks progress. Finally, Fitzgerald suggested that increased and sustained funding would support (1) the implementation of countries' JEE plans, (2) overall WHO operations and the WHO contingency fund for emergencies, and (3) research and development of new diagnostics.

BUILDING PREPAREDNESS CAPACITIES ON DAY-TO-DAY SYSTEMS

Nicole Lurie, former Assistant Secretary for Preparedness and Response at HHS, drew on her experiences with the Office of the Assistant Secretary for Preparedness and Response, CEPI, and the World Bank. She observed that in most countries, outbreak preparedness needs generally do not align with the population's other critical needs. That is, compared to outbreak mortality, more people worldwide die every day from hunger, poverty, violence, and routine infections such as malaria or cholera. Consequently, neither acute infectious disease outbreaks nor noncommunicable diseases, which increasingly affect people across the world, tend to be a priority in most countries—including the United States. She noted that the two issues are rarely considered in the same context, despite the generic skillset that would provide the first line of defense for both in terms of workforce, infrastructure, and public health. Lurie noted that outbreak-related research focused on a single disease is not sustainable, especially in developing countries, because it tends to be funder-driven and to dissipate when the disease du jour has grown quiet. Investment priorities should broaden beyond emerging infectious diseases to include multipurpose investments that link capacity-building efforts to outbreak preparedness, Lurie said. This would help ensure that both the day-to-day health concerns of governments and the interests of the global community are being addressed.

Potential Priorities for Capacity Building

Lurie maintained that preparedness should be built on day-to-day systems so that outbreak response occurs through systems already in place. Funding and interest in capacity building that arise during crises, she added, should be used to strengthen those day-to-day systems. She suggested that

surveillance systems should be multipurpose and should cover noncommunicable diseases as well as outbreaks; a robust and flexible system should be able to pivot to detect and respond to an outbreak signal. Over time in the United States, most of the funding for surveillance has shifted to a budget for preparedness, which must constantly be adjusted to deal with all types of diseases. The organization of these efforts needs to be reconsidered and restructured, she said.

Strengthening health systems is another priority, Lurie said, because the ability to deliver basic medical care is critical to outbreak preparedness. Basic capacities are often taken for granted, but in many parts of the world, providers are unable to oxygenate patients with influenza or administer basic intravenous fluids to patients with Ebola. Deficits in basic health care must be addressed in settings where responders cannot wash their hands or where intravenous fluids are not available. She suggested that the U.S. government could engage more robustly in supporting developing countries' efforts to build health systems that at least have basic capacities.

Making a Business Case for Capacity Building

Lurie explained that the business case for investment should focus on generic skillsets that apply to noncommunicable diseases as well as outbreak preparedness. Framed appropriately, she said, this could also attract more private-sector interest and momentum among parties investing in developing countries that need more functional surveillance and health delivery systems. She also suggested focusing on how to use existing funding more effectively rather than seeking more money in aggregate. Funders are currently channeling money into capacity building and preparedness in a siloed way. She noted that synergizing all the existing funding sources could optimize the results. At a minimum, better transparency and organization would make it easier for countries to deal with the large number of different funders.

Research and Development Priorities

Research should be a component of every outbreak response, Lurie said, because every outbreak presents opportunities to ask and to answer important questions. She suggested building a system to develop organized research capacity that could be executed when needed. This would require national and global systems to expedite the flow of research funding during a crisis and to build a strong system of global governance around research, she said. CEPI's commitment to fund research in the critical path for vaccine development is a positive development in this regard.

Additionally, Lurie suggested that vaccine manufacturing should be restructured. CEPI's mandate is to develop novel vaccines, move them

through Phase II studies focused on assessing efficacy, and then potentially test them during an outbreak. If one of the vaccines proved effective, the existing system would not have the capacity to produce billions of vaccines fast enough. It would require large investment and creativity, she said, to create more nimble, sustainable, and decentralized manufacturing capacities.

Finally, she said that an understanding of the culture, beliefs, knowledge, and attitudes of a given population is central to any outbreak response, regardless of the setting. Lurie suggested that anthropologists and social scientists should be deployed to better understand how to engage the population in outbreak control activities, such as accepting vaccines or using at-home diagnostic tools.

IMPROVING LOCAL, NATIONAL, REGIONAL, AND GLOBAL CAPACITIES FOR PREPAREDNESS: A PERSPECTIVE FROM THE PAN AMERICAN HEALTH ORGANIZATION

Ciro Ugarte, director of the health emergencies department at PAHO, explored some of the challenges to and priorities for preparedness from his experiences working at an international health agency in the Americas. He began by discussing the evolution of PAHO countries' core International Health Regulations capacities between 2011 and 2018, as they were reported annually to the World Health Assembly. Overall, the trend was generally positive, although capacities declined in some areas, such as human resources and funding, which reflects general challenges faced in the health sector. The core capacities to deal with emergencies were more disparate when divided by sub-regions in the Americas (see Figure 9-1). For countries with a limited capacity to respond to an emergency, he said, the highest priority is to protect their own populations. This makes governments less likely to share information, and they may even actively deny that a disease is present. Countries are also more likely to delay the process of reporting. He noted that although the number of reported events has increased among countries in the Americas, reporting often has been delayed by as many as 10 days (rather than 24–48 hours).

PAHO's Priorities for Improving Preparedness

Ugarte highlighted a set of priorities for improving preparedness-related capacities in the PAHO region. Developing institutional capacity is a priority, he said, because institutions and governance need to be properly designed and prepared to respond to large emergencies. Additionally, he noted that information management should be improved, such as centralized data collection and information sharing. Information sharing can be

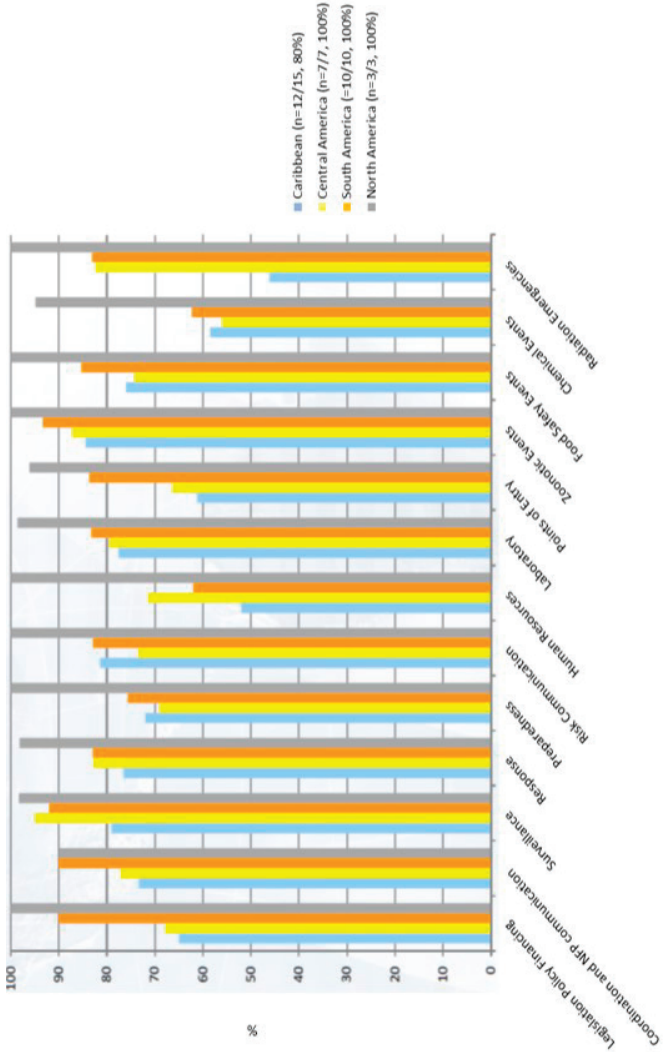

FIGURE 9-1 Status of core capacities by sub-region in the Americas.
NOTE: NFP = National Focal Point.
SOURCES: Ugarte presentation, November 28, 2018; data from WHO Global Health Observatory.

politically sensitive because of concerns about the economic impact of a publicized outbreak or concerns that the health sector will be blamed if an outbreak occurs. He said that developing a multisectoral approach is another priority because health sectors tend to be weaker than other sectors in terms of influence, funding, workforce, and response capacity. Strengthening regional solidarity and creating a mutual support system would be ways to cope with such challenges, and he cited the effective cooperation among Caribbean states as an example. Ugarte noted that resources devoted to preparedness efforts should be balanced with resources for countries' more urgent priorities.[3]

He said PAHO has identified five lines of action to address its preparedness priorities. Those actions include

- incorporating health crisis response into overall disaster plans and programs;
- developing human resource capacities;
- ensuring the provision of authoritative information since ministries of health often lack the authority to report information without higher-level political clearance;
- strengthening laboratory capacity; and
- improving early warning, surveillance, and response.

Challenge of Coordination

Both national and international preparedness and response capacities are critical, Ugarte said. A comprehensive approach should improve the coordination of international actors in a way that is integrated with strengthening national capacities. Coordination is the major challenge, he said, because "everybody wants to coordinate, but nobody wants to be coordinated." Various institutions have their own mandates, protocols, and processes that can be difficult to coordinate effectively during a response.

Ugarte used examples from the 2009 H1N1 influenza pandemic to illustrate the need for better coordination to achieve optimal benefits for an affected country. Prior to the pandemic, he said, UN agencies had been important partners supporting countries in strengthening preparedness. During the H1N1 pandemic response in Mexico, however, he said UN agencies drastically reduced their participation and tended to portray

[3] For example, outbreaks of measles and rubella have occurred in several countries in the Americas because the vaccine coverage has dropped below the first order of protection. This triggered a meeting among the region's ministers of health at PAHO to discuss the health implications of massive migration because blame was being placed on countries that were releasing migrants without vaccines.

their agencies as "victims" that needed more attention than Mexico. UN agencies withdrew many of their staff in the country at the same time that PAHO and WHO significantly increased their staff in Mexico, he said. Similarly, the Global Outbreak Alert and Response Network missions, coordinated by PAHO, helped some countries by providing opportunities for knowledge and information exchange. However, according to Ugarte, all of these factors led to an uncoordinated influx of foreign aid, and some network members maintained their institution's objectives or interests, which created differences and potential conflicts with the PAHO response team. For example, he reported that some actors sought to increase their own country's preparedness by sending home sensitive information without the adequate level of clearance and transparency.

Ugarte concluded that, ultimately, preparedness priorities should aim to enhance national and international capacity by strengthening and complementing local response capacity and improving the quality and appropriateness of external assistance. He emphasized the need for political endorsement of guidelines on how improve the quality of international cooperation, which is necessary to maintain the political will for preparedness efforts. Ensuring coordination among specialized organizations, agencies, centers of excellence, and relevant partners is also a way forward, as is the establishment of operational coordination procedures with national, regional, and global initiatives. Ugarte suggested focusing on excellence rather than visibility and on effectiveness rather than convenience. Both actual and perceived risks can motivate decisions that are not aligned with the desired priorities. Thus, emergency situations—whether actual or perceived—can be leveraged to increase political awareness of the importance of preparedness. He concluded that the potential impacts and benefits of bolstering pandemic preparedness should be couched in the appropriate political and economic language.

DISCUSSION

Following the presentations, Rima Khabbaz, director of the National Center for Emerging and Zoonotic Infectious Diseases at CDC, highlighted that some strategies for pandemic preparedness would benefit from different ways of thinking, different ways of acting, bringing different people to the table, and using different language to discuss the issues. Panelists touched on issues related to changes in organizational capacities and resource commitments that may integrate outbreak and pandemic preparedness. Although successes have been achieved through vertical investment in specific diseases, multipurpose investment and investment in credible local-level institutions that conduct day-to-day work are potentially useful strategies. Finally, she noted that investment in technologies

such as vaccines, diagnostics, and antivirals could also help to drive progress.

Some Immediate Priorities for Preparedness

To open the discussion, Khabbaz asked panelists to identify the most pressing, immediate step that should be taken to advance preparedness. Fineberg replied that the answer depends on the time horizon for the desired improvement. If the aim is to leverage existing technologies and tools, then the focus should be on organizational preparedness. If the aim is to lay the groundwork for improving the culture of response among the population, then the focus should be on improving public understanding of the importance of preparedness. Furthermore, if the aim is to establish the strongest position possible by 2030, then he said the focus should be on investing in research and in the development of necessary technologies. He suggested that a sensible strategy would be somewhere in the middle—making adjustments and investments to improve immediate capacity while also creating the possibility of dramatically better capacity in the future.

Lurie remarked that the investment portfolio for preparedness should include long-term investments coupled with short-term investments that achieve incremental change toward building the future system. However, it can be challenging to engage politicians to advocate for longer-term investments for which they will receive no credit for because they will no longer be in office when the investments come to fruition. Fitzgerald added that advocacy is a critical piece in an investment portfolio because it has the biggest leverage play—a $1 million investment in advocacy can yield a 500-fold return on investment.

Fitzgerald also suggested conducting network mapping to identify key players, their priorities and targets, and the ways in which they can be encouraged to contribute to a unified political movement around the preparedness agenda. She noted that many advocacy organizations, philanthropists, and high-level experts would probably be interested in forming a coalition or constituency. However, she said funding would be needed to accelerate those efforts. She suggested the need to strengthen and improve existing funding mechanisms rather than creating a new global funding mechanism for outbreak preparedness, which might be less politically palatable.

Ugarte remarked that although health emergencies have large impacts across many nonhealth sectors, the health sector is generally the hub of information about an outbreak. Multisectoral emergency management institutions may be reluctant to take the lead in a response because he said many are averse to the burden of responsibility. Multisectoral collaborations could be improved if the health sector worked more closely

with other sectors to strengthen general public health and well-being as well as outbreak response. He added that issues related to antiviral stockpiling are also a priority because many developing countries do not have the luxury of stockpiling, and if they do, they risk wasting limited resources if the drugs expire unused.

Building Support for Preparedness Across Sectors

Keiji Fukuda, director and clinical professor, School of Public Health, The University of Hong Kong, commented that in the context of addressing antimicrobial resistance, gaining multisectoral support and political buy-in are both important factors. Pandemic preparedness generally has the support of major scientific and technical bodies, but it lacks multisectoral support and a political champion. He asked about ways to shift the issue of preparedness from a technical to a political frame in order to gain the needed support. Fitzgerald replied that recruiting political champions is critical since they can leverage their existing relationships and engage in diplomatic outreach to bring others to the table—as modeled by CEPI. However, she remarked that each country and political environment needs a tailored approach.

Kumanan Rasanathan, board director of Health Systems Global, noted a tension between two agendas. The traditional technical agenda is focused on diagnostics, vaccines, and surveillance capacity. What needs to be done for this agenda is clear, but the necessary resources and political will are lacking. The other agenda is more focused on health systems strengthening and on engaging more players from all sectors of society in combined efforts to mainstream preparedness activities. Tensions between these agendas are evidenced by increasing public and private-sector investment in health systems around the world and by attempts to push for universal health care. He suggested that the agendas are not mutually exclusive, but the latter will warrant changes in messaging and cross-sectoral engagement with the broader community. Ugarte added to Rasanathan's comments by noting the importance of identifying what the health systems strengthening agenda needs from the emergencies perspective, and highlighted that antimicrobial resistance and infection prevention and control issues are core elements of health systems and need to be addressed. Efforts in that area may provide mutual, compounding benefits.

Lurie agreed that this tension existed and noted an additional need to share power, information, and influence to bridge these agendas. She added that one challenge to promoting multipurpose investment is the disparity between the investments that governments of developed countries assume developing countries need and those that governments of developing countries actually consider necessary. She suggested bringing

new players to the table so that they can contribute and engage with each other in a coordinated way. For example, she highlighted that the private and business sectors have expertise in operations, logistics, supply chains, and other capacities that are necessary to respond to an outbreak. Lurie further remarked that moving forward with preparedness would require cross-sectoral coordination, recognition, and respect. She referred to points raised in the earlier small-group discussions, which positioned the U.S. Federal Emergency Management Agency (FEMA) model as an example of an effective structure for complex interactions across a broad range of sectors and players (see Chapter 8 for more on the potential for a FEMA-style model). Fitzgerald also suggested establishing a FEMA-style model at a level higher than WHO, which currently lacks the mandate to bring many nonhealth players to the table, but a UN coordinating mechanism could serve that function.

Suerie Moon, director of research at the Global Health Centre at The Graduate Institute of International and Development Studies, reiterated the importance of coordination during a crisis because gaps in coordination can cause wasteful duplication of efforts. She asked if enough information is available and accessible to facilitate regional or global coordination in preparedness. Ugarte replied that information is available, but it is not sufficient for that level of coordination. However, he noted that in addition to increasing information-related capacities, it is also important to adjust communication and negotiating styles to foster organizations' willingness to coordinate, participate, and contribute in a collective way to strengthening preparedness.

Rafael Obregon, chief of communication for development section of the United Nations Children's Fund (UNICEF), asked about ways to encourage interest and investment in the social science component of outbreak preparedness and response, noting that both WHO and UNICEF have taken some initial steps to strengthen that component. Lurie commented that people with social science skills are widely available and could be engaged in preparedness through creative, effective communication strategies and through innovative approaches such as tailored, just-in-time training. Obregon also asked about strategies to encourage investment into underresourced, local-level health systems, which would build capacity, trust, and community engagement. Ugarte replied that political and strategic support for local-level systems can sometimes have an even greater impact than the actual value of financial investments, because they can engage local decision makers in the solution-finding process. This can be made difficult by the multilevel governance structures in decentralized countries, but it is possible to create these lasting bridges of health diplomacy in order to engage local officials in traditionally hard-to-reach settings.

CLOSING REMARKS

Fukuda closed the workshop by observing that the process of preparedness has core components and evolving aspects. He highlighted that a core component is the need to address the full spectrum of priorities and perspectives at the community, national, and global levels. Another core component, he added, is the need to focus, harmonize, and ensure functionality across a range of areas, including global governance, political attention and will, science and technology, operations on the ground, legal concerns, and trust-building. He suggested that preparedness efforts should target specific, focused steps to achieve continuous incremental gains within the broader, highly complex preparedness enterprise, with care taken to avoid fragmentation or silos. For example, vaccines are generally considered to be relatively technical and scientific work, but vaccines are also related to a broader scope of issues that can create stumbling blocks, such as on-the-ground operations, administrative and bureaucratic processes, and liability issues. Such issues, he noted, warrant as much attention as vaccine development and universal vaccine design.

Fukuda said that some countries and territories, such as Hong Kong, the Kingdom of Saudi Arabia, and Liberia, have made substantial improvements in overcoming challenges and strengthening preparedness capacities. The hope is that other countries could achieve similar progress without having to repeatedly experience crises. Fukuda envisioned that, ideally, preparedness would be positioned not only as a mechanism to respond to extraordinary and unusual situations but as an expected and required tenet in the activities delivered by bureaucracy, funding and technical organizations, and all sectors including and beyond health.

At the national level, Fukuda said, it is important to bring all stakeholders to the table. He underscored that particular attention is needed within national bureaucracies to empower and to implore agencies to act on preparedness and to convince political leadership of the importance of those actions. Governments should also focus on building trust with communities and providing them with the guidance they need to prepare and protect themselves, he said, because communities are the "energy supply" of the world, not global institutions and organizations.

At the global level, Fukuda reflected, it will be critical for the "politics of making progress" to tap into existing mandates and tools—including the SDGs and the global push for universal health coverage—to ensure that the efforts to strengthen preparedness are seen not as isolated issues but as contributing to a greater whole. At the same time, other capabilities for other diseases should be applied to pandemic preparedness. Different international organizations should be equally supported in their global-level preparedness strengthening activities, Fukuda added. Furthermore, to

ensure that the benefits of the PIP Framework are not lost, he said international mechanisms to share information and benefits need to be updated in a way that is transparent, understandable, and equitable. Fukuda urged these efforts should focus on creating platforms for sustainable cooperation toward mutually agreed-upon goals rather than on building yet another mechanism of coordination.

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Appendix A

Commissioned Paper

Readiness for Microbial Threats 2030: Exploring Lessons Learned Since the 1918 Influenza Pandemic

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ACRONYMS AND ABBREVIATIONS

DG	Director-General
DON	disease outbreak news
DORS	disease outbreak response system
ED	executive director
EIS	epidemic intelligence service
EOC	emergency operations centers
ERF	emergency response framework
FAO	Food and Agriculture Organization of the United Nations
GHSA	Global Health Security Agenda
GOARN	Global Outbreak Alert and Response Network
HSS	health systems strengthening
IHR	International Health Regulations
ILAR	Institute for Laboratory Animal Research
IMF	International Monetary Fund
MERS-CoV	Middle East respiratory syndrome coronavirus
MOH	Ministry of Health
OIE	World Organisation for Animal Health
PHEIC	public health emergency of international concern
R&D	research and development
SARS	severe acute respiratory syndrome
SDG	Sustainable Development Goal
UHC	universal health coverage
UN	United Nations
UNGA	United Nations General Assembly
UNSG	United Nations Secretary-General
WHA	World Health Assembly
WHO	World Health Organization
WTO	World Trade Organization

BACKGROUND

The world has made dramatic strides in tackling infectious diseases over the past century, including smallpox eradication, significant progress on polio eradication, and widespread vaccination. However, new threats have emerged—including 30 new zoonotic diseases in the past two decades alone. This uptick in new diseases may be the result of many factors, including economic growth, global travel, the proximity of humans to animals, or climate change, and the trend does not appear to be slowing. One hundred years after the 1918 pandemic influenza, we remain at risk of pandemic spread—perhaps more so than ever before. This continued risk highlights the need to be globally prepared. While many lessons on preparedness were gleaned following the 2014 Ebola outbreak in West Africa, we still lack a more comprehensive summary of lessons from different outbreak and pandemic events over the course of the past century.

To address this gap, we reviewed reports outlining recommendations and lessons from major epidemics that have occurred since the 1918 influenza pandemic. Six major types of outbreaks were chosen by the Forum on Microbial Threats (FMT) to survey.[1] We conducted a unique review of the literature for each outbreak to capture reports or studies published during, or in the years following, that pandemic (see reference list at the end of the commissioned paper). The subject of the review was *what needs to be accomplished to make progress in epidemic and pandemic preparedness moving forward*—or globally relevant lessons learned from each event. Where possible, we focused on global lessons (for more than one country) from each specific outbreak. This ultimately included global lessons abstracted from 16 peer-reviewed papers or reports. The process was not meant to be exhaustive but rather representative of different periods, disease types, and authorship (e.g., academic, practitioner, multilateral).

We found significant overlap in content across the reports. This finding was consistent with themes summarized by both Gostin (2016) and Moon et al. (2017) in *Toward a Common Secure Future: Four Global Commissions in the Wake of Ebola* and *Post-Ebola Reforms: Ample Analysis, Inadequate Action*, respectively. Moon et al. (2017) categorized recommendations from the 2014 Ebola outbreak in West Africa as follows:

1. Bolster country-level core capacities and compliance with the International Health Regulations (IHR).

[1] The following outbreaks were selected: (1) the 1957 and 1968 influenza pandemics, (2) the 2003 emergence of influenza A (H5N1) and severe acute respiratory syndrome (SARS), (3) the 2009 H1N1 influenza A pandemic, (4) the 2013 emergence of influenza A (H7N9), (5) the 2014–2016 Ebola outbreak in West Africa, and (6) the 2012–2015 Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in Saudi Arabia and in Korea.

2. Improve knowledge sharing and research.
3. Strengthen the World Health Organization (WHO), the United Nations (UN), and broader global health or humanitarian systems.

Below, we summarize highlights from the review using an adaptation of this same framework. Additionally, for each category, we provide summaries of recommendations and lessons (see Boxes A-1 to A-5), which are outlined in more detail in Tables A-1 to A-5.

CATEGORY 1: COUNTRY-LEVEL CORE CAPACITIES

Robust and sustainable health systems are a prerequisite for preventing, detecting, and responding to pandemics and to pandemic threats. The IHR are the current framework for country preparedness for infectious disease outbreaks and require 196 State Parties to develop and maintain core health system capacities in the face of acute public health risks such as infectious disease threats of international concern. Core capacities in this framework are organized into three categories related to prevention, detection, and response, which include subdomains (e.g., health workforce, laboratories, data systems, and risk communication), in order to identify and to contain threats before they cross national borders. While this review includes studies that were released prior to the development of the IHR, we use the IHR framework to organize recommendations and lessons from reviewed content (see Box A-1). Additional content was also reviewed on trade and travel, accountability mechanisms, and other suggestions to support countries as they work to achieve adequate core capacities.

BOX A-1
Recommendations and Lessons for Bolstering Country-Level Core Capacities

Strengthening Capacity to PREVENT

1. Response frameworks should include better scenario planning and less rigidity, considering variation that occurs among diseases. Ministries of health should be familiar with different suites of measures so that they can deploy them flexibly. (H1N1)
2. Effective primary care can help alleviate the overloading of emergency departments. (H1N1)
3. Prevention goals within the International Health Regulations (IHR) should align with those in the universal health coverage (UHC) agenda, and accountability should be built into both frameworks. (Ebola)

BOX A-1 Continued

Strengthening Capacity to DETECT

1. "Wide net" surveillance often makes sense in situations when there are nonspecific symptoms (H1N1), and nonhealth entities can support screening in places such as schools, businesses, and transportation sites. (SARS, H1N1)
2. National surveillance needs to be paired with rapid international verification, especially when a pandemic occurs in low-resource contexts with limited lab capacity. (H5N1)
3. Web-based search patterns can be used to identify potential risks early. (H1N1)
4. Surveillance efforts must be tied to animal health and focused on rural areas. (H1N1, H5N1)
5. "Timeliness of data management and risk assessment is essential for identifying unusual clusters (e.g., high death rates) and initiating appropriate responses" (Fisher et al., 2011). (H1N1)
6. When the disease is not fully understood, detection systems should include feedback loops on spread, so clinicians and other people who treat the disease can understand viral transmission and treatment effectiveness. (H1N1)

Strengthening Capacity to RESPOND

1. Strong health systems are key: "Underresourced, understaffed, and fragmented health services are unable to contain outbreaks of serious infectious diseases or to adequately respond to health emergencies" (Save the Children, 2015). (Ebola)
2. "Health care workers must be given priority for protection and treatment to enable them to perform their duties" (Lee et al., 2008). (H1N1)
3. Lack of epidemiological information on the disease hampers effective treatment. (H1N1)
4. Response plans, even those created for prior diseases, are effective and provide a blueprint for countries. However, there is need for practical testing of these plans at both hospital and above hospital levels. (H1N1)
5. Containment, as a strategy, is highly dependent on the disease. When containment efforts do not work, the importance of communicating risk to the public increases. (H1N1)
6. Risk communication and engagement with communities throughout outbreak events were noted as critical for each outbreak. Specific efforts featured included dedicated government websites and use of social media. (Multiple)

In this review, we found that 16 out of 16 papers included content on core national capacities on outbreak reporting (if not specifically those outlined in the IHR). Some of this content was presented in the form of lessons for future outbreaks while other content was framed as reflections (often made by practitioners or policy makers who actively addressed an outbreak event).

Recommendations and lessons regarding how the broader global health system could support countries' efforts to develop core capacities were also mentioned throughout the reviewed papers but were less common than lessons aimed at countries themselves. Suggestions for WHO included content on supporting country preparedness in the absence of a current pandemic and on what WHO's role should be during an actual outbreak (see Box A-2).

BOX A-2
Recommendations and Lessons for Bolstering the Global System Support for Country-Level Core Capacities

Role of the World Health Organization (WHO) in Supporting Country Capacity

1. WHO should prepare a template pandemic preparedness plan for countries. (H5N1)
2. WHO should develop benchmarks for core capabilities and support countries' efforts to achieve them. (Ebola)
3. WHO needs to "establish a more extensive public health reserve workforce" (WHO, 2005). (H5N1)
4. WHO is mandated to serve as the guardian of the International Health Regulations, and it may require involvement from multiple levels of the organization to accomplish this mandate (e.g., national country offices, regional offices, and headquarters). (H7N9)
5. WHO needs to "work with existing regional and sub-regional networks to strengthen linkages and coordination; the ultimate goal is to enhance mutual support and trust" (Sands et al., 2016). (Ebola)
6. WHO and other international guidelines cannot adapt as fast as local knowledge and should not eclipse clinical judgment. Adequate feedback loops are required so that guidelines are dynamic and respond to on-the-ground realities. (MERS-CoV)

BOX A-2 Continued

Roles of Other Global Actors in Supporting Country Capacity

1. The UN Secretary-General should ensure a minimum level of health-system functionality in fragile and failed states. (H7N9)
2. "The International Monetary Fund (IMF) should include pandemic preparedness in countries' economic and policy assessments" (Sands et al., 2016). (Ebola)
3. All development assistance for health should be contingent on pandemic preparedness at the national level. (Ebola)

Public Health Emergency of International Concern (PHEIC)[a] Reporting

1. The PHEIC reporting mechanisms should be used for the duration of a pandemic to communicate updates throughout the event. (H7N9)
2. An intermediate level prior to a formal PHEIC would incentivize countries to express risk at earlier stages—without the risks associated with communicating a full PHEIC. (Ebola)

[a]"A PHEIC is an extraordinary event that constitutes a public health risk to other State Parties through the international spread of disease and that potentially requires a coordinated international response" (WHO, 2016a).

CATEGORY 2: RESEARCH, DEVELOPMENT, AND KNOWLEDGE SHARING

There has been a persistent failure of timely vaccine deployment and lack of global knowledge/data sharing over time. The papers reviewed, consistent with prior work, recognize that for both effectively preventing and mitigating outbreaks timely sharing of information of research and health technology efforts is critical. While this topic was less well explored than national core capacities or global governance, several papers have outlined problems with vaccine readiness, sample sharing, and other issues related to the handling of epidemiological, genomic, or clinical data both during as well as after pandemics.

In this review, we found that 8 out of the 16 papers contained content that addressed pharmaceutical research and development (R&D) or sample sharing and information sharing (see Box A-3).

BOX A-3
Recommendations and Lessons for Improving Research, Development, and Knowledge Sharing

Vaccine, Diagnostic, and Therapeutic Readiness

1. "Public health measures such as antivirals, vaccination, and nonpharmaceutical interventions must be performed in concert to reduce the impact of a future pandemic" (Lee et al., 2008). (H1N1 1957–1968)
2. Very rapid and highly sensitive tests, which "substantially reduce the number of individuals that need to be quarantined without decreasing the effectiveness of the measure, need to be developed" (Tan, 2006). (SARS)
3. The development of a pandemic vaccine should be expedited: "Shorten the time between the emergence of a pandemic virus and the start of commercial production" (Behrens et al., 2006). (H5N1)
4. Scientific understanding and technical capacity need to be improved, because both are currently fundamental constraints on pandemic preparedness. (H1N1)
5. A comprehensive influenza research and evaluation program should be pursued. (H1N1)
6. "Investment in medical research and development (R&D) for diseases that largely affect the poor is deeply inadequate. Of the $214 billion invested in health R&D globally in 2010, less than 2 percent was allocated to neglected diseases" (UN High-level Panel on the Global Response to Health Crises, 2016). (Ebola)
7. Research and development (R&D) should not be left to market forces: The Ebola outbreak exemplified "how ill-suited the medical research and development model is for addressing the world's health priorities" (Heymann et al., 2015). (Ebola)
8. Drug quality issues should be addressed: They pose "social, economic, and political challenges to health security by undermining capabilities to curb both infectious and noncommunicable diseases while eroding public confidence in governments and international institutions" (Heymann et al., 2015). (Ebola)
9. R&D "armory" should be built. It currently has "many gaps, which Ebola and other outbreaks have revealed, that span vaccine development and capacity, diagnostic tools, therapeutics, protective equipment, and anthropological research" (Sands et al., 2016). (Ebola)
10. Resources should be dedicated to "R&D on prioritized pathogens to ensure the greater availability of critical vaccines and treatments when they are most needed" (UN, 2016). (Ebola)

Delivery Capacity for Pharmaceutical and Medical Goods

1. An outbreak should be contained or delayed at the source. An international stockpile of antiviral drugs should be established, and mass delivery mechanisms for antiviral drugs should be developed. (H5N1)
2. There is a worldwide need for greater production capacity and for faster throughput. (H1N1)
3. Advanced agreements for vaccine distribution and delivery should be encouraged. (H1N1)
4. Significantly greater resources for medical products should be prioritized, mobilized, and deployed, and development and regulatory approval processes should be harmonized. (Ebola)

Sample and Knowledge Sharing

1. "The exchange of epidemiological information on infectious diseases, especially the emergence of new infections, should be strengthened between the health authorities in Mainland China and Hong Kong" (Hung, 2003). (SARS)
2. It is important to reach an agreement on the sharing of viruses. (H1N1, Ebola)

Synergies with One Health

1. Feedback loops should be developed between human and animal health. (Multiple)
2. "Most of the affected countries could not adequately compensate farmers for culled poultry, thus discouraging the reporting of outbreaks in rural areas where the vast majority of human cases have occurred" (WHO, 2005). (H5N1)
3. "Domestic ducks were able to excrete large quantities of a highly pathogenic virus without showing signs of illness. Their silent role in maintaining transmission further complicated control in poultry and made human avoidance of risky behaviors more difficult" (WHO Communicable Disease Surveillance and Response Global Influenza Programme, 2005). (H5N1)
4. More investment in "One Health research should be requested to enhance understanding of the emergence, prevention, detection, and control of pandemic influenza viruses" (Monath et al., 2010). (H1N1)

CATEGORY 3: WHO AND THE GLOBAL SYSTEM

Following the 2014 Ebola outbreak in West Africa, seven major reports agreed that reforms needed to be put in place to improve the global governance mechanisms within WHO and the broader UN and humanitarian systems to strengthen the global response capacity to these type of events. While the reports also agreed on maintaining the global preparedness and response functions for global disease outbreaks within WHO, they did not agree on how best to do this. Since Ebola, WHO has undergone a number of reforms—which we do not fully cover here. Rather, in this review, we look at what postpandemic reports have suggested as necessary changes. In line with prior work on this topic, we use sub-themes—for example, WHO's specific role in outbreaks, as well as internal suggestions regarding leadership and human resources (see Box A-4). This includes issues related to WHO's operational capacity to respond to disease outbreaks on the ground as well as broader institutional reforms to all multilateral organizations, such as financing, that may not be limited to emergencies or outbreaks (see Box A-5). There is some overlap with the category on national core capacities, but in that category we had focused on the role of WHO in supporting countries, while in this category, we take a systems view of the global governance mechanisms in place.

We found that 7 of the 16 papers addressed broader issues of the global governance system (items that might be addressed by cross-national bodies, such as WHO or the UN). The inclusion of this topic, recommendations related to the global system (UN, WHO, or other multilateral organizations), increased during and after the 2014 Ebola outbreak. Therefore, the majority of recommendations are from reports on, or following, the 2014 Ebola outbreak. Prior to this time, many reports were produced by agencies themselves with minimal inward-looking recommendations or critiques of the global health system, however defined.

BOX A-4
Recommendations and Lessons for Strengthening World Health Organization's (WHO's) Capacity

WHO Actions and Internal Capacity for Future Outbreaks

1. WHO needs to develop operational capacity. (Ebola)
2. WHO should build capacity to support low- and middle-income countries in the development of their own vaccine manufacturing capacity, and national pandemics preparedness plans. (H5N1)
3. Greater resources are needed to be able to improve WHO capacities, and this would require a profound organizational transformation. (Ebola)
4. WHO should establish a Program/Center for Health Emergency Preparedness and Response that is governed by an independent technical governing board. (H5N1, Ebola)
5. The role of WHO as a broker of knowledge—with the ability to respond more effectively when at odds with local, quickly developing knowledge—should be reinforced. (Ebola)
6. WHO should enhance cooperation with non-state actors while recalibrating relationships with member states and recognizing the distinct roles that each actor plays. (Ebola)

WHO Leadership and Human Resources

1. The new Director-General's critical role should be to refocus WHO's purpose and structure, and remain accountable for incident management within WHO. (Ebola)
2. WHO should revise how elections are conducted for WHO officials and should specifically improve transparency and the democratic nature of elections. (Ebola)
3. WHO should invest in training health professionals, especially community health workers. (Ebola)
4. WHO staff need to be qualified to manage outbreaks and emergencies. Health workforces should include a broad range of actors from multiple sectors working at different levels, rather than a single global workforce of "white helmets." (Ebola)
5. WHO should increase its staff. (Ebola)

BOX A-5
Recommendations and Lessons for Strengthening System-Wide Capacity

Operations (Internal and External to World Health Organization [WHO])

1. Existing institutions should be leveraged rather than creating new ones. (Ebola)
2. Actors need to coordinate more effectively with each other and to establish clear lines of command. (Ebola)
3. During health crises, humanitarian actors should have access to guidelines and standard operating procedures. (Ebola)
4. Health cluster capacities and integration need to be developed along with the overall humanitarian system. (Ebola)

Accountability

1. Regular independent assessments should be commissioned. (Ebola)
2. Sustainable Development Goals (SDGs) should be used to target indicators as a baseline for accountability. (Ebola)
3. WHO should be required to use existing resources more efficiently, report against specific outcomes, develop indicators to assess progress, and rigorously track expenditures. (Ebola)

Financing and Aid

1. Investments need to increase for building robust health systems. (Ebola)
2. WHO should mobilize international financial support for IHR core capacities strengthening. (Ebola)
3. Contributions should increase for WHO, and WHO should establish a contingency fund for these type of emergencies. (Ebola)
4. Funding for WHO's Emergency Program's baseline capacity should be secured through predictable and reliable financing streams, including assessed contribution and different from funding for specific responses. (Ebola)
5. Effective mechanisms are needed to help countries in need through institutions like the IMF and World Bank. Initiatives need to provide budgetary support and rapid credit availability. (Ebola)
6. The creation of World Bank's Pandemic Emergency Finance Facility should be supported. (Ebola)

CONCLUSION

We found that country-level core capacities were the most common subject covered by the reports in this review. In earlier reports, recommendations on core capacities were more thoroughly explored, and targeted advice was provided at the country level. Later reports, particularly those following the 2005 IHR, focused on the effective implementation of IHR as opposed to its component parts. However, domains across the reports were similar (e.g., preparedness, detection, and response), which may reflect the incorporation of earlier recommendations into the IHR in 2005. Another notable difference in later reports was a shift toward taking a wider lens view (e.g., recommendations to strengthen capacities across countries) and examining the need to tie together global health agendas, such as the IHR and universal health coverage (UHC), as a primary component of the SDGs. This trend aligns with an increase in the number of global health actors over time, which, in turn, likely increases the relevance of dialogue on global coordination and accountability for country preparedness.

While some reports covered issues such as health technologies, pharmaceutical readiness, deployment, or knowledge sharing (e.g., biological samples or results from trials), several others provided recommendations focused primarily on vaccine readiness. Specifically, many of the reports discussed the persistent failure of timely vaccine deployment and the lack of global knowledge-sharing norms around vaccines. Unlike their suggestions around country-level core capacities, recommendations on vaccine readiness resulting from outbreaks over time were generally consistent, which suggests broader challenges have yet to be addressed in this domain. There have, however, been notable efforts to address these recommendations more recently (e.g., the Coalition for Epidemic Preparedness Innovations, the WHO's R&D "Blueprint," and other efforts summarized by Leigh et al. [2018]). Additionally, across reports, systems for the delivery of pharmaceuticals and other medical technologies were noted as impediments to effective response. However, authors offered few recommendations to improve delivery capacity or to engage other actors, such as the private sector or military, in doing so. Content on R&D differed among reports depending on disease context. For example, following influenza outbreaks, discussions included a focus on One Health and on the need to better align human and animal R&D strategies. This was not true for Ebola reports, where the zoonotic nature of the disease was less well understood. In line with country-level capacity recommendations, this category may benefit from a more dynamic approach to readiness given the diversity of medical technologies needed. Such an approach could include familiarizing ministries of health and other key actors with multiple scenarios so that outbreak responses are adaptive to disease types.

For reports following the 2014 Ebola outbreak, there was a notable increase in discussion of and recommendations regarding global governance mechanisms for health. As noted above, this may stem from diversification of the global health landscape over time and from the empowerment of additional global actors, such as those in academia, civil society, and the private sector, to assess and to comment on global performance—including WHO's performance. This category, which addresses accountability at a multinational level, is particularly relevant given the current Ebola outbreak in the Democratic Republic of the Congo. When faced with fragile or failed states, a focus on national core capacities alone becomes starkly inadequate. The global system should help countries as they develop and maintain core capacities on the ground but also should oversee global accountability, ensure clear and accurate knowledge transfer, and assume other roles that a single country cannot fill. This can be a delicate balance, and report recommendations highlighted the importance of ensuring that global guidelines do not eclipse local, real-time understandings of disease. This has been a consistent challenge to effective global and local response. Common recommendations included the need to better delineate roles and responsibilities, improve coordination, ensure accountability mechanisms, and consider drivers of trust in the relevant institutions.

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TABLE A-1 Category 1a: Country-Level Core Capacities—National Core Capacities

				National Core Capacities		
Publication	Disease	Year of Outbreak	Outlet	Prevent/Prepare	Detect	Respond (Treat and Control)
Twentieth Century Influenza Pandemics in Singapore	H1N1	1957–1968	*Annals Academy of Medicine Singapore*		(R) Identify the onset of the pandemic for early intervention (however, influenza remains a difficult surveillance target because it manifests in a variety of non-specific symptoms) (R) Collect viral samples in a routine way. If a pandemic originates in less developed regions with high baseline mortality rates, the signal may be missed (R) Focus global surveillance efforts on frontline efforts in East Asian farms	(R) Give protection and treatment priority to health care workers to enable them to perform their duties
The SARS Epidemic in Hong Kong: What Lessons Have We Learned?	SARS	2003	*Journal of the Royal Society of Medicine*			(B) Inadequate epidemiological information about the disease hampered the prompt application of effective control measures (B) Lack of specified infectious disease hospitals led to difficulties in designating hospitals for the isolation and treatment of SARS patients (B) Deficient communication between the secretary (ministry) level responsible for health policy and the management level responsible for operation of hospitals
SARS in Singapore—Key Lessons from an Epidemic	SARS	2003	*Annals Academy of Medicine Singapore*		(F) MOH adopted wide-net surveillance, isolation, and quarantine policy to detect all suspicious cases as early as possible and to isolate them (F) Temperature screening in hospitals and in the community (e.g., preventing the importation and exportation of SARS through temperature screening at the airport and sea ports)	(F) Major containment efforts were concentrated on hospitals (SARS was predominantly a nosocomial infection) (F) Early separation of potentially infectious patients (F) Enforced use of personal protective equipment for all hospital staff and the adoption of strict infection-control measures, including temperature monitoring of all hospital staff (F) Designation of one SARS hospital allowed the clinicians at that site to develop strong clinical expertise

						(R) Contain public anxiety and re-direct this energy into positive community bonding and action (R) Enact a strong and effective command, control, and coordination of responses
Responding to the Avian Influenza Pandemic Threat	H5N1	2003	*WHO Communicable Disease Surveillance and Response Global Influenza Programme*		(R) Use WHO, FAO, and OIE jointly established Global Early Warning and Response System for trans-boundary animal diseases (R) Develop infrastructure to complement national testing with rapid international verification in WHO-certified laboratories, especially as each confirmed human case yields information essential to risk assessment	(R) Prioritize interventions in the backyard rural farming system "wet markets" where live poultry are sold in overcrowded and often unsanitary conditions (R) Strengthen risk communication to rural residents (R) Generate better knowledge on animal and human disease through WHO, in collaboration with FAO and OIE, to make risk communication more precise and better able to prevent risky behavior (R) Identify risk groups to guide preventive measures and early interventions (R) Health authorities should start a continuous process of risk communication to the public as soon as pandemic is declared (R) Monitor the effectiveness of health and nonhealth interventions in real time
Pandemic Preparedness and Response—Lessons from the H1N1 Influenza of 2009	H1N1	2009	*New England Journal of Medicine*	(R) Accelerate the implementation of the IHR (2005) core capacities	(F) Web-based search patterns can yield valuable intelligence that can give the world a head start on the next emerging pandemic	

continued

Influenza A (H1N1-2009) Pandemic in Singapore—Public Health Control Measures Implemented and Lessons Learnt	H1N1	2009	*Annals Academy of Medicine Singapore*	(F) When previous DORS framework was not applicable to H1N1-2009, both MOH and its stakeholders had to reframe and relearn the context of public health control measures mid-response (F) Stakeholders benefited from the flexibility to assess and take appropriate measures locally (R) Ensure better planning for multiple scenarios and less rigidity in plans (R) MOHs should familiarize themselves with different suites of measures, which could be implemented in a modular fashion (R) Invest in an effective primary care response, which can prevent the overloading of emergency departments in times of acute need	(F) Local disease surveillance systems are critically important to informing pandemic situations (e.g., monitoring the progression of the pandemic in the community, identifying the start of sustained community transmission, and guiding the step-down of containment measures) (F) At-home learning or work-from-home options helped decrease risk when transmission was high (R) Work with clinics and community, not only large hospitals, to assess true prevalence of disease (R) Nonhealth care establishments (e.g., schools and businesses) should be involved in temperature and symptom screenings	(F) National Influenza Pandemic Readiness and Response Plan developed for SARS was useful in responding to H1N1 (F) Framework for organizing/coordinating "whole of government" strategy and creation of crisis management groups (F) Dedicated ambulance service created for suspected patients (F) A dedicated government website on influenza also facilitated the public's easy access to information (R) Consider DORS as a guide for increasing or scaling down response (R) Have a core group of clinicians (comprising public health, infectious disease, microbiology, and respiratory medicine specialists) meet regularly to review epidemiological and clinical information to make decisions (R) Develop real-time, targeted public health "operational" research to determine the effectiveness of specific public health policies and control measures (R) Work toward building trust among stakeholders, as well as a degree of system discipline. This must be developed and built in peacetime (R) Generate creative personnel strategies that will help to build and maintain health care surge capacity in peacetime
Lessons from Pandemic H1N1 2009 to Improve Prevention, Detection, and Response to Influenza Pandemics from a One Health Perspective	H1N1	2009	*ILAR Journal*		(R) Develop an effective global, strategic, integrated surveillance and response system (which requires human, animal, and environmental health professionals to work together for earlier detection and disease control) (R) Establish more comprehensive surveillance for infection and disease in occupational groups that work most closely with animals (i.e., poultry and swine workers, live market workers	(B) Misunderstandings of the relationship between pigs and H1N1 led to unnecessary confusion and policy action, such as trade bans on the sale of meat (R) Move away from naming flu strains based on potential animal hosts

					and vendors, abattoir workers, veterinarians, and animal health technicians)	
Pandemic Response Lessons from Influenza H1N1 2009 in Asia	H1N1	2009	*Respirology*	(R) Develop integrated analyses that combine microbiological/virological, immunological, clinical, epidemiological, and genetic data for comprehensive assessment of host–emerging pathogen interactions	(R) Strengthen timeliness of data management and risk assessments for identifying unusual clusters (e.g., high death rates) and initiating appropriate responses	(B) Planning and hierarchy of intensive care and high dependency units across Asia were inadequate and slowed the response (R) Need for practical and tested hospital and inter-hospital level response plans for public health emergencies and mass casualty events (R) Need for systems above the hospital level that allow for coordinated management of beds and other finite resources including equipment and manpower (R) Focus on risk communication when containment measures do not work (R) Establish a two-way communication system between administration and clinical providers to coordinate protocol dissemination and resources (R) Improve preexisting infection control practices
Early Response to the Emergence of Influenza A (H7N9) Virus in Humans in China: The Central Role of Prompt Information Sharing and Public Communication	H7N9	2013	*Bulletin of the World Health Organization*	(R) Strengthen coordination between public health and veterinary services during an emergency by engaging in joint preparedness planning beforehand	(R) Strengthen the relevant infrastructures, surveillance systems, and response capacity in preparation for future emergencies caused by emerging or existing disease threats	
Avian Influenza A (H7N9) Response: An Investment in Public Health Preparedness	H7N9	2013	WHO Publication	(F) Notable initiatives undertaken by China included enhancing public health emergency planning, establishing a Web-based reporting system, and strengthening the National Influenza Center as one of the six WHO collaborating centers	(R) Leverage surveillance capacity developed through previous events (e.g., SARS)	(F) Combined efforts of the human and animal health sectors through mutual sharing of information, close and timely communication, and coordinated response (F) Rumors spread faster than the virus itself, so a coordinated social media strategy was key to keeping the public up to date (R) Establish country–WHO partnerships, such as the China–WHO mission, to allow WHO to learn from people on the frontline and allow people on the frontline to communicate information quickly to regional actors

continued

Global Health Security: The Wider Lessons from the West African Ebola Virus Disease Epidemic	Ebola	2014	*The Lancet*	(F) Enhanced pharmacovigilance and quality assurance composed two broad policy responses that were essential to coordinate across governments		
A Wake Up Call: Lessons from Ebola for the World's Health Systems	Ebola	2014	*Save the Children Publication*	(R) Make public commitments to building universal health coverage, with little or no direct payments at the point of use, and promote the accountability of government and of health service providers (R) Increase investment in comprehensive health services, starting with primary care, and prioritize essential services, such as infectious disease outbreaks, and maternal and child health (R) Increase public finances by raising fair taxation, and clamping down on tax avoidance and evasion (R) Strengthen and invest in national preparedness plans for possible outbreaks of infectious diseases. Plans should comprise public health surveillance, alert and referral systems, and supply chain systems that can rapidly procure and/or distribute medical equipment and drugs in emergencies		(F) Under-resourced, understaffed, and fragmented health services are unable to contain outbreaks of serious infectious diseases or adequately respond to health emergencies
Middle East Respiratory Syndrome Coronavirus (MERS-CoV): What Lessons Can We Learn?	MERS-CoV	2013	*Journal of Hospital Infection*	(B) Poor prognosis associated with MERS-CoV, especially in patients with multiple comorbidities, and the lack of effective antiviral therapy make appropriate infection prevention and diagnosis challenging	(R) Reinforce dynamics of continuous vigilance and perseverance with diagnostic investigation of undiagnosed infectious diseases	(R) Update guidelines regularly, and incorporate local knowledge from the ground (R) Facilitate the communication of epidemiological, medical, and scientific developments in addition to presenting the public with factual material, timely updates, and relevant advice

NOTES: DORS = disease outbreak response system; FAO = Food and Agriculture Organization of the United Nations; IHR = International Health Regulations; ILAR = Institute for Laboratory Animal Research; MERS-CoV = Middle East respiratory syndrome coronavirus; MOH = Ministry of Health; OIE = World Organisation for Animal Health; SARS = severe acute respiratory syndrome; WHO = World Health Organization.
13 of 16 publications had relevant findings for this category and were included.

Key:
(B) Barriers to pandemic preparedness and response.
(F) Facilitators to pandemic preparedness and response.
(R) Recommendations for implementation moving forward.

TABLE A-2 Category 1b: Country-Level Core Capacities—Core Capacity Enablers

Publication	Disease	Year of Outbreak	Outlet	Accountability and PHEIC Reporting	Role of WHO and HSS	Regional and Non-WHO Global Actors	Trade and Travel
SARS in Singapore—Key Lessons from an Epidemic	SARS	2003	*Annals Academy of Medicine Singapore*	(F) Regular audits by MOH teams, supplemented by internal audits by hospitals, helped ensure a high level of compliance			
Responding to the Avian Influenza Pandemic Threat	H5N1	2003	*WHO Communicable Disease Surveillance and Response Global Influenza Programme*	(R) Give risk-prone countries an incentive to collaborate internationally	(R) WHO to establish a surveillance program for antiviral susceptibility testing, modeled on a similar program for anti-tuberculosis drugs (R) WHO to monitor the unfolding epidemiological and clinical behavior of the new virus in real time (R) WHO to prepare a template pandemic plan, which will give many developing countries a head start in national pandemic preparedness planning		
Pandemic Preparedness and Response—Lessons from the H1N1 Influenza of 2009	H1N1	2009	*New England Journal of Medicine*		(R) WHO to ensure necessary authority and resources for all national focal points (R) WHO to revise and streamline the management of pandemic preparedness guidance (R) WHO to establish a more extensive public health reserve workforce globally		(R) Reinforce evidence-based decisions on international travel and trade
Influenza A (H1N1-2009) Pandemic in Singapore—Public Health Control Measures	H1N1	2009	*Annals Academy of Medicine Singapore*		(F) WHO created a model country plan with the goal of giving developing countries a framework to assess their status		(R) Push nonhealth government sectors involved in mounting a "whole of government" response to the H1N1-2009 pandemic to include border

continued

Implemented and Lessons Learnt					of preparedness and to identify priority needs (R) WHO to provide support to countries in rehearsing these plans during simulation exercises		control (temperature screening, health declaration cards, and health alert notices for travelers), trade, and industry
Early Response to the Emergence of Influenza A (H7N9) Virus in Humans in China: The Central Role of Prompt Information Sharing and Public Communication	H7N9	2013	*Bulletin of the World Health Organization*	(R) Release any results of risk assessments as well as other epidemic-related data promptly and publicly	(F) WHO and China's National Health and Family Planning Commission jointly coordinated the response mission by internationally recognized influenza experts (R) WHO to strengthen relevant infrastructures, surveillance systems, and response capacity in preparation for future emergencies		
Avian Influenza A (H7N9) Response: An Investment in Public Health Preparedness	H7N9	2013	WHO Publication	(R) Establish transparent and open channels of communication with the global community, including regular situation updates (R) Support the continued use of IHR (2005) reporting mechanisms throughout the event in order to provide timely updates for relevant stakeholders and the public (e.g., EIS and DON)	(F) WHO activated an organization-wide mechanism involving the three levels of WHO from the country to regional to headquarters offices (F) The ERF provided guidance in line with emergency management system and ensured adequate human resource surge capacity for monitoring and assessment (F) The EOC at the regional office was the common platform used to coordinate the response (R) As a guardian of IHR (2005) WHO to coordinate and support the H7N9 response	(F) The Western Pacific regional office developed a framework for action for national health authorities to highlight areas of public health emergency response that may need specific action for avian influenza A (H7N9)	
Global Health Security: The Wider Lessons from the West African Ebola	Ebola	2014	*The Lancet*	(R) Use GHSA to make rapid progress in strengthening collective health security through country and inter-country		(R) Address future threats to health security comprehensively based on deeper understanding of prevention and	

Virus Disease Epidemic				capacities to prevent, detect, and respond to infectious disease threats; independent evaluations are crucial to accelerate progress		remediation of human security (R) Broaden approach beyond the IHR (2005); simply taking the IHR (2005) to a next step is too weak and narrow as an approach (R) Develop an initiative to drive better health within corporations	
The Neglected Dimension of Global Security: A Framework for Countering Infectious Disease Crises	Ebola	2014	*New England Journal of Medicine*	(R) Make all development assistance for health system strengthening contingent on country agreement to assessment (R) Countries to develop and publish plans to achieve benchmarks by 2020 (R) Create an intermediate alert level before declaring a PHEIC (R) Develop a daily high-priority "watch list" of outbreaks with potential to become PHEIC, summary to be published weekly	(R) Develop benchmarks for core capabilities and support countries in achieving them (R) Work with existing regional and sub-regional networks to strengthen linkages and coordination enhancing mutual support and trust, sharing of information and laboratory resources, and joint outbreak investigations among neighboring countries	(R) World Bank to convene funders to support lower-middle and low-income countries to achieve IHR (2005) core capacities (these countries should also develop plans for eventual financial self-sufficiency) (R) IMF to include pandemic preparedness in countries' Economic and Policy Assessments (R) UNSG to ensure minimal health systems functioning in fragile and failed states	(R) The proposed WHO Emergency Centre should create protocols to dissuade member states and the private sector from implementing unnecessary restrictions on trade and travel; WHA to implement
A Wake Up Call: Lessons from Ebola for the World's Health Systems	Ebola	2014	*Save the Children Publication*	(R) Civil society should engage with tax processes and advocate for progressive tax reforms and increased transparency (R) Civil society should monitor domestic		(R) Ensure that aid and global support is increased and better aligned to help build suitable and comprehensive health services, and increase	

continued

			budgets to track resource flows and advocate for increased and more equitable revenue and health expenditure (R) The SDGs should commit the world to support UHC, alongside priorities such as ending preventable maternal, newborn, and child deaths (R) The SDGs should aim (via target indicators) for universal coverage of key health services and for financial risk protection and should ensure that targets apply to all social groups		public financing for health (R) Ensure the multilateral initiatives—such as the Gavi, the Vaccine Alliance, the Global Fund, and the new proposed Global Financing Facility for reproductive, maternal, and child health—are aligned to support comprehensive and universal health services and can demonstrate that they are doing this (R) Implement domestic and international reforms to curb illicit financial flows and tax avoidance (R) Strengthen and respect the IHR (2005) and support globally coordinated support for health emergencies	
Protecting Humanity from Future Health Crises: UNSG's High Level Panel on Global Response to Health Crises	Ebola	2014	*UNGA Publication*	(R) IHR Review Committee to develop mechanisms to rapidly address violations of PHEIC temporary recommendations (R) All countries to fulfill full IHR (2005) compliance by 2020 (R) WHO to perform periodic compliance review through an "independent field-based assessment"	(R) WHO to work with existing regional and sub-regional networks to strengthen linkages and coordination, and thus to enhance mutual support and trust, sharing of information and laboratory resources, and joint outbreak investigations among neighboring countries (R) WHO regional directors to answer to WHO Emergency Centre ED in emergencies (R) WHO to lead efforts to mobilize international financial	(R) World Bank should convene funders to support lower-middle and low-income countries to achieve IHR (2005) core capacities; these countries should develop plans for eventual financial self-sufficiency (R) Regional and sub-regional organizations to develop or strengthen standing capacities to monitor, prevent, and respond to health crises	(R) IHR Review Committee to develop mechanism to address undue adoption of trade and travel bans (R) WTO and WHO to establish a commission of experts to increase coherence between the IHR (2005) and the WTO legal regime regarding trade restrictions imposed for public health reasons

				(R) Global community to perform country reviews on rotating basis (R) Mobilize domestic and international funding to support IHR (2005) core capacity compliance	support for building IHR (2005) core capacities		

NOTES: DON = disease outbreak news; ED = executive director; EIS = epidemic intelligence service; EOC = emergency operations centers; ERF = emergency response framework; GHSA = Global Health Security Agenda; HSS = health systems strengthening; IHR = International Health Regulations; IMF = International Monetary Fund; MOH = Ministry of Health; PHEIC = public health emergency of international concern; SARS = severe acute respiratory syndrome; SDG = Sustainable Development Goal; UHC = universal health coverage; UNGA = United Nations General Assembly; UNSG = United Nations Secretary-General; WHA = World Health Assembly; WHO = World Health Organization; WTO = World Trade Organization.
10 of 16 publications had relevant findings for this category and were included.

Key:
(B) Barriers to pandemic preparedness and response.
(F) Facilitators to pandemic preparedness and response.
(R) Recommendations for implementation moving forward.

TABLE A-3 Category 2: Research and Development

Publication	Disease	Year of Outbreak	Outlet	Vaccine, Diagnostic, and Therapeutic Readiness	Delivery Capacity for Pharmaceutical and Medical Goods	Sample Sharing and Knowledge Sharing	Synergies with One Health
Twentieth Century Influenza Pandemics in Singapore	H1N1	1957–1968	*Annals Academy of Medicine Singapore*	(R) Use the increased knowledge of influenza, and the availability of antivirals (and possibly prepandemic vaccines), to further reduce the impact of a future pandemic by combining pharmaceutical and non-pharmaceutical interventions based on available evidence (R) Perform public health measures, such as antivirals, vaccination, and non-pharmaceutical interventions, to reduce the impact of a future pandemic (R) Develop vaccines that can improve heterotypic immunity, better techniques for vaccine production, and more effective antiviral therapies which may reduce the pandemic's spread			
The SARS Epidemic in Hong Kong: What Lessons Have We Learned?	SARS	2003	*Journal of the Royal Society of Medicine*		(R) Strengthen the exchange of epidemiological information on infectious diseases, especially the emergence of new infections, between the health authorities in Mainland China and Hong Kong		
SARS in Singapore—Key Lessons from an Epidemic	SARS	2003	*Annals Academy of Medicine Singapore*	(R) Develop very rapid and highly sensitive tests for SARS infection, which would substantially reduce the numbers of individuals that need to be quarantined without decreasing the effectiveness of the measure			

Responding to the Avian Influenza Pandemic Threat	H5N1	2003	*WHO Communicable Disease Surveillance and Response Global Influenza Programme*	(R) Expedite the development of a pandemic vaccine (shorten the time between emergence of a pandemic virus and the start of commercial production, and increase the supply of influenza vaccines) (R) Improve approaches to environmental detection of the virus (R) Assist developing countries that plan to manufacture their own vaccines	(R) Contain or delay spread at the source by establishing an international stockpile of antiviral drugs, developing mass delivery mechanisms for antiviral drugs, and conducting surveillance of antiviral susceptibility	(R) Compile and compare clinical data on human cases in order to elucidate modes of transmission, identify groups at risk, and find better treatments	(B) Most affected countries were not able to adequately compensate farmers for culled poultry. This discouraged reporting of outbreaks in rural areas where the majority of human cases occurred (B) Domestic ducks were able to excrete large quantities of pathogenic virus without showing signs of illness. Their silent role maintained transmission and further complicated control in humans and poultry
Pandemic Preparedness and Response—Lessons from the H1N1 Influenza of 2009	H1N1	2009	*New England Journal of Medicine*	(R) Ensure better antiviral agents and more effective influenza vaccines, greater production capacity, and faster throughput (R) Pursue a comprehensive influenza research and evaluation program (R) Improve scientific understanding and technical capacity (beyond institutional, political, and managerial difficulties)	(R) Develop better antiviral agents and more effective influenza vaccines, greater production capacity, and faster throughput (R) Recommend encouraging advance agreements for vaccine distribution and delivery	(R) Reach an agreement on the sharing of viruses, access to vaccines, and other benefits	
Influenza A (H1N1-2009) Pandemic in Singapore—Public Health Control Measures	H1N1	2009	*Annals Academy of Medicine Singapore*			(F) Frequent information reviews guided local decisions on the implementation	

continued

Implemented and Lessons Learnt						of public health control measures	
Lessons from Pandemic H1N1 2009 to Improve Prevention, Detection, and Response to Influenza Pandemics from a One Health Perspective	H1N1	2009	*ILAR Journal*				(R) Invest in One Health research to enhance understanding of the emergence, prevention, detection, and control of pandemic influenza viruses
Avian Influenza A (H7N9) Response: An Investment in Public Health Preparedness	H7N9	2013	WHO Publication			(R) Ensure that the timely release of data does not jeopardize future publication of the data in scientific journals	
Global Health Security: The Wider Lessons from the West African Ebola Virus Disease Epidemic	Ebola	2014	*The Lancet*	(R) Address issues of drug quality, which pose social, economic, and political challenges to health security by undermining ability to address diseases while eroding public confidence in governments and international institutions (R) Prevent market forces from being the only driver of medical research			
The Neglected Dimension of Global Security: A Framework for Countering Infectious Disease Crises	Ebola	2014	*New England Journal of Medicine*	(R) Need to address the many gaps in our R&D armory, as Ebola and other outbreaks have shown, which range from vaccine development and capacity, diagnostic tools, therapeutics, and protective equipment to anthropological research. Relying on the disparate efforts of the R&D community—academia, government, industry, and civil society—has not worked	(R) Enhance our scientific armory against infectious disease, including prioritization, mobilization, and deployment of significantly greater resources and harmonization of development and regulatory approval processes		

Protecting Humanity from Future Health Crises: UNSG's High Level Panel on Global Response to Health Crises	Ebola	2014	*UNGA Publication*	(B) Investment in medical R&D for diseases that largely affect the poor is deeply inadequate. Of the $214 billion invested in health R&D globally in 2010, less than 2 percent was allocated to neglected diseases (R) Dedicating resources to R&D on prioritized pathogens will ensure the greater availability of critical vaccines and treatments when they are most needed			

NOTES: ILAR = Institute for Laboratory Animal Research; R&D = research and development; SARS = severe acute respiratory syndrome; UNGA = United Nations General Assembly; UNSG = United Nations Secretary-General; WHO = World Health Organization.
11 of 16 publications had relevant findings for this category and were included.

Key:
(B) Barriers to pandemic preparedness and response.
(F) Facilitators to pandemic preparedness and response.
(R) Recommendations for implementation moving forward.

TABLE A-4 Category 3—Global Governance

				System Wide			WHO		
Publication	Disease	Year of Outbreak	Outlet	Cooperation and Operational Response	Accountability	Financing/Aid	New Bodies and Actions for Future Outbreaks	Function and Role	Leadership/Human Resources
Avian Influenza A (H7N9) Response: An Investment in Public Health Preparedness	H7N9	2013	WHO Publication				(F) The WHO Western Pacific regional office developed a framework for national health authorities to highlight areas of public health emergency response that may need specific action for avian influenza (the framework was based on the Asia Pacific Strategy for Emerging Diseases [2010], which covered the key technical areas [e.g., command and control, surveillance, risk assessment, etc.])		
The Neglected Dimension of Global Security: A Framework for Countering Infectious Disease Crises	Ebola	2014	*New England Journal of Medicine*	(R) WHO and UN to establish clear mechanisms for coordination and escalation in health crises (R) Use existing institutions rather than creating new bodies (e.g., United Nations Mission for Ebola Emergency Response)	(R) Commission an independent assessment in 2017 and then every 3 years following 2017	(R) IMF to develop capacity to provide budgetary support to governments that raise outbreak alerts through the existing Rapid Credit Facility (R) Develop a World Bank Pandemic Emergency Facility	(R) WHO to establish a WHO Centre for Health Emergency Preparedness and Response governed by independent technical governing board (R) WHO Emergency Centre to coordinate global health emergency workforce by strengthening and expanding GOARN	(R) WHO to take the lead in the global system to identify, prevent, and respond to potential pandemics (R) WHO to increase its capability and resources while demonstrating better leadership across actors (R) WHO to enhance means of cooperation with non-state actors, including local and	(R) Next DG should reenergize and refocus WHO on core priorities and on relationship building with other actors, such as other multilateral agencies and non-state actors; (R) Next DG needs stature and courage to engage with other global leaders, accept accountability, and hold countries accountable

continued

A Wake Up Call: Lessons from Ebola for the World's Health Systems	Ebola	2014	*Save the Children Publication*	(R) Develop disease surveillance systems with strong regional networks for better forecasting and control	(R) Use SDG target indicators to hold globe accountable to UHC (key health services) and for financial risk protection (R) Ensure that SDG targets apply to all social groups in a country and are not just reported as national averages (e.g., "no target met unless met for all") (R) Civil society to monitor domestic budgets to track resource flows and to advocate for increased and more equitable revenue in	(R) Ensure that aid and global support is increased and better aligned to help build suitable and comprehensive health services, and increase public financing for health (R) Ensure that multilateral initiatives are aligned to support comprehensive and universal health services and can demonstrate that they are doing this (R) Implement domestic and international reforms to curb illicit financial flows and tax avoidance		international civil society organizations, the private sector, and the media	(R) WHO to revise how elections are conducted for WHO officials, specifically: improve transparency and democratic nature of elections

					global health expenditure				
Protecting Humanity from Future Health Crises: UNSG's High Level Panel on Global Response to Health Crises	Ebola	2014	*UNGA Publication*	(R) Reinforce a clear line of command throughout the UN system (e.g., WHO DG reports to UNSG, WHO regional directors report to WHO Emergency Centre ED, ED to become UNSG's Emergency Coordinator) (R) Integrate UN health and humanitarian crisis trigger systems e.g., ERF Grade 2 or 3 heath crisis automatically triggers an interagency multisectoral assessment		(R) Increase assessed contributions to WHO by at least 10 percent with a share mandatorily directed to support the proposed Emergency Centre (R) Build a "Contingency Fund" of at least $300 million by 2016 that is financed according to assessment scale and managed by the proposed Emergency Centre (to be immediately replenished when depleted) (R) Guarantee that aid is disbursed according to Paris Declaration principles, especially alignment of support, harmonization, and mutual accountability (R) Support the creation of a World Bank Pandemic Emergency Financing Facility (national governments should decide how funds are spent in-country)	(R) WHO to establish a WHO Centre for Emergency Response with a multisectoral advisory board (R) WHO Emergency Centre and Inter-Agency Standing Committee to establish Standard Operating Procedures for humanitarian actors in health crises (R) WHO Emergency Centre to incorporate GOARN and foreign medical team programs in coordinating the global health emergency workforce	(R) WHO to serve as the single global health leader, determining and executing global health priorities (R) WHO to build unified and effective operational capacity (R) WHO to work closely with development actors to ensure complementarity between development programs and efforts to build health care systems and public health (R) WHO to establish a culture of emergency response and to develop the capacity and instinct to lead major operations	(R) WHO to increase investment in training health professionals at national level (especially community health workers)

Report 2: Advisory Group on Reform of WHO's Work in Outbreaks and Emergencies	Ebola	2014	*WHO*	(R) WHO to work with health cluster partners to build dedicated capacity for coordination, planning, information management, and communications (R) Integrate cluster partners' capacities in emergency operations (R) Articulate linkages between the Emergency Program, the Health Clusters, and overall humanitarian system		(R) Fund Emergency Program baseline capacity through predictable and reliable financing streams, including assessed contributions (this money should be different from emergency funds deployed in specific responses) (R) Maximize the use of existing funding mechanisms, such as the Central Emergency Response Fund, to support emergency operations (R) Seek full capitalization of the Contingency Fund	(R) WHO to develop the internal capacity to function as an operational organization (R) WHO to define and promote acceptance of common professional standards on health interventions, on sharing information and handling personal health data, and on building robust capacity for systematized information management and protocols for information sharing	(R) WHO to develop the capacity to function as and position itself as an operational organization since working in outbreaks and emergencies is part of WHO's core mandate (R) Reflect WHO's mandate (working in outbreaks and emergencies) in the focus of its governing bodies (R) Demonstrate that WHO is independent and impartial while reviving and improving relationships with member states and partners (R) Engage in a profound organizational transformation rather than piecemeal reform (i.e., a single merger of organizational units within WHO will not suffice; it will need new organizational	(R) Next DG should remain accountable for incident management within WHO (R) Ensure that WHO's mandate to work in outbreaks and emergencies is reflected in the capabilities of its staff (R) WHO to facilitate the diversification of the health workforce: engaging multiple actors from multiple sectors and at multiple levels, rather than a single global workforce of "white helmets" (R) WHO to increase its staff

continued

								structures and procedures)	
Middle East Respiratory Syndrome Coronavirus (MERS-CoV): What Lessons Can We Learn?	MERS-CoV	2013	*Journal of Hospital Infection*		(R) Global system to ensure adequate assessment of patients presenting with febrile illness prior to international air travel		(R) WHO to act as a knowledge broker: WHO guidelines should not prevail over clinical judgment during a pandemic because such guidelines are inevitably based on incomplete evidence		

NOTES: DG = director-general; ED = executive director; ERF = emergency response framework; GOARN = Global Outbreak Alert and Response Network; IMF = International Monetary Fund; MERs-CoV = Middle East respiratory syndrome coronavirus; SDG = Sustainable Development Goal; UHC = universal health coverage; UN = United Nations; UNGA = United Nations General Assembly; UNSG = United Nations Secretary-General; WHO = World Health Organization.
6 of 16 publications had relevant findings for this category and were included.

Key:
(B) Barriers to pandemic preparedness and response.
(F) Facilitators to pandemic preparedness and response.
(R) Recommendations for implementation moving forward.

Appendix B

Workshop Statement of Task

An ad hoc committee under the auspices of the National Academies of Sciences, Engineering, and Medicine will plan a 1.5-day public workshop that will examine the lessons that have been learned and applied, and the world's current readiness to prevent, detect, and respond to pandemic influenza and other potential novel diseases from a century of outbreaks. Workshop participants will reflect on the challenges of improving readiness; discuss how to move beyond barriers; assess how the latest advances in global, regional, and national governance structures, systems, and capacities to fight against the next influenza pandemic can make a difference; and explore areas that need more work, including immediate and short-term actions that will have the greatest impact on global health security by 2030.

Specifically, this workshop will feature invited presentations and discussions on topics including

- Recent progress achieved in monitoring global health security and pandemic preparedness at the national and global levels, including advances in developing national action plans stemming from the International Health Regulations and the Joint External Evaluation, building strong public health capacities that incorporate a One Health approach, and developing risk analysis and assessment tools to guide resource allocation;
- Critical challenges and opportunities in developing and evaluating medical countermeasures, including seasonal vaccines, a universal

influenza vaccine, and novel diagnostics and therapeutics, and strategies to secure their adequate supply and distribution, particularly ensuring access to high-risk populations;
- Various methods and tools, such as effective emergency operations centers, surveillance systems, and sequencing technologies, to shorten the time between onset and detection, lab confirmation, and public communication of major disease outbreaks; and
- The ethical and operational challenges and opportunities for enabling meaningful coordination, cooperation and sharing of information and technological benefits among various stakeholders, including multilateral organizations, national governments, private sector, and civil society.

Workshop speakers and discussants will contribute perspectives from government, academia, and private and nonprofit sectors from the local to global levels.

Appendix C

Pre-Workshop Agenda

A Century After the 1918 Influenza Pandemic:
Why Are We Still Concerned Today?

MONDAY, NOVEMBER 26, 2018

2:00 pm ET	Welcome **Victor J. Dzau,** National Academy of Medicine
2:10 pm	Opening Remarks **Keiji Fukuda,** The University of Hong Kong School of Public Health
2:20 pm	Keynote Presentation From the 1918 Influenza Pandemic to 2009 H1N1 Pandemic to Now: Is the World Ready to Respond to the Next Outbreak? **Laurie Garrett,** Anthropos Initiative Q&A with Audience

Panel Discussion on Global Progress to Prepare for the Next Influenza Pandemic
Suzet McKinney, Illinois Medical District, *Moderator*

3:00 pm	Expanding the Frontiers of Science to Counter the Threat of Pandemic Influenza: How Will Understanding the Biology of the Virus Help Us Prepare for the Future? Where Should Our Priorities Be? **Yoshihiro Kawaoka,** University of Wisconsin–Madison
	The Latest Advances in Medical Countermeasures: Are We Close to a Universal Flu Vaccine? **Anthony Fauci,** National Institute of Allergy and Infectious Diseases
	Global Governance to Bolster Preparedness for Pandemic Influenza: A Critical Look into the International Health Regulations and Pandemic Influenza Preparedness Frameworks **David Fidler,** Indiana University Bloomington
	Dismantling the Silos: The Evolution and Benefits of One Health as a Unifying Theme for Pandemic Influenza Preparedness **Jacqueline Katz,** U.S. Centers for Disease Control and Prevention
4:15 pm	Q&A with Audience
5:00 pm	Outbreak Exhibit and Reception

Appendix D

Workshop Agenda

Readiness for Microbial Threats 2030: Exploring Lessons Learned Since the 1918 Influenza Pandemic

TUESDAY, NOVEMBER 27, 2018

11:00 am ET Welcome Remarks
Peter Daszak, Chair, Forum on Microbial Threats

Workshop Overview and Goals
Keiji Fukuda, Workshop Chair

Keynote Address
Impact of Outbreaks and Pandemics on People, Communities, and Economies
Rick Bright, Biomedical Advanced Research and Development Authority

Plenary Presentation
A Century of Evolving Pandemic and Emerging Diseases Challenges
Arnold Monto, University of Michigan

Session I: Major Lessons Learned Since the 1918 Influenza Pandemic

Part A: National and Community Perspectives and Lessons
Suerie Moon, The Graduate Institute of International and Development Studies, Geneva, *Moderator*

1:00 pm	**Abdullah Assiri,** Ministry of Health, Saudi Arabia **Mosoka Fallah,** National Public Health Institute, Liberia **Gabriel Leung,** The University of Hong Kong **Amanda McClelland,** Prevent Epidemics, Resolve to Save Lives
1:35 pm	Q&A

Part B: Private-Sector and Institutional Perspectives and Lessons
Jacqueline Katz, U.S. Centers for Disease Control and Prevention, *Moderator*

2:15 pm	**Wenqing Zhang,** World Health Organization **Karen Midthun,** PATH **Clement Lewin,** Sanofi Pasteur **Bruce Gellin,** Sabin Vaccine Institute **Steven Solomon,** World Health Organization
3:00 pm	Q&A
3:45 pm	Break

Part C: Global Perspectives and Lessons
Keiji Fukuda, The University of Hong Kong School of Public Health, *Moderator*

4:00 pm	**Makarim Wibisono,** Indonesian Defense University **John E. Lange,** United Nations Foundation **Anne Huvos,** World Health Organization **Steven Solomon,** World Health Organization
4:35 pm	Q&A
5:20 pm	Observations from Day 1 **Keiji Fukuda,** Workshop Chair
5:30 pm	Adjourn
5:35 pm	Reception

WEDNESDAY, NOVEMBER 28, 2018

8:30 am Welcome and Recap Day 1
Keiji Fukuda, Workshop Chair

Session II: Overcoming Critical Impediments to Achieve Greater Preparedness

Panel Discussion: How Can the Cycle of Panic and Neglect Be Ended and the Business Case Made for Sustained Political and Financial Support for Preparedness?
Kumanan Rasanathan, Health Systems Global, *Moderator*

8:40 am **Julie L. Gerberding,** Merck & Co., Inc.
Jimmy Kolker, American Association for the Advancement of Science
Suzet McKinney, Illinois Medical District
Peter Sands, The Global Fund to Fight AIDS, Tuberculosis and Malaria

9:40 am Q&A

10:30 am Break

10:45 am Small-Group Discussions
Jonna Mazet, University of California, Davis, *Moderator*

12:00 pm Lunch

Session III: Top Priorities and Actions for Preparedness by 2030

Panel Discussion: Short Visionary Statements on the Priorities for Better Preparedness by 2030 and Next Steps Forward
Rima Khabbaz, U.S. Centers for Disease Control and Prevention, *Moderator*

1:00 pm **Harvey V. Fineberg,** Gordon and Betty Moore Foundation
Gabrielle Fitzgerald, Panorama
Nicole Lurie, Former Assistant Secretary for Preparedness and Response
Ciro Ugarte, Pan American Health Organization

2:00 pm	Final Synthesis Discussion with the Audience
2:45 pm	Closing Remarks **Keiji Fukuda,** Workshop Chair **Peter Daszak,** Chair, Forum on Microbial Threats
3:00 pm	Adjourn

Appendix E

Biographical Sketches of Pre-Workshop and Workshop Speakers and Moderators

Abdullah M. Assiri, M.D., FACP, is an adult infectious diseases consultant; assistant deputy minister of preventive health; International Health Regulations national focal point in the Ministry of Health, Saudi Arabia; and adjunct associate professor in the Hubert Department of Global Health at Emory University.

Rick A. Bright, Ph.D., is the deputy assistant secretary for preparedness and response and the director of the Biomedical Advanced Research and Development Authority (BARDA), which is a component of the Office of the Assistant Secretary for Preparedness and Response in the U.S. Department of Health and Human Services. He oversees the advanced development and procurement of medical countermeasures against an array of threats to national security and the public's health, including chemical, biological, radiological, nuclear threats and pandemic influenza, and emerging infectious diseases. Dr. Bright began his career in vaccine and therapeutics development at the U.S. Centers for Disease Control and Prevention, with a focus on influenza viruses, antiviral drugs, and the development of novel assays for high throughput surveillance for resistance to antiviral drugs. For this work, Dr. Bright was a recipient of the Charles C. Shepard Science Award for Scientific Excellence. He has extensive experience in the biotechnology industry in which he served in senior leadership and executive management roles. Dr. Bright has also held senior scientific leadership positions in nongovernmental organizations for which he championed innovative vaccine development and international vaccine manufacturing capacity expansion in developing countries. He serves as an international

subject matter expert in vaccine, drug, and diagnostics development and has served as an advisor to the World Health Organization and the U.S. Department of Defense. Dr. Bright joined BARDA in 2010, and prior to becoming director in late 2016, he served as director of BARDA's Influenza and Emerging Infectious Diseases Division. Dr. Bright received his Ph.D. in immunology and virology from Emory University and his B.S. in biology and physical sciences from Auburn University.

Peter Daszak, Ph.D., is president of EcoHealth Alliance, a U.S.-based organization that conducts research and outreach programs on global health, conservation, and international development. Dr. Daszak's research has been instrumental in identifying and predicting the impact of emerging diseases across the globe. His achievements include identifying the bat origin of severe acute respiratory syndrome, identifying the underlying drivers of Nipah and Hendra virus emergence, producing the first ever global emerging disease "hotspots" map, developing a strategy to find out how many unknown viruses exist that could threaten to become pandemic, identifying the first case of a species extinction due to disease, and discovering the disease chytridiomycosis as the cause global amphibian declines. Dr. Daszak is a member and chair-elect of the National Academies of Sciences, Engineering, and Medicine's Forum on Microbial Threats. He is a member of the National Research Council (NRC) Advisory Committee to the U.S. Global Change Research Program, the Supervisory Board of the One Health Platform, the One Health Commission Council of Advisors, the Center of Excellence for Emerging and Zoonotic Animal Diseases External Advisory Board, the Cosmos Club, and the Advisory Council of the Bridge Collaborative; he has served on the Institute of Medicine committee on global surveillance for emerging zoonoses, the NRC committee on the future of veterinary research, the International Standing Advisory Board of the Australian Biosecurity Cooperative Research Centres; and has advised the director for medical preparedness policy on the White House National Security Staff on global health issues. Dr. Daszak is a regular advisor to the World Health Organization (WHO), World Organisation for Animal Health, and the Food and Agriculture Organization of the United Nations, and is actively involved in the WHO Expert group on Public Health Emergency Disease Prioritization. Dr. Daszak won the 2000 Commonwealth Scientific and Industrial Research Organisation medal for collaborative research on the discovery of amphibian chytridiomycosis, is the EHA institutional lead for USAID-EPT-PREDICT, is on the editorial boards of *Conservation Biology*, *One Health*, and *Transactions of the Royal Society of Tropical Medicine & Hygiene*, and is editor-in-chief of the journal *EcoHealth*. He has authored more than 300 scientific papers, and his work has been the focus of extensive media coverage, ranging from popular press articles to television appearances.

Victor J. Dzau, M.D., is the president of the National Academy of Medicine (NAM), formerly the Institute of Medicine (IOM). In addition, he serves as vice chair of the National Research Council. Dr. Dzau is chancellor emeritus and James B. Duke Professor of Medicine at Duke University and the past president and chief executive officer of the Duke University Health System. Previously, Dr. Dzau was the Hershey 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. He is an internationally acclaimed leader and scientist whose work has improved health care in the United States and globally. His seminal work in cardiovascular medicine and genetics laid the foundation for the development of the class of lifesaving drugs known as ACE inhibitors, used globally to treat hypertension and heart failure. In his role as a leader in health care, Dr. Dzau has led efforts in innovation to improve health, including the development of 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. He has served as a member of the Advisory Committee to the director of the U.S. National Institutes of Health (NIH), chaired the NIH Cardiovascular Disease Advisory Committee, and currently chairs the NIH Cardiovascular Stem Cell Biology and Translational Consortia. Currently, he is a member of the Board of the Singapore Health System, member of the Health Biomedical Sciences International Advisory Council of Singapore, and Advisory Council of the Imperial College Health Partners, UK. He chairs the International Scientific Advisory Committee of the Qatar Genome Project, chairs the Scientific Boards of the Peter Munk Cardiac Center, University of Toronto, and Institute of Cardiovascular and Medical Sciences, University of Glasgow. Since arriving at the National Academies, Dr. Dzau has designed and led important initiatives such as the Commission on a Global Health Risk Framework for the Future; the Human Genome Editing Initiative; and Vital Directions for Health and Health Care. The launch of the NAM Grand Challenge for Healthy Longevity represents his vision to inspire across disciplines and sectors to coalesce around a shared priority and audacious goal to advance health.

Mosoka P. Fallah, Ph.D., M.P.H., M.A., co-founded the National Public Health Institute of Liberia (NPHIL) 20 months after the Ebola crisis that ravaged his native country. He was appointed by President Ellen Johnson-Sirleaf of Liberia as the deputy director for technical services and oversees the Divisions of Infectious Disease Epidemiology, National Public Health Laboratory, and Medical and Public Health Research, among others. He was recently appointed as part-time faculty in the Department of Social Medicine at the Harvard Medical School. Dr. Fallah is the Liberian principal investigator of a 5-year natural history study on Ebola that is sponsored

by the U.S. National Institutes of Health and that follows the largest cohort of Ebola survivors in the world. He also served as chair of the Department of Biochemistry at the A.M. Dogliotti College of Medicine at the University of Liberia. While still a Ph.D. student at the University of Kentucky, he founded Refuge Place International to address the very high number of maternal and neonatal deaths in Liberia. He then attended the Harvard T.H. Chan School of Public Health to study global health and concentrated in infectious disease epidemiology. In 2013, Dr. Fallah returned to Liberia to work on maternal and child health in a country that was ravaged by civil war and was rebuilding its health system. Just as he opened Refuge Place International in Chicken Soup Factory, a slum in Liberia, the Ebola outbreak occurred, and the organization was shuttered. With his skills in epidemiology and program management, Dr. Fallah became the head of the Liberian Ebola response and launched an active case-finding system, which became a model for epidemic control. Because he was raised in Monrovia, he had prior experience building trust within communities that struggled to deal with Ebola. He also gained extensive experience working in other humanitarian crises with Doctors Without Borders in Liberia during the height of the civil war. With more than 10 years of experience in development work, he has consulted for Action Against Hunger, Chemonics, the President's Malaria Initiative, the United Nations Development Programme, the U.S. Agency for International Development, and the World Health Organization. Dr. Fallah has worked extensively with the Liberian Ministry of Health, medical centers, and other nonprofit organizations to jumpstart his flagship program in Liberia. For his work in the Ebola response, he was named a *Time Magazine* Person of the Year in 2014.

Anthony S. Fauci, M.D., is director of the National Institute of Allergy and Infectious Diseases (NIAID) at the U.S. National Institutes of Health, where he oversees an extensive research portfolio focused on infectious and immune-mediated diseases. As the long-time chief of the NIAID Laboratory of Immunoregulation, Dr. Fauci has made many seminal contributions in basic and clinical research and is one of the world's most-cited biomedical scientists. He was one of the principal architects of the President's Emergency Plan for AIDS Relief, a program that has saved millions of lives throughout the developing world.

David Fidler, J.D., M.Phil., is adjunct senior fellow for cybersecurity and global health at the Council on Foreign Relations and is the James Louis Calamaras Professor of Law at the Indiana University Maurer School of Law. He is an expert in international law, cybersecurity, national security, terrorism, counterinsurgency, international trade, biosecurity, and global health. Professor Fidler has served as an international legal consultant to

the World Bank (on foreign investment in Palestine), the World Health Organization, the U.S. Centers for Disease Control and Prevention (on global health issues), the U.S. Department of Defense's Defense Science Board (on bioterrorism), the Scientists Working Group on Biological and Chemical Weapons of the Center for Arms Control and Non-Proliferation, U.S. Joint Forces Command (on rule of law issues in stability operations), the Interagency Afghanistan Integrated Civilian-Military Pre-Deployment Training Course organized by the U.S. Departments of Defense, State, Agriculture and the U.S. Agency for International Development, and various initiatives undertaken by nongovernmental organizations in the areas of global health and arms control. He served as chair for an International Law Association study group on terrorism, cybersecurity, and international law.

Harvey V. Fineberg, M.D., Ph.D., is president of the Gordon and Betty Moore Foundation. He previously served as president of the National Academy of Medicine (formerly Institute of Medicine), provost of Harvard University, and dean of the Harvard T.H. Chan School of Public Health. He is a trustee of the China Medical Board and of the Carnegie Endowment for International Peace. He helped found and served as president of the Society for Medical Decision Making and chaired the World Health Organization Committee to Review the International Health Regulations (2005) and Response to Pandemic Influenza A (H1N1) 2009. Dr. Fineberg is co-author of the books *Clinical Decision Analysis*, *Innovators in Physician Education*, and *The Epidemic That Never Was*, an analysis of the controversial federal immunization program against swine flu in 1976.

Gabrielle Fitzgerald, M.P.A., is a global leader who believes that innovative approaches and catalytic coalitions are needed to solve the most challenging issues. Her focus is on designing and driving strategies that measurably impact people, organizations, and countries. Ms. Fitzgerald is the founder and chief executive officer of Panorama, an action tank dedicated to helping ambitious leaders solve global problems. For more than two decades, she has led teams and collaborated with partners to spark global change. Prior to founding Panorama, she directed the $100 million Ebola program at the Paul G. Allen Family Foundation, investing in creative approaches to combat the Ebola outbreak in West Africa. Ms. Fitzgerald previously served as the director of global program advocacy at the Bill & Melinda Gates Foundation, leading the team that advanced policy and advocacy agendas for the organization's global issues. In 2014, she won the Gold Medallion award from Johns Hopkins Bloomberg School of Public Health's Center for Communication Programs for her leadership on malaria. Earlier in her career, Ms. Fitzgerald led the public affairs strategy for HIV/AIDS at the U.S. Agency for International Development and served as the communications

director for the U.S. Committee for Refugees. She also served as a speechwriter for President Clinton at The White House. Ms. Fitzgerald holds n M.P.A. from the Maxwell School at Syracuse University and a B.A. from American University in Washington, DC.

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

Laurie Garrett, Ph.D. (honoris causa), has been a finalist for the Pulitzer Prize three times, receiving it in 1996 for coverage of the Kikwit Ebola epidemic. She is the only writer to have received the Pulitzer, Peabody, and Polk (twice), as well as four Overseas Press Club awards. For 13 years, she was senior fellow for global health at the Council on Foreign Relations. Prior to that she was a correspondent with Newsday, and National Public Radio. Dr. Garrett is the author of *The Coming Plague: Newly Emerging Diseases in a World Out of Balance*, *Betrayal of Trust: The Collapse of Global Public Health*, and *I Heard the Sirens Scream: How Americans Responded to the 9/11 and Anthrax Attacks*. She graduated with honors from the University of California, Santa Cruz, and did graduate studies in immunology at the University of California, Berkeley, and Stanford University. She was a fellow at the Harvard T.H. Chan School of Public Health and former president of the National Association of Science Writers. She

is currently the founder of the Anthropos Initiative and a featured writer for *Foreign Policy*.

Bruce Gellin, M.D., M.P.H., is president of global immunization at the Sabin Vaccine Institute in Washington, DC. In this role, Dr. Gellin oversees Sabin's mission to make vaccines more accessible, enable innovation, and expand immunization across the globe. With a focus on low- and middle-income countries, this work helps countries make evidence-based decisions about vaccine introduction and implementation and strengthens policy, financing, and political will for country ownership of immunization. Before joining Sabin, Dr. Gellin served in the U.S. Department of Health and Human Services as deputy assistant secretary for health and director, National Vaccine Program Office (NVPO) within the Office of the Assistant Secretary for Health. NVPO was created by U.S. Congress to provide leadership and coordination among federal agencies and other immunization stakeholders, including states and municipalities, health care providers, and private-sector entities such as vaccine manufacturers. Dr. Gellin has had broad experience in public health aspects of infectious diseases and has held positions at the National Institute of Allergy and Infectious Diseases, the U.S. Centers for Disease Control and Prevention, The Rockefeller Foundation, the Vanderbilt University School of Medicine, and the Johns Hopkins Bloomberg School of Public Health. In addition, he was the founder and executive director of the National Network for Immunization Information, an organization he founded to be a resource of up-to-date, authoritative information about vaccines and immunizations. He has been a regular consultant to the World Health Organization. He currently has faculty appointments at the Georgetown University School of Medicine and the Vanderbilt University School of Medicine. Dr. Gellin is a graduate of the University of North Carolina (Morehead Scholar), Cornell University Medical College, and the Columbia University School of Public Health. He is an infectious disease expert with training in epidemiology. He has written extensively about public health aspects of infectious diseases in both medical and nonmedical texts, peer-reviewed medical literature, and has served as a medical advisor to *Encyclopedia Britannica*.

Julie L. Gerberding, M.D., M.P.H., is executive vice president and chief patient officer at Merck & Co., Inc., where she is responsible for a broad portfolio of patient engagement, communications, policy, philanthropic, and other functions. She joined Merck in 2010 as president of vaccines, and was instrumental in increasing access to the company's vaccines to people around the world. Previously, Dr. Gerberding was director of the U.S. Centers for Disease Control and Prevention, where she led the agency through more than 40 emergency responses to public health crises. She

serves on the boards of Cerner Corporation and the MSD Wellcome Trust Hilleman Laboratories, a nonprofit that develops new technologies for developing countries.

Anne Huvos, J.D., DESS, joined World Health Organization (WHO) headquarters in 2006, when she began working on the formal and informal processes and negotiations that would lead to adoption of the Pandemic Influenza Preparedness (PIP) Framework. She has been leading the PIP Framework Secretariat since the framework's adoption by the World Health Assembly in 2011. Under her leadership, implementation of the framework has demonstrated its value as a model for strengthening public health security through an innovative partnership with public, private, and nongovernmental sectors. The PIP Framework has been instrumental in strengthening global pandemic influenza preparedness and response capacities in countries where they are weak, and establishing agreements to provide to WHO access to critical pandemic response supplies, in real time, at the time of a pandemic.

Jacqueline M. Katz, Ph.D., is the deputy director of the Influenza Division and the director of the World Health Organization (WHO) Collaborating Center for Surveillance, Epidemiology, and Control of Influenza at the U.S. Centers for Disease Control and Prevention (CDC). She received her Bachelor of Science degree in microbiology and biochemistry and her doctoral degree in microbiology from the University of Melbourne in Melbourne, Australia. She did her postdoctoral training in influenza virology and was later an assistant member in the Department of Virology and Molecular Biology at St. Jude Children's Research Hospital, Memphis, Tennessee. Dr. Katz joined CDC in 1992 as the chief of the Immunology and Viral Pathogenesis Section, Influenza Branch, Division of Viral and Rickettsial Diseases. From 2006 until 2014, Dr. Katz was the chief of the Immunology and Pathogenesis Branch, Influenza Division. Dr. Katz has been a board member of the International Society for Influenza and other Respiratory Diseases (isirv) since 2007 and the deputy chair since 2012. She is an associate editor for *Influenza and Other Respiratory Viruses* journal. She is the author and co-author of more than 300 research articles, reviews, and book chapters and is the recipient of three CDC Charles C. Shepard Science Awards for excellence in laboratory and methods publications. Dr. Katz is recognized internationally for her studies on the immunology and pathogenicity of influenza viruses, studies at the animal–human interface to understand the extent of and risk factors for human infection with novel influenza viruses of animal origin, and WHO-related work on influenza vaccine virus selection.

Yoshihiro Kawaoka, D.V.M., Ph.D., was educated in Japan, receiving his D.V.M. in 1978 and his Ph.D. in 1983 from Hokkaido University. Dr. Kawaoka established the technique of reverse genetics, which allows the generation of "designer" influenza viruses. This technology—coupled with his findings regarding the weakening of deadly influenza viruses—has been used to develop candidate bird flu virus vaccines. Reverse genetics is also used to generate live attenuated influenza vaccines (e.g., FluMist). Dr. Kawaoka discovered what makes bird flu viruses so deadly and what makes bird flu jump from birds to humans. He also discovered why the 1918 Spanish flu virus was so deadly. As a founder of FluGen, Dr. Kawaoka is developing a universal flu vaccine, which is currently in clinical trials. In addition to his influenza research, Dr. Kawaoka studies Ebola virus, and his group worked in Sierra Leone during the Ebola outbreak in 2014–2016 and continues to work with Ebola survivors. He is currently developing an Ebola vaccine, which will enter clinical trials in 2019. In recognition of his achievements, Dr. Kawaoka was awarded the Robert Koch Award in 2006; he received the Medal of Honor (Purple Ribbon) in 2011 and the Japan Academy Award in 2016 from the Emperor of Japan for his research in the field of influenza virology. In 2013, he was elected as a foreign associate of the U.S. National Academy of Sciences. In 2015, he received the United Nations Educational, Scientific and Cultural Organization Carlos J. Finlay Prize for Microbiology.

Rima F. Khabbaz, M.D., is the director of the National Center for Emerging and Zoonotic Infectious Diseases (NCEZID) at the U.S. Centers for Disease Control and Prevention (CDC). From 2010 to 2017, she was CDC's deputy director for infectious diseases and director of the Office of Infectious Diseases, where she helped lead the efforts of CDC's infectious disease national centers and advance the agency's cross-cutting infectious disease priorities including the integration of advanced molecular detection technologies into public health. During that time, she also served on an interim basis as acting director of the National Center for Immunization and Respiratory Diseases, acting director of the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, and acting director of NCEZID during leadership transitions. Her previous CDC positions include director of the National Center for Preparedness, Detection, and Control of Infectious Diseases; director, acting director, and associate director for epidemiologic science in the National Center for Infectious Diseases (NCID); and deputy director and associate director for science in the Division of Viral and Rickettsial Diseases. Her first job at CDC was an epidemic intelligence service officer in NCID's Hospital Infections Program. She later served as a medical epidemiologist in NCID's Retrovirus Diseases Branch, where she made major contributions to defining the epidemiology of the

non-HIV retroviruses, specifically human T lymphotropic viruses (HTLV) I and II, in the United States and to developing guidance for counseling HTLV-infected persons. Following the hantavirus pulmonary syndrome outbreak in the southwestern United States in 1993, she led CDC's efforts to set up national surveillance for this syndrome. She also played a key role in developing and coordinating CDC's blood safety and food safety programs related to viral diseases. She has served in leadership positions during many of CDC's responses to outbreaks of new and/or reemerging infections, including Nipah, Ebola, West Nile virus, SARS, and monkeypox, and she led the CDC field team to the nation's capital during the public health response to the anthrax attacks of 2001. Dr. Khabbaz is a graduate of the American University of Beirut in Lebanon, where she obtained both her bachelor's degree in science (biology/chemistry) and her medical doctorate degree. She trained in internal medicine and completed a fellowship in infectious diseases at the University of Maryland, Baltimore. In addition to her CDC position, she serves as clinical adjunct professor of medicine (infectious diseases) at Emory University. Dr. Khabbaz is a fellow of the Infectious Diseases Society of America (IDSA), a member of the American Epidemiological Society, and a member of the American Society for Microbiology and of the American Society for Tropical Medicine and Hygiene. She is a graduate of the Public Health Leadership Institute at the University of North Carolina and the National Preparedness Leadership Initiative at Harvard University. She served on IDSA's Annual Meeting Scientific Program Committee and serves on the society's Public Health Committee. She also is a member of the National Academies of Sciences, Engineering, and Medicine's Forum on Microbial Threats.

Jimmy Kolker, M.P.A., served as assistant secretary for global affairs at the U.S. Department of Health and Human Services (2014–2017). In this role, Ambassador Kolker was the department's chief health diplomat, representing the United States at World Health Organization and The Global Fund for AIDS, Tuberculosis and Malaria meetings. Ambassador Kolker had a 30-year diplomatic career with the U.S. Department of State, where he served as the U.S. Ambassador to Burkina Faso (1999–2002) and to Uganda (2002–2005). From 2005 to 2007, he was deputy U.S. Global AIDS Coordinator, leading the implementation of the President's Emergency Plan for AIDS Relief. He was deputy chief of mission at U.S. embassies in Botswana and Denmark and won awards for political reporting at earlier posts in Mozambique, Sweden, the United Kingdom, and Zimbabwe. From 2007 to 2011, Ambassador Kolker was chief of the AIDS Section at UNICEF's New York headquarters. Now retired, Ambassador Kolker is a visiting scholar at American Association for the Advancement of Science, a nonresident senior associate with the CSIS Global Health Policy

Center, and a fellow of Georgetown University's Center for Global Health Science and Security. He serves on three foundation boards and three non-governmental organization advisory councils.

John E. Lange, J.D., M.S., is senior fellow for global health diplomacy at the United Nations Foundation, serving as the foundation's primary focal point for global health diplomacy activities and its wide-ranging work with the World Health Organization. He chairs the leadership team of the Measles & Rubella Initiative and earlier served as co-chair of the Global Polio Eradication Initiative's Polio Partners Group. He worked from 2009 to 2013 at the Bill & Melinda Gates Foundation, where he engaged in high-level global health advocacy with international organizations and African governments. Ambassador Lange had a distinguished 28-year career in the Foreign Service at the U.S. Department of State, where he was a pioneer in the field of global health diplomacy. He served as the Special Representative on Avian and Pandemic Influenza; Deputy Inspector General; Deputy U.S. Global AIDS Coordinator at the inception of the President's Emergency Plan for AIDS Relief; and U.S. Ambassador to Botswana (1999–2002), where HIV/AIDS was his signature issue. Ambassador Lange led the U.S. Embassy in Dar es Salaam, Tanzania, as Chargé d'Affaires during the August 7, 1998, terrorist bombing. Earlier, he had tours of duty in Geneva, Lomé, Paris, and Mexico City. Ambassador Lange is the author of a case study on pandemic influenza negotiations, has delivered numerous lectures and writes a blog on global health issues, and has served on global health and security committees of the National Academies of Sciences, Engineering, and Medicine. He has an M.S. degree from the National War College, and J.D. and B.A. degrees from the University of Wisconsin–Madison.

Gabriel Mathew Leung, M.D., M.P.H., G.B.S., J.P., is the fortieth Dean of Medicine (2013–present), inaugural Helen and Francis Zimmern Professor in population health, and holds the chair of Public Health Medicine at The University of Hong Kong (HKU). He was the last head of community medicine (2012–2013) at the university as well as Hong Kong's first undersecretary for food and health (2008–2011) and fifth director of the chief executive's office (2011–2012) in government. He is an elected member of the National Academy of Medicine and was awarded the Gold Bauhinia Star (second highest civilian honor) by the Hong Kong government for distinguished service in protecting and promoting population health. A specialist in public health medicine, Dr. Leung's interdisciplinary work revolves around topics that have major population health impact locally, where Hong Kong is a reliable and unique epidemiologic sentinel for Mainland China, or where the SAR is best placed to address the fundamental science at hand globally. Dr. Leung is one of Asia's leading epidemiologists

and global health exponents, having authored more than 450 scholarly papers with an h-index of 58 (Scopus). His research defined the epidemiology of two novel viral epidemics, namely SARS-CoV in 2003 and influenza A(H7N9) in 2013. He also led Hong Kong government's efforts against pandemic A(H1N1) in 2009. He was founding co-director of HKU's World Health Organization Collaborating Centre for Infectious Disease Epidemiology and Control (2014–2018). In parallel, Dr. Leung leads several large-scale longitudinal cohorts (Children of 1997, FAMILY, Department of Health Elderly Health Service cohort), tracking tens of thousands of lives to study the fundamental causes of noncommunicable conditions and to explain the health impacts of contemporary social phenomena. A final strand of his work concerns the economics and policy issues of health systems. His team is the government's health accountant and projects health care human resources needs into the future. Regionally, Dr. Leung has tirelessly worked to build capacity throughout the Asia Pacific. He served as founding chair of the Asia Pacific Observatory on Health Systems Policies (2010–2014) and continues to lead its Strategic Technical Advisory Committee (2018–present).

Clement Lewin, Ph.D., M.B.A., has been in the vaccines industry for more than 20 years joining Sanofi Pasteur as associate vice president of R&D Strategy in 2015. Prior to joining Sanofi Pasteur, he held was at several companies including Merck Vaccines Division, Chiron Vaccines, and Acambis. Prior to his current role, Dr. Lewin spent 7 years at Novartis Vaccines, most recently as vice president, head of medical affairs and immunization policy for North America, and was responsible for medical affairs activities and relationships with public-sector stakeholders such as the U.S. Centers for Disease Control and Prevention and the National Vaccine Program Office; in his role, he helped launch several vaccines. In addition to his experience in vaccines, Dr. Lewin was at Bayer Pharmaceuticals as director of global scientific affairs for their anti-infective franchise. He obtained his B.Sc. and Ph.D. from the University of London after 5 years as a research fellow at the Universities of London and Edinburgh. During that period, he published more than 50 papers in peer-reviewed journals on mechanisms of action and resistance to antibacterials. He left research to obtain an M.B.A. with distinction from Cornell University and then joined the life sciences practice of Pittiglio Rabin Todd & McGrath specializing in product development issues. Dr. Lewin was the Biotechnology Innovation Organization liaison to the Advisory Committee on Immunization Practices from 2004 to 2014. He served on the National Vaccine Advisory Committee from 2009 to 2012. He was on the advisory board of Bio Ventures for Global Health and a board member of the Alliance for Biosecurity from 2006 to 2008.

Nicole Lurie, M.D., M.S.P.H., is currently the strategic advisor to the chief executive officer of the Coalition for Epidemic Preparedness Innovations. She is also a senior lecturer at Harvard Medical School, a member of the research faculty at Massachusetts General Hospital, and is an honorary fellow at the Leonard Davis Institute for Health Economics at the University of Pennsylvania. Dr. Lurie recently completed an 8-year term as Assistant Secretary for Preparedness and Response at the U.S. Department of Health and Human Services (HHS). In that role, she led the HHS response to numerous public health emergencies, ranging from infectious disease to natural and manmade disasters, and was responsible for many innovations in emergency preparedness and response. She also chaired the Public Health Emergency Medical Countermeasures Enterprise, a government-wide organization ultimately responsible for the development of medical countermeasures, including vaccines against pandemics and emerging threats. Following that, she served as senior advisor to the director of the Indian Health Service, where she worked on issues related to quality of care, and as a consultant to the World Bank and World Health Organization. Prior to federal service, Dr. Lurie was the Paul O'Neill Professor of Policy Analysis at RAND, where she started and led the public health preparedness program and RAND's Center for Population Health and Health Disparities. She has also had leadership roles in academia, as professor of medicine and public health at the University of Minnesota, as medical advisor to the commissioner, Minnesota Department of Health, and as principal deputy assistant secretary for health at HHS. Dr. Lurie received her B.A. and M.D. degrees from the University of Pennsylvania, and completed her residency and public health training at the University of California, Los Angeles. Her research has focused on access to and quality of care, health system redesign, equity, mental health, public health, and preparedness. She is recipient of numerous awards and is a member of the National Academy of Medicine. Dr. Lurie continues to practice clinical medicine in a community clinic in Washington, DC.

Jonna A. K. Mazet, D.V.M., M.P.V.M., Ph.D., earned her doctorate of veterinary medicine, master of preventative medicine, and her Ph.D. in epidemiology from the University of California, Davis (UC Davis). In addition to her faculty appointment in the Department of Medicine and Epidemiology in the UC Davis School of Veterinary Medicine, she serves as the executive director of the UC Davis One Health Institute (OHI). Dr. Mazet specializes in emerging infectious diseases and wildlife epidemiology, and as director of OHI, focuses on global health problem solving. In her role at UC Davis, she assists government agencies and the public with emerging health challenges, and is active in international One Health research programs such as tuberculosis in Africa, novel pathogen detection in less

developed countries, and pathogen pollution of California coastal waters. Dr. Mazet founded California's Oiled Wildlife Care Network, the premier model wildlife emergency management system worldwide, and remains a consulting expert on wildlife emergency preparedness and response, serving on multiple government and nongovernmental organization (NGO) advisory panels. Dr. Mazet is the principal investigator and global director of the novel viral emergence early warning project, PREDICT, that has been developed with the U.S. Agency for International Development's Emerging Pandemic Threats Program. She leads a network of global NGOs and governmental agencies to build capacity within the PREDICT-engaged countries to develop surveillance systems and complete the necessary research to halt the next pandemic, like influenza, severe acute respiratory syndrome, Ebola, and HIV that have preceded the program.

Amanda McClelland, M.P.H.T.M., B.R.N., is senior vice president of the Resolve to Save Lives initiative from Vital Strategies with more than 14 years of experience in global health, working in response to natural disasters, conflict, and public health emergencies. With a focus on local prevention and response, Ms. McClelland has spent much of the past decade working with frontline health workers and communities on prevention, early detection, and response to health crises. As part of Resolve to Save Lives' mission, she supports the building of local capacity at the country level to implement effective International Health Regulations and improve country capacity to prevent, find, and stop outbreaks.

Suzet M. McKinney, Dr.P.H., M.P.H., currently serves as chief executive officer/executive director of the Illinois Medical District (IMD). IMD, a 24/7/365 environment that includes 560 acres of medical research facilities, labs, a biotech business incubator, universities, raw land development areas, 4 hospitals, and more than 40 health care–related facilities, is one of the largest urban medical districts in the United States. Dr. McKinney is the former deputy commissioner of the Bureau of Public Health Preparedness and Emergency Response at the Chicago Department of Public Health (CDPH), where she oversaw the emergency preparedness efforts for the department and coordinated those efforts within the larger spectrum of the City of Chicago's public safety activities, in addition to overseeing the department's Division of Women and Children's Health. Dr. McKinney previously served as senior advisor for public health and preparedness at the Tauri Group, where she provided strategic and analytical consulting services to the U.S. Department of Homeland Security (DHS), BioWatch Program. Her work at DHS included providing creative, responsive, and operationally based problem solving for public health, emergency management, and homeland security issues, specifically chemical and biological early detection systems

and the implementation of those systems at the state and local levels. Dr. McKinney serves on numerous committees and advisory boards. Current board memberships include the board of directors for Susan G. Komen Chicago, Thresholds (mental health), and the African-American Legacy of the Chicago Community Trust. Dr. McKinney is co-chair of the National Academies of Sciences, Engineering, and Medicine's Forum on Medical and Public Health Preparedness for Disasters and Emergencies and is a member of the Standing Committee on Health Threats Resilience.

Karen Midthun, M.D., currently serve as a senior advisor on regulatory issues to the Center for Vaccine Innovation and Access at PATH. Before joining PATH, she spent 23 years at the U.S. Food and Drug Administration, with positions including director, Center for Biologics Evaluation and Research (CBER) (2009–2016); deputy director, CBER (2003–2009); and director, Office of Vaccines Research and Review (2000–2003). Dr. Midthun also held an academic appointment at the Johns Hopkins Bloomberg School of Public Health (1987–1993), where she was an investigator of vaccine clinical trials. She received her medical degree from George Washington University and trained in internal medicine and infectious diseases at Johns Hopkins University and the National Institute of Allergy and Infectious Diseases.

Arnold S. Monto, M.D., is the Thomas Francis, Jr., Collegiate Professor of Public Health and professor of epidemiology at the University of Michigan School of Public Health in Ann Arbor. The major focus of his work has been the epidemiology, prevention, and treatment of acute infections in the individual and the community. Respiratory infections, particularly influenza, have been a major interest to Dr. Monto, with special reference to the evaluation of vaccines in various populations and the assessment of the value of antivirals. He has worked on these issues in tropical and temperate regions. He led the studies of respiratory infection in Tecumseh, Michigan, a landmark study of infection in the community. He has studied various approaches to influenza vaccine use, particularly to control transmission of the virus in the community. Dr. Monto is involved in assessing the efficacy of various types of influenza vaccine in prophylaxis and antivirals in prophylaxis and therapy of influenza, including implications of resistance. He now heads an observational study of effectiveness of influenza vaccines in various settings, including households. His recent activities have included evaluation of face masks and hand hygiene in the control of influenza transmission and determination of efficacy of the traditional inactivated and live attenuated influenza vaccines. Dr. Monto has been a member of the National Allergy and Infectious Diseases Advisory Council of the U.S. National Institutes of Health and is currently a member of the Vaccine and

Related Biological Products Advisory Committee of the U.S. Department of Agriculture. He was past president of the American Epidemiological Society, the 2009 recipient of the Alexander Fleming Award of the Infectious Diseases Society of America for lifetime achievement, and the 2012 recipient of the Charles Merieux Award of the National Foundation for Infectious Diseases. He was a member of the emergency committee making recommendations to the World Health Organization during the most recent influenza pandemic.

Suerie Moon, Ph.D., M.P.A., is director of research at the Global Health Centre, The Graduate Institute of International and Development Studies, Geneva, and adjunct lecturer on global health at the Harvard T.H. Chan School of Public Health. She has served on a number of advisory bodies, including most recently the World Health Organization Fair Pricing Forum Advisory Group, Expert Advisory Group to the United Nations Secretary-General's High-Level Panel on Access to Medicines, and Proposal Review Committee of UNITAID. Prior to joining The Graduate Institute, she was study director of the Harvard-London School of Hygiene & Tropical Medicine Independent Panel on the Global Response to Ebola, and co-founded and led the Forum on Global Governance for Health, a focal point at Harvard University for research, debate, and strategic convening on issues at the intersection of global governance and health. Her research and teaching focus on global governance, the political economy of global health (focusing on innovation and access to medicines; outbreak preparedness and response; trade, investment, and intellectual property rules; and development assistance for health), the evolution of international regimes, and innovative policies for addressing global problems. She received a B.A. from Yale University, an M.P.A. from Princeton University, and a Ph.D. from the Harvard Kennedy School of Government.

Kumanan Rasanathan, M.B.Ch.B., M.P.H., is a public health physician with 20 years of experience in health and related sectors, and currently works as coordinator, health systems, at the World Health Organization (WHO) in Cambodia, where he leads a team working on health systems and services, antimicrobial resistance, and maternal and child health, with the Royal Government of Cambodia. He was previously chief, Implementation Research Unit and Delivery Science Unit and senior adviser health for the United Nations Children's Fund in New York, working on implementation research focused on improving child service delivery, universal health coverage, district health systems strengthening, health systems resilience post-Ebola, integrated community case management, the Sustainable Development Goals agenda, and multisectoral approaches to child health. Prior to this, Dr. Rasanathan worked for WHO in Geneva on primary health

care and the social determinants of health, and in a number of different countries as a clinician, researcher, policy maker, program manager, and advocate. He started his public health career running Phase I and II vaccine clinical trials leading to the licensure and rollout of meningococcal B vaccine in New Zealand.

Peter A. Sands, M.P.A., is the executive director of The Global Fund to Fight AIDS, Tuberculosis and Malaria. Since June 2015, Mr. Sands has been a research fellow at Harvard University, dividing his time between the Mossavar-Rahmani Center for Business and Government at Harvard Kennedy School and the Harvard Global Health Institute, part of the Harvard T.H. Chan School of Public Health, and working on a range of research projects in financial markets and regulation, fintech, and global health. Mr. Sands's engagement with global health issues includes: chairing the National Academy of Medicine's Commission on a Global Health Risk Framework for the Future, which in January 2016 produced the highly influential report *The Neglected Dimension of Global Security: A Framework to Counter Infectious Disease Threats*; chairing the World Bank's International Working Group on financing preparedness, which in May 2017 published *From Panic and Neglect to Investing in Health Security: Financing Preparedness at a National Level*; authoring several papers on infectious disease crises in the *New England Journal of Medicine*, *The Lancet*, and *British Medical Journal*; being the lead non-executive director between 2011 and 2017 on the Board of the United Kingdom's Department of Health, which provides oversight and policy direction to the United Kingdom's National Health Service; and being an active member on both the National Academy of Sciences' Committee on Ensuring Access to Affordable Drugs and the Forum on Microbial Threats. Mr. Sands is a board member or advisor to several startups in the fintech and meditech arenas, such as Noble Markets (United States) and Cera (United Kingdom). He was group chief executive of Standard Chartered PLC from November 2006 to June 2015. He joined the Board of Standard Chartered PLC as group finance director in May 2002, responsible for finance, strategy, risk and technology, and operations. Prior to this, Mr. Sands was a senior partner at worldwide consultants McKinsey & Co. Before joining McKinsey, he worked for the United Kingdom's Foreign and Commonwealth Office. He has served on various boards and commissions, including as a director of the World Economic Forum and co-chairman of Davos, governor of the United Kingdom's National Institute for Economic and Social Research, member of the International Advisory Board of the Monetary Authority of Singapore, member of the Browne Commission on Higher Education Funding in the United Kingdom, member of the China People's Association for Friendship with Foreign People's Global CEO Council, co-chair of

the UK-India CEO Forum, board director of the Institute of International Finance, chairman of the International Monetary Conference, member of the International Advisory Board of Lingnan University, China, and trustee of the Camden Roundhouse, London. Mr. Sands graduated from Brasenose College, Oxford University, with a first-class degree in politics, philosophy, and economics. He also received a Master in Public Administration from Harvard University, where he was a Harkness Fellow.

Steven Solomon, J.D., is principal legal officer at the World Health Organization (WHO) in Geneva, Switzerland, where he focuses on WHO governance and international health law matters. He served as the WHO legal adviser to the negotiations that led to the Pandemic Influenza Preparedness (PIP) Framework. Prior to joining WHO, Mr. Solomon served as deputy legal counselor at the United States Mission to United Nations Organizations in Geneva, negotiating a variety of human rights and humanitarian law instruments. He was an attorney with the U.S. Department of State for several years before that handling multilateral negotiations related to the control of conventional weapons as well as international humanitarian law. After law school, before joining the U.S. Department of State, Mr. Solomon was a lawyer in private practice at the Washington, DC, law firm of Williams & Connolly. He also worked on Capitol Hill. Mr. Solomon has written widely on matters pertaining to international law, including global health and humanitarian law matters.

Ciro Ugarte, M.D., served as director of norms and deputy director-general at the National Institute of Occupational Health in Peru in 1987 and 1988. He was executive director and director-general of the Office of National Defense of the Ministry of Health of Peru, from 1988 until 1999. During that period, he also held positions as: president of the Peruvian Society of Emergency Medicine, official representative of the Peruvian Government to the International Committee of the Red Cross, member of the National Committee of the Peruvian Red Cross Society, consultant of the Office of U.S. Foreign Disaster Assistance, and member of the United Nations Disaster Assessment and Coordination Team. In 1999, he coordinated the United Nations Inter-Agency Disaster Team in Honduras. In 2000, he joined Pan American Health Organization (PAHO), where he served as sub-regional advisor for South America, regional advisor, and director of the Department of Emergency Preparedness and Disaster Relief in Washington, DC. In 2016, he was appointed as director of the new PAHO department, Health Emergencies. Dr. Ugarte has extensive experience in disaster risk reduction, emergency preparedness, and disaster response. He has coordinated the implementation of public health measures and health care at national and international levels in case of earthquakes, tsunamis, volcanic eruptions,

severe floods, El Niño phenomenon, landslides, hazardous materials incidents, armed conflicts, terrorist attacks, crisis of hostages, chemical emergencies, mass gatherings, meetings of head of states, epidemics of cholera, yellow fever, dengue, malaria, hepatitis, and pandemic influenza, among others.

Makarim Wibisono, Ph.D., is the former United Nations special rapporteur on the Occupied Palestinian Territories, the president of the Economic and Social Council (ECOSOC) of the United Nations in New York in 2000, and the chairman of the United Nations Commission of Human Rights in Geneva in 2005. He was also appointed as the executive director of the ASEAN Foundation, the special advisor to the minister of health, and to the speaker of the House of Representatives of Indonesia, as well as a member of the World Health Organization Review Group. He attained his bachelor degree in international relations from the Gadjahmada University; master of arts degree from the School of Advanced International Studies at Johns Hopkins University in Washington, DC; master of arts in political economy and doctorate degree from The Ohio State University in Columbus, Ohio; and professor from Airlangga University, Surabaya. Ambassador Wibisono started his career at the Department of Foreign Affair of Indonesia in 1972 and climbed his position into becoming the director-general of Foreign Economic Relations and director-general for Asia, Pacific, and African Affairs. He was also appointed as the ambassador extraordinary and plenipotentiary, permanent representative of Indonesia to the United Nations in New York in 1997 to 2001, and ambassador extraordinary and plenipotentiary, permanent representative of Indonesia to the United Nations and other international organization in Geneva in 2004 to 2007. Ambassador Wibisono's recent activities include serving as the vice chairman of the Governing Board of the Indonesian Council of World Affairs, the former advisor of the National Commission on Human Rights, senior fellow of the Center for Strategic and International Studies, and currently as professor and lecturer at Airlangga University, the Defense University, the National Resilience Institute, and other various universities and institutions in Indonesia.

Wenqing Zhang, M.D., has headed the Global Influenza Program of the World Health Organization (WHO) in its headquarters in Geneva, Switzerland, since November 2012. In this role, Dr. Zhang provides leadership and coordinates global activities on influenza surveillance, virus monitoring, detection of emerging novel viruses, risk assessment and evidence for policies, vaccine virus, and pandemic preparedness including pandemic influenza vaccine response. From 2002 to 2012, Dr. Zhang coordinated the WHO Global Influenza Surveillance and Response System (GISRS), building

a functional global system of surveillance, preparedness, and response. In response to 2009 A (H1N1) influenza pandemic, Dr. Zhang directed the laboratory response and capacity aspects of WHO response. Before joining WHO, Dr. Zhang worked for 9 years in the Chinese Academy of Preventive Medicine, Ministry of Health on tuberculosis, schistosomiasis, and iodine deficiency disorder projects with WHO, the World Bank, the United Nations Children's Fund, and the United Nations Industrial Development Organization. Dr. Zhang has an M.D., with postgraduate training in system evaluation and epidemiology, and holds a bachelor's degree in biomedical engineering.