

Johns Hopkins Center for Health Security

# Preparedness for a High-Impact Respiratory Pathogen Pandemic

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## EXECUTIVE SUMMARY

This report examines the current state of preparedness for pandemics caused by “high-impact respiratory pathogens”—that is, pathogens with the potential for widespread transmission and high observed mortality. Were a high-impact respiratory pathogen to emerge, either naturally or as the result of accidental or deliberate release, it would likely have significant public health, economic, social, and political consequences. Novel high-impact respiratory pathogens have a combination of qualities that contribute to their potential to initiate a pandemic. The combined possibilities of short incubation periods and asymptomatic spread can result in very small windows for interrupting transmission, making such an outbreak difficult to contain. The potential for high-impact respiratory pathogens to affect many countries at once will likely require international approaches different from those that have typically occurred in geographically limited events, such as the ongoing Ebola crisis in Democratic Republic of the Congo (DRC).

Numerous high-level reviews have been commissioned in recent years to take stock of global preparedness for infectious disease outbreaks, epidemics, and pandemics. These reviews have assessed current preparedness structures and capabilities, have identified existing gaps, and have proposed recommendations for strengthening outbreak prevention, detection, and response. But preparedness for a high-impact respiratory pathogen pandemic has received little specific focus in these high-level reviews. While there has been some focus on improving international and national capacities for pandemic influenza, specifically after the 2009 H1N1 pandemic, there have been few (if any) high-level reviews or recommendations focusing on the possibility of other high-impact respiratory pathogens with pandemic potential. The lack of global attention on and consideration of this threat speaks to the urgency of addressing preparedness for epidemics and pandemics that might be caused by high-impact respiratory pathogens. While there is overlap between the systems and capabilities required to respond to any disease outbreak, a high-impact respiratory pathogen poses serious additional challenges that deserve special consideration.

In preparing this report, *Preparedness for High-Impact Respiratory Pathogen Pandemics*, we reviewed dozens of high-level reviews of global preparedness and conducted interviews with international experts in pandemic preparedness and response. The state of national and global readiness in 10 functional areas were examined: global preparedness mechanisms; multisectoral involvement and coordination; surveillance, monitoring, and assessment; health systems and clinical management; community engagement; risk communication; research and development for medical countermeasures; nonpharmaceutical interventions; accidental release and biosafety; and deliberate use and biosecurity. In our findings, we detail capabilities and gaps that would likely hamper efforts to

respond to a high-impact respiratory pathogen. The report identifies priority actions for countries, international organizations, and other stakeholders to pursue that would mitigate the public health, economic, social, and political consequences of the emergence of a high-impact respiratory pathogen. These conclusions are summarized below.

## SUMMARY OF CONCLUSIONS

### **1. Countries should build up their national core public health capacities.**

- Countries should continue to build and improve core public health capacities across the globe in accordance with International Health Regulations (IHR) core capacity obligations.
- Member states should pursue Joint External Evaluation (JEE) assessments if they have not already completed one, and they should ensure that WHO has the resources it needs to continue to play a coordinating role.
- Countries should develop, cost, finance, and implement sustainable national action plans to improve their core capacities and conduct exercises to test the extent to which capacities will function as planned during emergencies.
- The IHR core capacities are unlikely in their current formulation to adequately prepare countries and the international community for high-impact respiratory events. Therefore, evaluations of risk-specific exercises (eg, pandemic influenza) and actual events should be compared to the capacities in JEEs and national action plans and should be used to update, modify, or enhance ongoing capacity development efforts.
- Donors should work with countries to address remaining shortfalls and to incentivize additional national investments, including participation in initiatives such as the Global Health Security Agenda and the Alliance for Health Security.
- Data will be essential to motivate political leaders and measure progress. Additional sources of data should be sought by World Health Organization (WHO) and the Global Preparedness Monitoring Board (GPMB) that could provide ongoing assessment of global progress toward IHR capacity development.

### **2. National and global surveillance capacities should be improved, with a focus on helping improve the management of epidemic response.**

- Donors should work with countries to strengthen global, regional, and national surveillance capacities, which will be essential for detecting a potentially high-impact respiratory pathogen before transmission becomes widespread.
- Rapid systems of data exchange are needed to better understand and fully monitor the near-term impacts and severity of an event, such as the percentage of cases

developing severe illness. Data sharing from nontraditional sources, such as the private sector, can help to paint a fuller picture of pandemic impacts.

- Real-time decision making about the availability and mobilization of resources is needed to help control the spread and identify and monitor availability of resources that are needed (eg, medical supplies) to support the response. The development of platforms and initiatives that link applied infectious disease modelers with public health decision makers can enable a more rapid public health response.
- If a pandemic were initiated by a deliberate event, countries and the international community would need to have in place agreements about what information needs to be shared, particularly in view of security concerns that may limit the degree to which affected and nonaffected countries are willing to share information.
- New surveillance technologies are needed to increase the capacity and speed with which highly specific surveillance and diagnostic data become available. Philanthropies and other international organizations should continue to encourage the development and uptake of molecular diagnostic testing for respiratory pathogen nucleic acids—specifically, simple, point-of-care, multiplex devices; diagnostic tools such as microfluidic devices that can be used outside of traditional laboratories; and technologies that could facilitate tracking of patients on a large scale.

### **3. Frameworks for sample and benefit sharing need to be developed that apply to high-impact respiratory pathogens beyond influenza.**

- Member States and industry need to continue to uphold and monitor adherence to the Pandemic Influenza Preparedness (PIP) framework, including rapid cross-border specimen sharing and the timely delivery of benefits to developing countries for building national capacity.
- PIP framework stakeholders will need to work together to preserve and maintain the framework in view of recent advances in biotechnology. For example, physical specimens and genetic sequencing data should be shared promptly with vaccine developers. Stakeholders will also need to continue to address the public health implications of the Nagoya Protocol to the Convention on Biological Diversity (CBD).
- Difficult past experiences in transferring virus specimens for other diseases (eg, H1N1, Zika, Ebola) across borders have underscored the difficulty of negotiating bilateral material transfer agreements in the middle of a crisis. Therefore, WHO, Member States, and industry will need to engage in pre-event negotiations to facilitate the rapid sharing of samples and epidemiologic data for respiratory diseases besides pandemic influenza, as well as the subsequent distribution of benefits across the globe.



- Whether or not new noninfluenza benefit-sharing agreements are directly modeled on PIP, they will need to take into account the emergence of a broad range of respiratory pathogens with high-impact potential, be based on the principle of reciprocity and mutually reinforcing interests, and involve the participation of a wide range of partners.

#### **4. Countries and WHO need to assess and improve health systems' readiness for infectious disease emergencies.**

- Countries should assess the readiness of health facilities to effectively treat patients with transmissible diseases with high case fatalities. The central role of health facilities in mitigating or amplifying disease spread during communicable disease emergencies has not played a prominent enough role in current national or international core capacity assessment efforts, such as the JEE process.
- WHO should work with member countries to develop a corresponding assessment tool for health systems and facilities, aligned with countries' ongoing work to undergo JEEs and to advance universal health care, so that countries have a means of assessing the readiness of the broader health sector for infectious disease emergencies.
- WHO should lead an expert-informed process to develop technical guidance to inform the clinical management of patients with highly contagious respiratory diseases during a severe outbreak, to include recommendations on personal protective equipment (PPE), treatment courses, and disinfection guidelines, and allocation of scarce resources. This guidance should be salient in both high-income and low-income settings.
- Countries should work to establish mechanisms for bi-directional information exchange between frontline healthcare providers directly treating patients and experts at external networks who can provide critical subject matter expertise, guidance, and analysis of relevant information from multiple sources to devise best practices.
- An incident command/incident management system (ICS/IMS) and emergency operations centers (EOCs) that bring together public health officials and healthcare leaders should be established at local, state/provincial, and national levels to help broadly coordinate a response, rather than acting ad hoc during a crisis.
- Countries should plan for the possibility of interruptions in the availability of essential basic supplies and equipment. Health facilities need plans for continuing operations in the event that supplies are no longer available from their primary sources. Countries with sufficient resources should consider establishing stockpiles of critical or high-volume products.

## **5. Countries and international health authorities should more fully incorporate community engagement and social science in preparedness.**

- WHO should develop guidance that illustrates concrete use cases for community engagement before, during, and after a potential severe outbreak of a high-impact respiratory pathogen.
- Countries should incorporate community engagement into their national preparedness planning and mechanisms. Initial outreach and engagement with communities should occur before a disease outbreak so that strong existing relationships could be leveraged for good during response efforts.
- National and subnational authorities will need to involve local stakeholders in decision making and preparedness planning around high-impact respiratory pathogens, and countries need to develop more inclusive plans that community leaders can take ownership of. The kind of community engagement used to help prepare for smaller outbreaks or expected disease events could also be used to help plan for and consider larger ones.
- National health authorities and international organizations should develop and more fully utilize social science research capacities. Social scientists should be consulted on potential community-level chokepoints, sites for cooperation, and meaningful reframing of public health objectives in locally relevant terms and practices.

## **6. Countries and WHO should develop and exercise plans for risk communication during high-impact respiratory events.**

- International, national, and local responders should prioritize risk communication as an important response element on par with other priority public health efforts.
- WHO should establish a standing communications advisory committee to elevate the importance of timely, accurate, and effective risk communication.
- Countries need dedicated efforts to build public trust in local public health workforces and collaboration with influential partners before, during, and after crises. Public trust is an essential component of effective communication, and partnerships with well-respected community members, who are able to engage with other local residents in culturally competent ways, can also be critical for facilitating effective response activities.
- In an era of rapid exchange of information, misinformation, and disinformation, risk communication frameworks and practices should be modernized to utilize decentralized and distributive information networks, moving beyond a command and control model. The WHO and national public affairs offices need to embrace

and invest in leading technologies and strategies around communication in order to remain effective.

## **7. R&D aimed at rapid vaccine development for novel threats and distributed surge manufacturing should be a top global pandemic planning priority.**

### **Medical Countermeasures (MCM) Research and Development**

- There are a range of promising approaches to accelerate rapid vaccine development that should be concomitantly pursued and funded given the uncertainty in knowing which might bring the most important leaps forward.
- Traditional approaches of big pharma and biotech to vaccine and medicine development for infectious diseases will remain fundamentally important in the near term, though this process is expensive and time-consuming.
- Nucleic acid (RNA and DNA)-based vaccines are widely seen as highly promising and potentially rapid vaccine development pathways, though they have not yet broken through with licensed products.
- Advancements in non-nucleic acid-based platform technologies offer some hope of improving the speed with which vaccines for novel pandemic threats are developed and should be expanded.
- Contemporary advances in sequencing and structure function analysis—aided by artificial intelligence and big data analytic approaches—are yielding improvements in both speed and precision of immunologic design and should be supported.
- Similar gains are evident in the antimicrobial arena; as machine learning enters the drug discovery field, approaches to identifying appropriate targets for microbial control are shortening the times to leads and subsequent sensitivity and specificity studies.

### **Distribution and Dispensing**

- Mass vaccination strategies should be developed and put in place to increase immediate access. A standing collaboration among international organizations, national governments, and the private sector will be needed to enable and coordinate global distribution to ensure maximal effectiveness and equitable access.
- The uptake of novel, needle-free administration technologies—specifically, those that enable either simplified or, potentially, self-administration—should be a priority to improve our collective ability to administer these countermeasures in clinically relevant timeframes.

- Industry, national regulatory bodies, public health authorities, and other stakeholders should invest in and promote the use of technologies that enable a rapid, streamlined approach to the administration of MCMs.
- WHO should encourage and support the creation of a public-private partnership dedicated to planning for and executing the prioritization and distribution of MCMs in a severe outbreak.

### **Surge Manufacturing in Crisis**

- Regulatory agencies should consider regulating some platform technologies by platform, rather than by product.
- The relevant regulatory bodies, global authorization agencies, and public and private manufacturers should develop and exercise response plans.
- National regulatory agencies should establish mechanisms dedicated to decreasing timelines associated with regulatory requirements for MCMs in emergencies, while continuing to ensure safety and efficacy.
- WHO, industry, national regulatory bodies, and other stakeholders should work together to enable and radically increase MCM surge production and access globally. Localized distributed manufacturing could be one solution to this need if the technology and regulatory challenges can be addressed.
- Given the current geographic disparities in where such production and manufacturing efforts are conducted, access and benefit-sharing agreements will be needed.

### **Other Research and Development**

- During an event involving a high-impact respiratory pathogen, there thi

## **8. Frameworks and plans articulating the evidence and role for nonpharmaceutical interventions need to be established.**

- Nonpharmaceutical interventions (NPIs) have a greater likelihood of being implemented effectively if well analyzed ahead of time than if considered ad hoc during a crisis. Countries and international organizations need to better analyze the potential value and impact of NPIs; determine in which contexts, if any, a particular NPI would be effective; and conclude in which contexts they are likely do more harm than good.
- WHO and other public health authorities should have the capacity to provide risk/benefit analysis to national governments, driven by scientific evidence where it exists, *before* NPIs are initiated in a crisis.
- During an emergency, it should be expected that implementation of some NPIs, such as travel restrictions and quarantine, might be pursued for social or political purposes by political leaders, rather than pursued because of public health evidence. WHO should rapidly and clearly articulate its opposition to inappropriate NPIs, especially when they threaten public health response activities or pose increased risks to the health of the public.
- WHO and national authorities will need to provide strong evidenced-backed reasoning for the necessity of NPIs in order to effectively implement them and to communicate their role and necessity to the public, especially for NPIs such as social distancing that inherently limit civil liberties. Therefore, they should undertake directly or support research on NPIs and disseminate their findings on these analyses.

## **9. National governments should strengthen biosafety around high-impact respiratory pathogens.**

- Biosafety needs to become a national-level political priority, particularly for countries that are funding research with the potential to result in accidents with pathogens that could initiate high-impact respiratory pandemics.
- All nations should be advised to adopt national-level comprehensive biosafety norms for research involving high-impact respiratory pathogens.
- Countries that fund such research should have oversight systems in place that consider the risks and benefits of this kind of work, and they should have maximally stringent biosafety requirements for any laboratory that is allowed to pursue this type of research.
- WHO should develop stronger interest and capability in monitoring research with the potential to result in accidents involving high-impact respiratory pathogens, and it should advise member nations about the risks and benefits related to this work.

## **10. National governments need to prepare for the deliberate use of a respiratory pathogen.**

- Preparation for a deliberate event must include recognition that the deliberate release of a high-impact respiratory pathogen could substantially add to the extraordinary consequences that would follow a naturally occurring pandemic event with the same agent.
- The United Nations (UN), WHO, and the international community will need to take steps to better understand their respective roles during a deliberate event, including greater clarity on which international agency would lead the response.
- Countries should support the adoption of synthesis screening approaches intended to identify work being done on high-impact respiratory pathogens.
- National governments and WHO should plan to engage in a coordinated and collaborative response to deliberate events. For example, pre-event planning is needed among public health officials, military, law enforcement, and/or intelligence communities in order to set expectations about appropriate roles and responsibilities and best practices for data sharing.
- Continued research into the science of attribution, as well as the strengthening of surveillance systems, international collaboration, and implementation of treaty agreements, particularly the Biological Weapons Convention (BWC), are all needed for an effective response to the deliberate use of a biological weapon with a high-impact respiratory pathogen.



## RISKS POSED BY HIGH-IMPACT RESPIRATORY PATHOGENS

The far-reaching tolls of epidemics and pandemics caused by high-impact respiratory pathogens\* have been documented throughout history. Just over 100 years ago, a new influenza virus spread across the globe, sickened an estimated one third of the world's population, and killed upwards of 50 million people. The toll of this event extended well beyond its health impacts. High burdens of illness and rapid transmission led to high rates of worker absenteeism, which had effects on communities' abilities to maintain public safety and basic infrastructure.<sup>1</sup> Occurring in the midst of a world war, influenza and pneumonia killed more soldiers than did armed conflict, according to US military reports, and the need to care for the sick and the dead diverted resources from combat operations.<sup>2</sup>

Though there have been many medical advances since 1918 that would aid in a response to a high-impact respiratory pathogen event, were such an event to occur again, it would still have severe societal consequences. Today's global population is more than 4 times greater than it was 100 years ago. In 1918, shipping played an important role in spreading influenza around the world, but today's travelers can travel anywhere in the world in less than 36 hours, meaning that global spread would be likely to be far more rapid.<sup>3,4</sup> The World Bank has estimated that a severe pandemic such as the one that occurred in 1918 could cost the modern economy from 1% to 4.8% of global gross domestic product. Even if the next pandemic is not as severe as the one in 1918, it will likely have significant consequences. The World Bank estimates that "mild" and "moderate" pandemics, such as those that occurred in 1957 and 1968, could still cause more than 10 million deaths and reduce global economic activity by 0.7%.<sup>5</sup>

National and regional epidemic events, though geographically limited in scope, are capable of taking significant tolls and causing major international disruption. The Ebola epidemic in West Africa in 2014-2016 sickened more than 30,000 people and is estimated to have cost the 3 affected countries \$2.8 billion in lost GDP.<sup>6</sup> The 2003 SARS epidemic spilled over national borders to sicken more than 8,000 people in more than 20 countries and is estimated to have cost the global economy upwards of \$40 billion.<sup>7</sup> Had the virus been more easily transmissible outside of clinical environments, the public health impacts of this event would likely have been much greater.

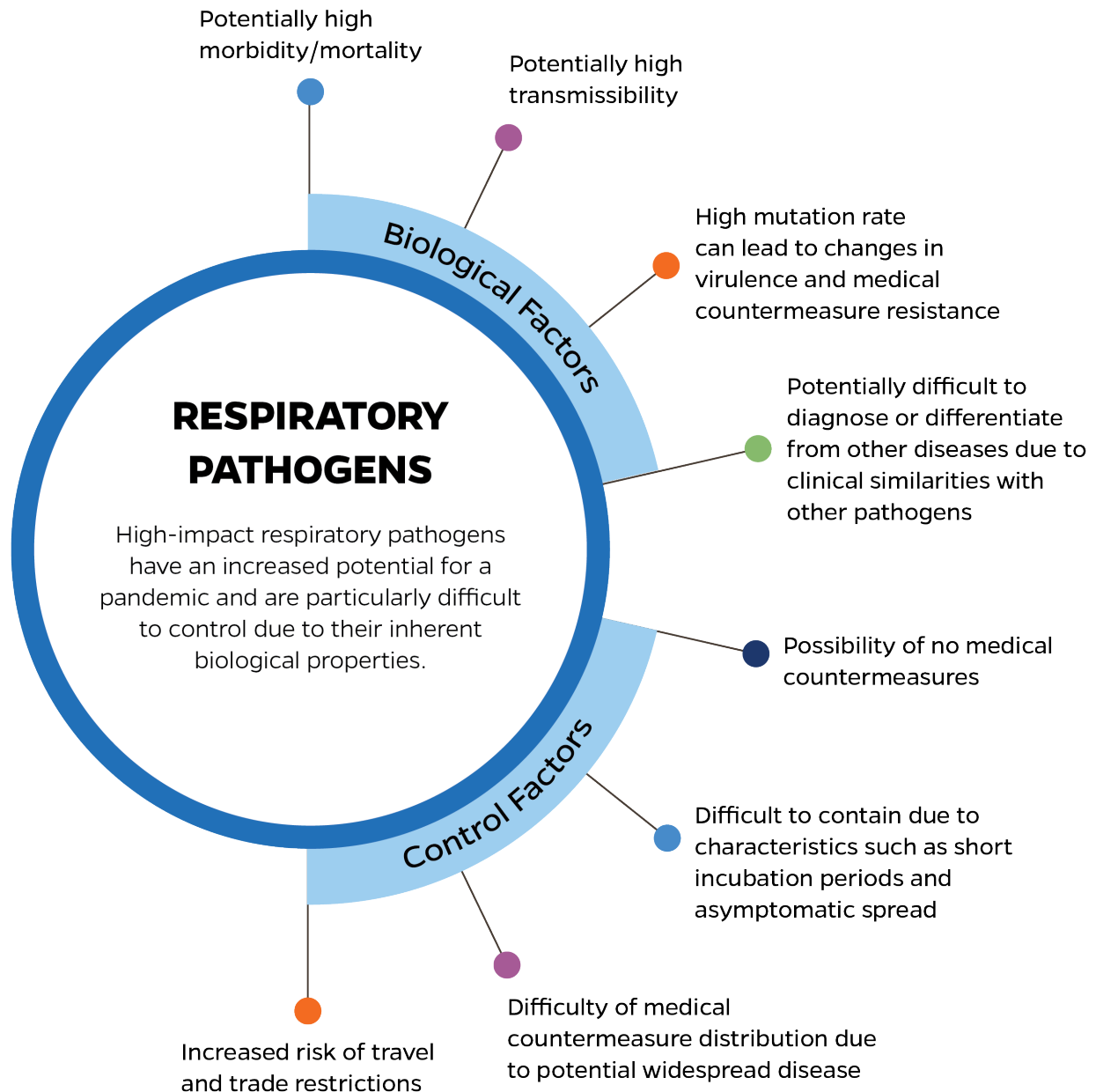
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\* For the purposes of this report, we define "high-impact respiratory pathogens" as pathogens that are readily transmissible by the respiratory route (via droplets and airborne transmission); that, due to their typically short incubation periods and high probability of person-to-person transmission, have the potential for widespread (possibly pandemic) spread; and, due to their high observed percent mortality (generally on the order of at least 1%, possibly substantially higher), may have significant public health, economic, social, and political consequences. We expect that, were such a pathogen to emerge, either naturally, or as the result of accidental or deliberate release, many countries would be affected at once, which would require different international approaches than typically occur in geographically limited events.

While the economic impact of pandemics, epidemics, and outbreaks depends, in part, on the severity of the health effects of these events, the actions that countries take in an attempt to control the spread of disease can also exacerbate its tolls. The 2009 H1N1 influenza pandemic, which was generally assessed to be mild in terms of its health effects (and therefore, for this report, would not qualify as a high-impact respiratory pathogen), offers a recent instructive example of this. In 2009, countries that were initially affected experienced drops in tourism revenues as other countries implemented bans and other restrictions on travel in response.

Additionally, some countries responded by employing trade restrictions, which did little to alter the spread of the pandemic but increased its economic costs.<sup>8,9</sup> Such actions are common during significant disease events. For example, during the West Africa Ebola outbreak, more than a third of States Parties to the International Health Regulations (IHRs) implemented restrictions on travel that exceeded recommendations made by the World Health Organization.<sup>10</sup> From these experiences, we can expect that countries would likely be inclined to take similar measures in response to a high-impact respiratory pathogen.

Figure 1: Potential Challenges Posed by High-Impact Respiratory Pathogens



The potential for an epidemic or pandemic caused by a high-impact respiratory pathogen is increasing. Data show that the frequency of outbreaks of newly emerging diseases is rising.<sup>11</sup>

Novel pathogens continue to emerge, often first in animals, then with subsequent spill-over into human populations living in close contact with animals, due to changing patterns of animal management and land use. Global conditions enable pathogens to spread widely and quickly in people. International travel, mass displacement, migration, and urbanization enable pathogens to spread in new, susceptible populations.<sup>9</sup> The rising incidence of chronic illnesses and drug-resistant infections place individuals at greater risk of infection and complications from respiratory viruses.<sup>12</sup> Declining levels of protection from vaccines due to the influence of anti-vaccination sentiments in some communities is enabling previously declining respiratory viruses to cause significant outbreaks.<sup>13</sup> Climate-related changes have altered the geography of habitats suitable for spread of certain pathogens and have changed patterns of migration, as humans move to escape consequences of extreme weather events.<sup>14</sup> All of these factors increase the chance that new high-impact respiratory pathogens will emerge and spread, raising the possibility that an epidemic or pandemic will occur.

Novel high-impact respiratory pathogens have a combination of qualities that contribute to their potential to initiate a pandemic (see [Figure 1](#)). Respiratory pathogens can be particularly difficult to contain. Their tendency to have short incubation periods and their potential for asymptomatic spread can mean very small windows are available for interrupting transmission. Individuals infected with respiratory viruses may infect many more people at a time as compared to pathogens spread by other means. These factors increase both the pandemic potential of respiratory pathogens and the likelihood that there will be serious public health, economic, and social impacts with their spread. Some viral groups have characteristics that give them a higher probability of being a future source of a novel pandemic pathogen (see [Box 1](#) and [Table 1](#)). In anticipating the implica-

and then use biological weapons that have characteristics of a novel, high-impact respiratory pathogen, the consequences could be as severe as or greater than the consequences that would follow a naturally occurring pandemic with such pathogens<sup>16</sup> (see Box 3). Similarly, a laboratory accident involving such pathogens could have a terrible impact if it led to a disease rapidly spreading in a community. Taken together, naturally occurring, accidental, or deliberate events caused by high-impact respiratory pathogens pose pandemic risks that elsewhere have been termed “global catastrophic biological risks.”<sup>17</sup>

Global efforts to prepare for significant disease outbreaks have revealed large national and international readiness gaps around detection and containment, including challenges related to tools, personnel, and surveillance systems. After-action reports conducted after recent events, such as the 2014-2016 Ebola epidemic in West Africa and the 2009 influenza H1N1 pandemic, showed systematic failures in global governance and response.<sup>18,19</sup>

High-impact respiratory pathogens—whether they are well known, novel strains of recognized diseases, or as-yet unrecognized (such as a “Disease X” noted by the World Health Organization Research and Development (R&D) Blueprint, or a Clade X, which was the subject of a recent tabletop simulation)—warrant special consideration, given the substantial global risks they pose.<sup>20,21</sup> This report examines global progress toward and gaps surrounding preparedness for high-impact respiratory pathogens, and it provides conclusions to strengthen that preparedness.

### Box 1: Viral Groups Most Likely to Be a Source of Pandemic-Initiating Pathogens

Of the multiple ways in which a microorganism can be transmitted between humans (eg, body fluids, vector-borne, fecal-oral, foodborne, respiratory), the respiratory route poses greatest concern in terms of pandemic risk. As noted in a recent report titled *Characteristics of Pandemic Pathogens*, several features of respiratory transmission are important determinants of pathogen risk.<sup>15</sup>

The primary reason respiratory transmission (which includes pathogens spread by both airborne and respiratory droplet transmission) is the transmission route posing the greatest pandemic risk is that standard public health measures may not easily interrupt transmission. By contrast, each of the other major forms of disease transmission can be interrupted with sanitation, hand-washing, or other forms of intervention. Respiratory transmission can occur with coughing or simply breathing (in aerosol transmission), making containment much more challenging.

Recent high-impact outbreaks of respiratory viruses make this case. In 2009, for example, a novel pandemic influenza virus emerged in Mexico and achieved prolific spread across the planet, causing disruption and widespread illness. Similarly, the 2003 emergence of SARS, caused by a zoonotic coronavirus, was characterized by billions of dollars of economic losses, worldwide circulation fostered by superspreading respiratory events, and severe disruptions. MERS, also caused by a coronavirus of animal origin, bears many of the hallmarks of SARS, including superspreading respiratory events, though it has thus far spread less widely than SARS. These respiratory-borne viruses are testament to the challenges of containment of respiratory pathogens.<sup>22,23</sup>

Another important aspect of pathogen transmission is the timing of transmission. While this is a factor in all modes of transmission, it takes on a heightened role in respiratory transmission because of the relative ease with which respiratory transmission takes place. If an infection is contagious in its incubation period—that is, prior to symptom onset—spread will likely have taken place before awareness of the risk of the infection. This phenomenon is exemplified by diseases like influenza, in which contagiousness precedes symptoms.<sup>24</sup> Coupled with contagiousness during incubation period is the ability of a microbe to cause a spectrum of illness or have a time course of severity. If a pathogen is capable of causing asymptomatic or mildly symptomatic infections that either do not or only minimally interrupt activities of daily living, many individuals may be exposed. Viruses that cause the common cold, including coronaviruses, have this attribute and are important factors in the widespread nature of the common cold. This mild illness phenotype was also seen in 2 US importations of MERS. Modeling studies have identified this factor as being decisive in outbreak control.<sup>25</sup>

Many respiratory viruses possess RNA (as opposed to DNA) genomes, which may also confer special status on this group in terms of pandemic potential. An RNA genome is often characterized by high degrees of mutability, some of which may confer vaccine escape, antiviral resistance, heightened viral shedding, or increased pathogenicity. RNA viruses also tend to replicate in the cytoplasm of host cells and not the nucleus, a feature that may tie them less to one species and allow more promiscuity of host type (exceptions exist).<sup>26</sup>

Salient features of several classes of respiratory-borne viruses are summarized in the table below. While only a subset of these have caused documented pandemics, these groups all have viruses that have characteristics consistent with increased pandemic potential. Other than influenza and enterovirus, no systematic surveillance occurs for these viruses and there are no vaccines or unequivocally effective antivirals.<sup>15</sup>

**Table 1: Viral Groups with Characteristics Most Consistent with Pandemic Pathogens**

Viral Group	Important Members	Special Features
Orthomyxovirus	Influenza	Contagious during incubation period, demonstrated pandemic capacity, airborne and droplet transmission, high mutability
Respirovirus*	Human parainfluenza viruses 1 and 3	Highly contagious, spectrum of illness, capacity to cause severe infection, no countermeasures
Henipavirus*	Nipah	Zoonotic origin, limited human-to-human spread, very high mortality, no countermeasures
Rubulavirus*	Human parainfluenza viruses 2 and 4	Highly contagious, spectrum of illness, capacity to cause severe infection
Coronavirus	MERS, SARS	Zoonotic origin, human-to-human spread, high mortality, no countermeasures
Enterovirus**	EV-D68, EV-D71	Highly contagious, spectrum of illness, capacity to cause severe infection, no countermeasures
Rhinovirus**	Human rhinovirus C	Highly contagious, ubiquitous, spectrum of illness, capacity to cause severe infection, no countermeasures

\*These 3 are paramyxovirus genera.

\*\*These 2 are picornavirus genera.



## Box 2: Measles Is Bad Enough. What if It Were Worse?

Measles is a highly contagious viral disease that causes serious and sometimes fatal clinical syndromes in children and adults worldwide.<sup>27</sup> Measles is characterized by high fever, runny nose, cough, and a red blotchy rash, among other symptoms.<sup>28</sup> It is spread via droplets, either airborne or through direct contact, when an infected person coughs or sneezes.<sup>29</sup> Deaths due to measles usually occur following complications such as pneumonia or acute encephalitis.<sup>30</sup> These complications are seen more often in children under 5, pregnant women, and people who are immunocompromised.<sup>31</sup> The measles vaccine is safe for most people over 12 months of age and is 93% effective after 1 dose; it is 97% after 2 doses.<sup>27</sup>

With easily identifiable clinical symptoms, lack of carrier state, lack of an animal reservoir, a safe vaccine, and relatively low mortality, measles would be expected to be easily controlled compared to other viruses that commonly cause disease in humans.<sup>30</sup> But while measles was declared eliminated from the United States in 2000, it has since seen a resurgence due to a combination of factors, including the lack of access to care and the rise of vaccine hesitancy.<sup>32,33</sup> Measles has experienced a global resurgence as well, with a tripling of reported cases worldwide in the first quarter of 2019 compared to last year.<sup>34</sup> Its persistence can be explained in part by its high transmissibility. Each person infected with measles is capable of infecting between 12 and 18 additional people.<sup>27</sup> Comparatively, each Ebola case in the 2014 outbreak was only capable of infecting 1.5 to 2.5 additional persons.<sup>35</sup>

With proper medical care and vaccination coverage, mortality from measles is approximately 1% in developed countries, but it can range from 10% to 30% in countries lacking sufficient healthcare infrastructure or where access to health services is limited.<sup>28</sup> These mortality rates are often higher in vulnerable populations, including children, the elderly, and nonvaccinated or immunocompromised individuals.<sup>31</sup>

Measles infection rates and mortality rates were much higher before the introduction of the measles vaccine in 1963, with more than 130 million cases and 7 million deaths annually worldwide.<sup>31</sup> Despite the effectiveness of the measles vaccine, the world continues to experience a global resurgence of cases. It is also important to remember that there is a certain level of baseline immunity to measles, particularly among older generations for whom measles was a practically ubiquitous childhood disease.<sup>28</sup>

What if a disease as transmissible as measles had a case fatality as high as SARS or Ebola, for which there was no effective vaccine and no population level immunity? Analyzing what it would take to control this kind of event helps to crystallize what kind of national and global systems would need to be in place to respond novel, high-impact respiratory pathogens.

## Box 3: Anticipating Challenges During the Deliberate Release of a High-Impact Respiratory Pathogen

Previous epidemics and pandemics caused by high-impact respiratory pathogens, such as the 1918 influenza, showed how such pathogens can lead to widespread health, social, and economic damages.<sup>36</sup> Now, with advances in biology, a high-impact respiratory pathogen could be engineered to create transmissibility and lethality. The deliberate release of such a pathogen could substantially add to the already extraordinary consequences that would follow a naturally occurring pandemic event.

A key difference between deliberate release scenarios and those in which a high-impact respiratory pathogen emerges and spreads via natural mechanisms would be the possibility for there to be multiple attacks, or “reload,” in a deliberate event. A sophisticated assailant could use a bioweapon to target areas of public health vulnerability or to deliberately inflict harm on the population or particular segments of it. The ability to effectively respond to such a deliberate event would depend, in part, on an understanding of the risk of subsequent attacks. Activities in the nonhealth domain, such as attribution and interdiction, would be critical capabilities alongside medical and public health response. Currently, there is no clarity on which agency would lead the response to a deliberate event and what responsibilities this would entail (ie, operating the public health response or the investigation and attribution).<sup>37</sup>

Severe epidemics and pandemics have demonstrated how contagious disease emergencies can exacerbate societal divisions, by fomenting social and political tensions and generating stigma against vulnerable groups who may be blamed.<sup>38</sup> The potential for such negative societal consequences could be even worse in a deliberate event. Groups who are perceived as aligned with the perpetrator of an attack may experience backlash.<sup>39</sup> Public fear and uncertainty could be high in the aftermath of a deliberate event, requiring highly effective risk communication and public outreach. Geopolitical ramifications should be b b. ■ bac(3) ■ ar anA

## WHAT PREVIOUS REVIEWS TELL US ABOUT PREPAREDNESS FOR HIGH-IMPACT RESPIRATORY PATHOGENS

Numerous high-level reviews have been commissioned in recent years to take stock of global preparedness. These reviews—whether comprising a panel of subject matter experts, a written report, or both—have sought to assess current preparedness structures and capabilities, identify existing gaps, and propose recommendations for strengthening outbreak prevention, detection, and response. Assessments from the United Nations, the World Health Organization, the World Bank, the World Economic Forum, the US National Academies of Science and Medicine, nonprofit organizations, and academic institutions have all contributed valuable analyses and recommendations on this topic.

Many of these initiatives\* were commissioned following the 2014-2016 Ebola outbreak in West Africa and reflect on the challenges associated with that response.<sup>42-45</sup> While some recommendations from these Ebola-action reviews are generalizable to other epidemic and pandemic events (eg, strengthening IHR implementation), others focus on identifying and recommending improvements needed to prepare for an outbreak of Ebola virus disease or other hemorrhagic fever, and, as such, their findings are not necessarily applicable to high-impact respiratory pathogens.<sup>7,46-51</sup> Some reviews provide recommendations that are intended to be generalizable for any disease outbreak, with the goal of improving overall international and national preparedness capabilities. For example, the National Academy of Medicine report provided recommendations to the World Health Organization, the World Bank, the International Monetary Fund, and national governments to strengthen public health preparedness, improve existing global systems for outbreak response, and increase research and development efforts.<sup>46</sup> A review by the National Academy of Science calls for initiatives such as national governments building information-sharing mechanisms into their institutions, growing the role of nontraditional response actors such as philanthropists, and increasing research and development efforts, particularly with at-home diagnostics.<sup>52</sup>

However, while there is overlap between the systems and capabilities required to respond to any disease outbreak, a high-impact respiratory pathogen poses additional challenges

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\*Among the reports we considered, those specific to the West Africa Ebola outbreak include the Harvard-LSJTM Independent Panel on the Global Response to Ebola, the European Parliament Report on the Ebola Crisis, the 2015 Ebola Interim Assessment Panel, and the IHR Review Committee on Ebola. Other reports that were commissioned in light of the Ebola crisis and focus on recommendations to improve general preparedness systems include the UN Panel on Protecting Humanity of Future Health Crises; the Global Health Crisis Task Force; the World Economic Forum report, *Managing the Risk and Impact of Future Epidemics: Options for Public-Private Cooperation*; the International Vaccines Task Force report, *Money & Microbes: Strengthening Clinical Research Capacity to Prevent Epidemics*; the National Academy of Medicine Report, *The Neglected Dimension of Global Security*; the International Working Group on Financing Preparedness report, *From Panic and Neglect to Investing in Health Security: Financing Pandemic Preparedness at a National Level*; and the reports of the Independent Oversight and Advisory Committee for the WHO Health Emergencies Programme.

that deserve special consideration. A small number of high-level reviews do specifically examine global preparedness for a major outbreak of pandemic influenza, such as the report of the Committee on the Functioning of the International Health Regulations in relation to the 2009 H1N1 pandemic, known as the Fineberg Report. Convened following the global transmission in 2009 of the H1N1 virus, the Fineberg Report made several high-level recommendations for improving the IHR and public health emergency response in the context of pandemic influenza. The chief recommendations included: faster implementation of IHR core capacity requirements, the creation of a global public health workforce, building the evidence base for decisions on international trade and travel restrictions, making the IHR Emergency Committee declaration process more transparent, developing uniform and agreed-upon measures to assess the severity of pandemic and seasonal influenza strains, and establishing advance agreements with manufacturers for vaccine distribution.<sup>19</sup>

Of note, several of these recommendations were later adopted, including the committee's calls for agreements on influenza virus sample sharing and access to benefits, which culminated in the Pandemic Influenza Preparedness (PIP) Framework.<sup>53</sup> Another framework, the WHO Global Influenza Strategy for 2019-2030, also followed reports recommending the establishment of robust international and national preparedness capacities for seasonal and pandemic influenza; development of vaccines, antivirals, and treatments; and implementation of measures to increase country prevention, preparedness, and response capacities.<sup>54</sup>

Other high-level reviews with a specific focus on preparedness for influenza outbreaks include reviews of the PIP Framework and accompanying processes, such as the Global Action Plan for Influenza Vaccines, the WHO Global Influenza Surveillance and Response System (GISRS), and the WHO Pandemic Influenza Vaccine Deployment Initiative. Numerous recommendations have been made for improving both the PIP Framework and its implementation, including the possibility of adding other diseases (such as animal or seasonal influenza) into the framework; implementation of the Nagoya Protocol to the Convention on Biological Diversity, which could influence influenza virus sample sharing and the equitable distribution of and access to vaccines and other benefits; and ongoing participation of the pharmaceutical sector and other private sector manufacturers in the legal process. It is important to note, however, that the PIP Framework does not apply to respiratory pathogens other than pandemic influenza.<sup>45,53,55</sup>

It should be noted that the 2009 H1N1 pandemic was relatively mild by the standards of other strains of pandemic influenza, such as the 1918 H1N1 pandemic. Thus, its applicability may have limits in the context of a more virulent outbreak of a respiratory pathogen. The Fineberg Report paved the way for subsequent high-level reviews of the global health

architecture, especially following the 2014-2016 Ebola epidemic. Many of these high-level assessments have also emphasized the challenges of IHR core capacity implementation and WHO operational response capacity.<sup>18,19,44</sup>

The IHR is the legal framework governing global disease detection and response, including novel strains of pandemic influenza.<sup>56</sup> A consistent strong theme among high-level assessments is the lack of compliance among countries in fulfilling the IHR core capacity requirements. Numerous reviews show that there is wide agreement that IHR implementation for national health systems should be strengthened, including a need for enhanced monitoring and evaluation of core capacity requirements, backed by appropriate financial and technical support and other incentives for country implementation.<sup>18,19,45</sup>

The leadership role and operational capabilities of WHO, which would be expected to lead in the event of a high-impact respiratory disease outbreak, have been widely examined and documented, specifically through the UN Panel on Protecting Humanity from Future Health Crises and the subsequent UN Global Health Crises Task Force.<sup>47,48</sup> While most high-level reviews have reaffirmed the central role of WHO in outbreak response, they have also called for wide-ranging reforms, which culminated in the establishment of the WHO Health Emergencies Programme. Monitoring of WHO's new Health Emergencies Programme and its operational, leadership, and management processes is done through reports of the Independent Oversight and Advisory Committee for the WHO Health Emergencies Programme. Recurring recommendations for WHO from these reports include strengthening emergency response leadership and operations; clarifying public health emergency procedures and accountability; increasing mobilization of financial support for health systems programming; increasing support for country research, development, and manufacturing capacities for medical countermeasures; and enhancing coordination with national governments, the United Nations system, and development and humanitarian actors.<sup>49</sup>

The importance of community engagement and social mobilization has emerged as a key theme among recent assessments. A 2019 report commissioned by the Wellcome Trust and UK Department for International Development (DFID) advocate for “people-centered” approaches to epidemic preparedness and response. The report recommended “making social science a permanent core part of the preparedness and response architecture,” including developing social science capacity in organizations such as WHO and the UN, as well as integrating social science with the Joint External Evaluation (JEE).<sup>57</sup> A 2019 Center for Global Development after-action review of the 2014 Ebola epidemic observed the central role of behavior and community-driven methods in scaling up the response. Especially during a global event with millions of cases, during which traditional control strategies may be infeasible or unavailable, the report called for limiting transmission via

“a strategic shift toward behavioral interventions,” including equipping communities with the basic knowledge and tools needed to protect themselves.<sup>58</sup>

Some of the high-level analyses have argued that community engagement is highly relevant when considering public reactions (positive and negative) to outbreak responses, linking strong equitable health systems to preexisting constructive relationships with communities, and framing risk communication as a means to apply nonpharmaceutical interventions broadly and successfully. Reviews examining pandemic influenza vaccine focus principally on technical or operational challenges for research, development, production, and administration, rather than ultimate population uptake—a social challenge. Still other disease outbreak and health security frameworks and analyses do not address community engagement at all, or they treat it as an unelaborated aspect of risk communication.<sup>19,49,55</sup>

In addition, multiple reports\* have recognized that a response to a severe outbreak will increasingly need to incorporate actors from all sectors, including the private and business sectors. Recommendations on this issue consist of engaging with private stakeholders, incorporating private-sector actors into national strategies and preparedness planning, strengthening outbreak response capacity, and strengthening surveillance and data systems.



mendations related to strengthening and increasing preparedness systems and structures generally, or specifically related to other forms of outbreak threat. While there has been some focus on improving international and national capacity for pandemic influenza—specifically after the 2009 H1N1 pandemic and subsequent Fineberg Report—there have been few (if any) high-level reviews or recommendations focusing on the possibility of other high-impact respiratory pathogens with pandemic potential.<sup>19,60,61</sup> The lack of global attention to and consideration of this threat illustrates the vital need to address preparedness for epidemics and pandemics that might be caused by high-impact respiratory pathogens.

# HOW CAN THE WORLD BETTER PREPARE FOR OUTBREAKS CAUSED BY HIGH-IMPACT RESPIRATORY PATHOGENS?

## Global Preparedness Mechanisms

Global preparedness mechanisms, which encompass international treaties, frameworks, and agreements, articulate the international roles and national capacities required to prevent, detect, and respond to a high-impact respiratory pathogen event. Published guidance documents, standard operating procedures, and frameworks denote international outbreak emergency response capacities and processes, as well as considerations for data sharing, travel and trade restrictions, and other aspects of the international response.

As many of these international frameworks have been conceived only within the past 20 years, they remain untested during a high-impact respiratory pathogen event that causes serious illness or death in tens or hundreds of millions of people or more. Though not an example of a high-impact respiratory pathogen as defined in this report due to its lower mortality, the emergence and global spread of a novel influenza A H1N1 virus in 2009 provided an opportunity to test modern preparedness mechanisms. The ultimate health impacts of the 2009 influenza pandemic may have been lower than initially feared; however, international conflicts arose about the development and sharing of vaccines and other medical countermeasures and what actions should be taken to limit transmission.<sup>19,45</sup>

It remains to be seen the extent to which the global preparedness system will be prepared to respond to an epidemic or pandemic event caused by a high-impact respiratory pathogen. But as observed in the 2009 pandemic, individual country needs might quickly outstrip international resources and capacities, and national interests might overtake the imperative to adhere to international agreements on sample sharing, vaccine access, and emergency medical assistance.<sup>60</sup> During a high-impact scenario, the limitations of current international frameworks would come into immediate focus.

## The International Health Regulations

The International Health Regulations (2005), an international treaty that outlines WHO's and Member States' responsibilities in disease preparedness and response efforts, represents an important and useful framework for building consensus and aligning global health stakeholders on questions of disease prevention, detection, and response. The revision of the IHR in 2005 can be largely attributed to the emergence and international spread of SARS in 2003. Though the initial call to revise the IHR came during the 1998 World Health Assembly and more there had been an international push to modernize

the IHRs for many years, SARS highlighted critical gaps in the authority and scope of the IHR itself, the obligations of WHO and other international bodies, and the duties of countries, specifically their national reporting commitments. The revised IHR requires States Parties to develop core public health capacities to prevent, detect, prepare for, and respond to any disease outbreaks. Unlike its predecessor, the revised IHR includes a focus on novel pathogens that have the potential to spread beyond borders, threaten other countries, and may be considered as a potential Public Health Emergency of International Concern (PHEIC).<sup>56,62</sup>

The capacities that have been identified as core to the IHR are not only useful for the detection of and response to rare events, but, rather, they have day-to-day benefits in helping to identify, measure, and respond to routine health events. For example, a robust national process and a system to enable the collection, analysis, and dissemination of surveillance data is an essential tool for identifying and understanding patterns and drivers behind a wide range of health threats. Similarly, all countries need to be able to communicate with their populaces about health issues and protective actions that they can take. The processes and systems used to conduct risk communication and national surveillance can be multipurpose, serving everyday health priorities, but then tapped, and modified or expanded, if necessary, during emergencies.<sup>56</sup>

Arguably, the IHR's greatest value lies in early efforts of detection and control, before a respiratory pathogen becomes widespread. The IHR requires countries to develop the capacities to detect and report potential PHEICs, with the goal of providing early warning of events that could spread beyond borders and threaten other countries.<sup>63</sup> Past detection of significant zoonotic events, such as Middle East Respiratory Syndrome (MERS) and H7N9, have occurred in a manner that was generally in accordance with IHR protocols, and many countries have adhered to the IHR through transparency in their reporting to WHO. If surveillance and reporting systems can quickly detect and notify WHO of a novel respiratory pathogen that has acquired human-to-human transmissibility, global decision makers may be able to act to limit the spread of the disease by adopting evidence-based nonpharmaceutical interventions. This could, in turn, buy time to mobilize a research agenda to better understand the nature of the threat, collect and share samples, and develop medical countermeasures.

However, the IHR faces challenges in its implementation and content. There is a large disparity in countries' efforts to strengthen their core capacities to prepare for, detect, and respond to potential pandemics. There is a lack of legal provisions to penalize countries for not conforming to WHO recommended measures during emergencies on travel and trade restrictions, and there are concerns related to the criteria for PHEIC declarations.<sup>56,64</sup> The influence of IHR provisions on travel and trade and on a PHEIC declaration

during a high-impact respiratory pathogen event would be more limited than in a geographically circumscribed event such as Ebola, since disease would spread quickly across the world.

### **Joint External Evaluation**

The IHR requires signatories to develop core public health capacities to prevent, detect, and respond to any disease outbreaks. The Joint External Evaluation (JEE) process was developed as a voluntary, multisectoral program to assess national-level IHR implementation and identify critical gaps and challenges in national preparedness mechanisms.<sup>65</sup> To date, more than 85 countries have voluntarily undergone a JEE and have published the results, as determined by the number of available JEE mission reports.<sup>66</sup>

While the number of countries that have completed JEEs is encouraging, the small number of these that have followed through to address gaps in their JEEs is concerning and suggests that new strategies are needed to keep countries motivated to complete the intended full JEE process that would result in improved core capacities. Data will be essential to motivating political leaders and to measuring progress. Efforts should be made to ensure assessments of core capacity developments are conducted regularly. Currently, it is planned that the JEEs will be repeated every 5 years. However, given the pace with which JEEs are being conducted and the current level of resources allocated to the JEE process, it is unlikely that this timetable will be met.

The JEE is broadly capacity-focused so that it can address a range of threats. Because of this focus, it does not encourage or call on countries to develop plans specific to the unique needs of high-impact respiratory pathogens.<sup>65</sup> There are additional capacities that would likely be needed during a potential high-impact respiratory pandemic that are currently not captured in the JEE. These include the healthcare system's capability to cope with serious respiratory disease, the capacity to manage continuity of critical government functions despite widespread illness and absenteeism, and the capacity to rapidly acquire medical countermeasures and other equipment when other countries are concurrently seeking the same countermeasures and materials (eg, masks).

### **Deliberate Release Scenarios**

It is often said that responding to a deliberate biological event would be just like responding to a natural pandemic. While there are a number of similarities related to medical and public health response, there are also critical distinctions that need to be understood and prepared for. The deliberate release of a high-impact respiratory pathogen would complicate application of international frameworks and global decision-making and response models. The activation of national and international security and intelligence apparatuses, which would be called on to identify the source of a deliberate event

and attribute blame or responsibility, could interact with the public health response in unforeseen ways. Central involvement of the security sector, the possibility that countries may be less likely to share information during a deliberate event, and the potential for major societal fissures are just some of the elements that would complicate or interfere with current international response frameworks in ways that would make them less effective in addressing the response to a major deliberate event.<sup>67</sup>

The Biological and Toxin Weapons Convention (BWC) prohibits the development, production, stockpiling, and acquisition of biological weapons. This prohibition serves a crucial normative global role. In addition to explicitly committing countries to preventing the development and proliferation of biological weapons for both state and non-state actors, the BWC also includes provisions that promote international collaboration to support capacity building and the prevention of disease. States Parties to the BWC are obligated to provide response assistance in the event of a deliberate biological event, including for respiratory diseases with pandemic potential, but the scope of this assistance is not clarified. Beyond these goals, the BWC also serves as a forum in which countries, international organizations (eg, WHO), and civil society can engage on a range of topics relevant to the prevention, detection, and response to a range of biological threats, deliberate or otherwise. Unfortunately, the BWC remains under-resourced, particularly as it relates to coordinating response assistance in the aftermath of a deliberate event. In addition, the BWC was given neither an investigatory mandate nor enforcement provisions in the event of a deliberate event or state noncompliance.<sup>68</sup>

### **Pandemic Influenza Preparedness (PIP) Framework**

The PIP framework provides a global approach to encourage influenza virus sample sharing and to commit manufacturers to equitably providing vaccines, treatments, and diagnostics during influenza pandemics and annually contributing funds to WHO for influenza pandemic preparedness.<sup>53</sup> The PIP framework is widely considered to be a significant global achievement, but it has limits. Neither seasonal nor animal influenza are covered under the framework, limiting its applicability to pandemic influenza strains. Questions persist about which of the remaining countries<sup>\*</sup> will ratify the Nagoya Protocol to the Convention on Biological Diversity, and about the implications of this provision for viral sample sharing. Numerous barriers, ranging from intellectual property restrictions to slow inter-country coordination, limit the speed with which specimens are shared across borders. Slow or nonexistent specimen sharing affects the development, validation, and production of new medical countermeasures, as well as the continuing participation of industry and R&D stakeholders, which expect to benefit from their voluntary contributions to the framework.<sup>55</sup> According to the 2018 Annual Progress Report, only 21

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\* At the date of this publication, 120 States Parties have ratified the Protocol, including the European Union, which obligates its member countries to be subject to the Protocol's requirements.

countries have received support through the benefit-sharing mechanism of the PIP framework have written, exercised, or begun developing influenza pandemic preparedness plans.<sup>69</sup>

A related, ongoing concern among government and R&D stakeholders is that the deployment of potentially billions of vaccines (were such a stockpile of effective vaccines to be available at some time during a pandemic) to countries will be of questionable benefit if the plans, infrastructure, and distribution networks are not in place to vaccinate their populations. As such, the WHO Global Influenza Strategy promotes stronger country capacity by encouraging countries to implement tailored influenza programs, including national pandemic preparedness plans; establish infection prevention and control practices; and develop better vaccines, treatments, and diagnostics.<sup>54</sup> The Partnership for Influenza Vaccine Introduction (PIVI) provides technical assistance to middle- and low-income countries for routine seasonal influenza vaccination programs. These programs can support local vaccine markets by establishing predictable vaccine demand, while aiding countries in identifying the networks that will be needed to distribute vaccines to high-priority populations during a pandemic.<sup>70</sup> It will be important for WHO to continue to call on countries to develop pandemic influenza preparedness plans, practice sustainable seasonal influenza immunization programs, and prepare a logical system of vaccine allocation within countries and regions.

While agreements exist for influenza preparedness ([see Box 4](#)), similar international frameworks that promote preparedness measures (including virus sample sharing) more broadly for other respiratory pathogens do not exist. In the absence of a PIP-style framework for other respiratory diseases, countries seeking access to specimens must negotiate bilateral material transfer agreements with potentially dozens or more countries, a challenging and time-consuming process that is vulnerable to legal bottlenecks. It remains to be seen whether the PIP framework could emerge as an ad hoc model for access and benefit sharing during a severe respiratory epidemic or pandemic or if countries will scramble to arrange their own bilateral agreements.<sup>55</sup>



## Box 4: Pandemic Influenza: A Preparedness Model for Other Respiratory Pathogens?

While a range of high-threat respiratory diseases are known to exist, preparedness for pandemic influenza has received by far the greatest attention from international, national, and local stakeholders. For example, researchers and manufacturers possess the technical know-how and ability to develop, test, and manufacture medical countermeasures for the influenza virus, a capability that does not yet exist for coronavirus, enterovirus, and other contagious respiratory subgroups.

Preparedness for seasonal influenza, including routine surveillance, annual immunization campaigns, and specimen sharing, has contributed to a practical knowledge base and infrastructure that can be leveraged following the emergence of a strain with human pandemic potential. Fears that a pandemic strain may be overdue, especially following the devastation caused by past biological events, including the 1967-68 and 1918-19 influenza pandemics, have also focused global attention on this pathogen.

Pandemic influenza preparedness comprises a range of international and national agreements and frameworks pertaining to areas as diverse as medical countermeasures, surveillance and detection systems, cross-border specimen sharing and access to benefits, infection prevention and control practices, and networks of distribution for medical countermeasures. An interdisciplinary range of stakeholders are actively involved in these processes, including the scientific research community, academia, international agencies, national health ministries, the private sector and pharmaceutical industry, the healthcare sector, intellectual property lawyers, and others. These programs are not without their shortcomings or criticisms, and their effectiveness during a high-impact influenza pandemic remains to be seen. Nevertheless, there exists a stark disparity between the level of readiness for pandemic influenza and other potential high-impact respiratory pathogens. It is important to more fully understand the systems that have been built for influenza and consider the extent to which they would be of value for responding to other high-impact respiratory pathogens, and the extent to which they could be a model for building new systems for other respiratory threats.

**Pandemic Influenza Preparedness (PIP) framework**—PIP was adopted by the World Health Assembly in 2011 to improve sharing of influenza virus samples with human pandemic potential, as well as access to and sharing of other benefits, such as medical countermeasures and surveillance data. Other areas of the framework include laboratory and surveillance capacity building, regulatory capacity building, community engagement and risk communication, and planning for deployment. PIP was negotiated together with WHO Member States and the pharmaceutical industry, which contributes financially to framework implementation and commits to donating a percentage of vaccine product to lower-income countries.<sup>53</sup>

**National Pandemic Influenza Preparedness Plans**—At the behest of WHO, approximately 95 Member States have published national pandemic influenza preparedness plans. These plans articulate the capacities and capabilities needed to respond to an outbreak of pandemic influenza in humans, including intersectoral coordination and partnerships, risk communication, and surveillance and monitoring. However, only 17 countries have published or revised their plans since 2014, and 99 countries are still without a publicly available plan. In addition, national plans vary widely in terms of their level of quality and comprehensiveness.<sup>71</sup>

**WHO 2019-2030 Global Influenza Strategy\***—The WHO Global Influenza Strategy provides a framework for WHO, Member States, and other partners to address influenza with the aim of strengthening seasonal prevention and control and preparedness for influenza pandemics. The strategy outlines 4 overarching objectives for the next decade: promoting research and innovation to address unmet public health needs, strengthening global influenza surveillance and data utilization, expanding seasonal influenza prevention and control policies to protect vulnerable populations, and strengthening pandemic preparedness and response for a safer world.<sup>54</sup>

**Partnership for Influenza Vaccine Introduction (PIVI)**—PIVI was established based on the recognition that a strong in-country vaccine delivery system not only reduces the burden of annual seasonal influenza and other vaccine-preventable illnesses, but it can also save lives during a pandemic event. An initiative of the US CDC, PIVI partners with national health ministries to train healthcare workers in flu vaccine delivery and establish networks of vaccine distribution to ensure vaccines can be delivered to the most vulnerable populations.<sup>70</sup>

**Global Influenza Surveillance and Response System (GISRS)**—GISRS is a global monitoring, surveillance, and response system for seasonal, pandemic, and zoonotic influenza. Among its many functions, GISRS acts as a global alert for novel or emerging influenza viruses and recommends the composition of the vaccine for the upcoming influenza season. GISRS is comprised of National Influenza Centers (NICs), WHO Collaborating Centers, Essential Regulatory Laboratories, and H5 Reference Laboratories.<sup>72</sup>

\* Examples of other relevant WHO initiatives include the Global Action Plan (GAP) for Influenza Vaccines, the WHO Pandemic Influenza Vaccine Deployment Initiative, the WHO Initiative for Vaccine Research, the WHO National Immunization Technology Advisor Group (NITAG), and other WHO specialized advisory committees.

## Emergency Response Mechanisms

With the establishment of the WHO Health Emergencies Programme following the Ebola epidemic in West Africa, the international response system received an overhaul in the way it responds to disease outbreaks. WHO now provides operational capabilities in addition to its traditional expert technical and normative roles. Through the Health Emergencies Programme, WHO was clearly defined as the coordination and technical lead for any international response to health crises, including managing collaborations with any health partners in the field. Also, with the establishment of the Health Emergencies Programme, a new financing mechanism, the Contingency Fund for Emergencies, was developed to facilitate cash flow and provide the initial funds necessary to mount a response to health emergencies.<sup>73</sup>

In this new approach, WHO leads the international response to major internationally important outbreaks, and it would be the lead agency for the health response to any high-impact respiratory pathogen event. Large-scale disease outbreak response efforts require multisectoral collaboration, and so WHO closely coordinates with the broader UN humanitarian system in these responses. Mechanisms to alert relevant authorities—including the Inter-Agency Standing Committee\*, UN country offices, non-governmental organization (NGOs), and private-sector partners—are in place.<sup>73,74</sup> This kind of coordination would be expected and critical in the response to a high-impact respiratory pandemic.

While many processes to initiate and scale up response efforts would apply across all diseases, additional considerations unique to high-impact respiratory pathogens may not be adequately addressed in these response guidelines, including the WHO's Emergency Response Framework.<sup>74</sup> During such a pandemic scenario, regional, national, and local needs could severely outpace existing international capacities and resources, and countries could not expect emergency medical response teams to assist them. Donated medical countermeasures, personal protective equipment, and other technical assistance

\* The Inter-Agency Standing Committee is the UN's primary mechanism for coordination of any (UN or otherwise) agencies in a humanitarian assistance. The Inter-Agency Standing Committee is composed of the heads of UN and non-UN organizations that are involved in humanitarian response to emergencies, including health crises (source: <https://inter-agencystandingcommittee.org/>).

that they might receive in geographically limited outbreaks might not be available. During a large-scale respiratory outbreak, widespread humanitarian needs might arise, such as food insecurity or poverty associated with job losses. Concerns have been raised regarding the existing mechanisms intended to deal with these issues, citing inadequate coordination and planning among WHO and the broader humanitarian system, including various UN agencies and the UN Secretary-General.<sup>42,52</sup> In a large disease outbreak scenario, there may also be decreased international interest in supporting other countries' responses as nations deal with the health crisis in their own borders ([see Box 5](#)).

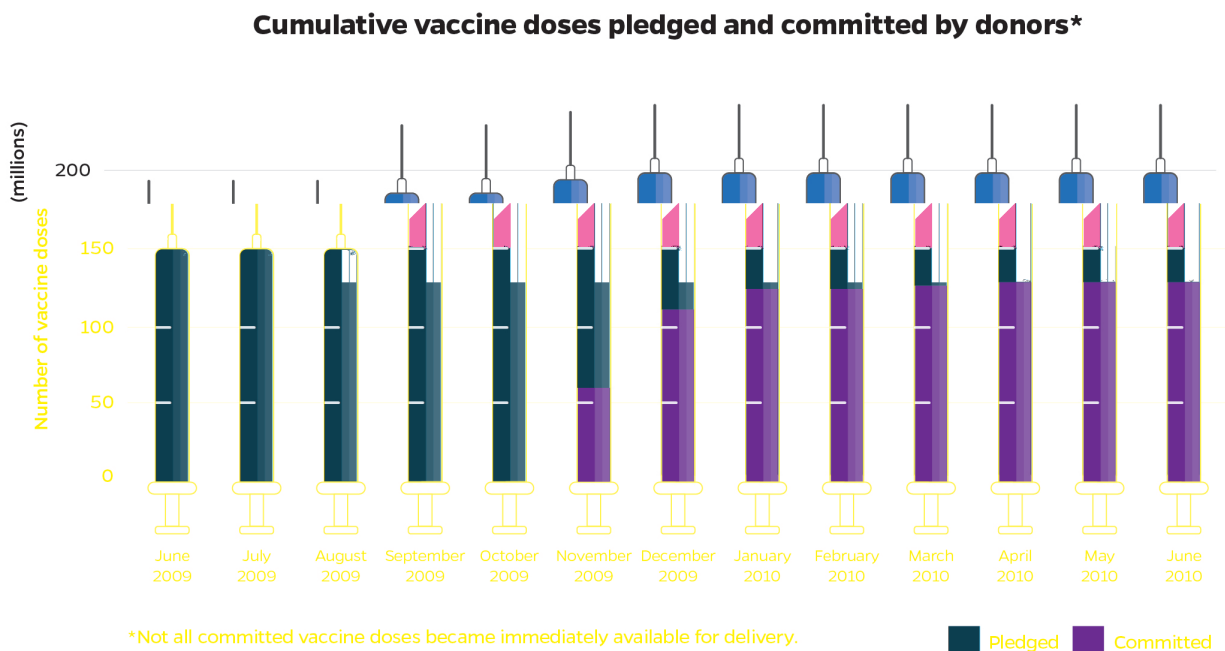
## Box 5: The Potential Problem of National Sovereignty in Pandemics

The landscape of international response for a pandemic may look very different from what is seen for regional epidemics or locally contained outbreaks that are geographically limited. Where outbreaks are geographically more limited, international organizations, NGOs, and other governments can more readily provide personnel, equipment, and financial support to control the outbreak and limit the risk of spread. However, in the event of a high-impact respiratory pathogen causing a pandemic affecting numerous countries around the world, international organizations and NGOs are unlikely to have the capacity to provide support to all countries in need. The capacity of these organizations would likely be exhausted quickly, with little chance of replenishment due to high demand and scarcity of resources. Similarly, other countries would be focused on either combating the disease outbreak within their own borders or ramping up preparedness efforts to prevent the introduction of the disease into their territory. This may include decisions not to share vaccines with other countries until all domestic needs are met, as was seen in Australia during the 2009 H1N1 influenza pandemic when a manufacturing company was told that it had to fill all vaccine requirements for its host country before exporting to other places.<sup>75</sup>

With an expectation of more limited international support in a pandemic, a country would need to rely to a much greater extent on its own ability and resources. Challenges existing in epidemics and smaller disease outbreaks will be exacerbated in a large-scale pandemic, and the issue of scarcity of resources, coupled with high demand, needs to be considered ahead of time.

An example of this issue was seen during the response to the 2009 H1N1 influenza pandemic. While information sharing occurred early in the outbreak, as the cases continued to rise and vaccine production was under way, concerns over equity of access to the vaccine arose. Countries initially announced their support of efforts to provide the vaccine for countries without access and declared they would share a percentage of their vaccine with low- and middle-income countries. However, as shown in Figure 2, the committed number of vaccines shared was considerably lower than the original pledged amounts. While various factors contributed to this actuality, including delay in vaccine production and pledges including amounts to be used in future emergencies, the large disparity between pledged and committed amounts drive home the concern that in a pandemic scenario, a country's national capacity will be even more important as international support, particularly from other affected countries, will be limited and exhausted quickly.<sup>76</sup>

**Figure 2: Vaccine Doses Pledged and Committed During 2009 Influenza Pandemic**



## Multisectoral Involvement and Coordination

Preparedness for an epidemic or pandemic caused by a high-impact respiratory pathogen would require the involvement and coordination of multiple sectors. There is a high likelihood that a pandemic caused by a high-impact respiratory pathogen would cause harm that extends beyond the health sector, so it is crucial that other major sectors be involved in both preparedness planning and response efforts.

The possibility of wide geographic spread and/or deliberate use of respiratory pathogens would mean that government human health resources alone would be insufficient to detect and respond to the spread of a novel respiratory pathogen. The continued development and sustainment of operational and effective OneHealth partnerships among human, animal, plant, and environmental health sectors is essential for preparedness. The collaboration among WHO, World Organisation for Animal Health (OIE), and Food and Agriculture Organization (FAO) has shown commitment to the OneHealth approach, and they have recently developed a guide outlining a OneHealth approach to zoonotic diseases.<sup>77</sup> However, many reviews have underscored the continued lack of integration among the human, animal, plant, and environmental health sectors. One example of the consequence of a lack of such integration is the delayed ability of the human health sector to recognize Ebola as the cause of an outbreak in West Africa in 2014, which was in part due to the human health community's belief that the virus was not present in the region—a finding that had been previously predicted by animal health experts.<sup>78</sup>

Preparedness for high-impact respiratory pathogens will also require involvement from nonhealth actors, including other government, private, and nongovernment organizations. This section highlights 3 specific sectors—financial, private sector, and security—that are critical in pandemic preparedness and response.

### Financial

Financing for outbreak preparedness and response will require involvement of public, private, and NGO actors, supporting both international organizations and national health systems across multiple areas, including preparedness and response activities. Though funding for global preparedness has traditionally involved resources from national governments, there have been limits to government-centric approaches to financing, with inconsistent political commitments to funding for preparedness.<sup>7</sup> Estimates from the World Bank suggest that the cost\* of developing the core public health capacities needed to prepare for public health emergencies is well below the cost of responding to

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\* The World Bank notes that for low- and middle-income countries that have costed their National Action Plans for Health Security, the investments needed to develop core public health capacities necessary to prevent, detect, and respond to potential public health emergencies may be less than US\$1 per person per year (source: <https://www.worldbank.org/en/topic/pandemics>).

such events, but governments continue not to make such investments in advance of an emergency. Many assessments have called on national governments to break the cycle of “panic and neglect”—a term meant to describe the episodic way in which national budgets are often used to fund preparedness. There are similar funding shortfalls for advancing preparedness on the global level. While multiple existing mechanisms provide emergency funds for global response operations, such as WHO’s Contingency Fund for Emergencies, the UN Central Emergency Response Fund, and the Pandemic Emergency Financing Facility, these funds generally are not available to support preparedness activities.

While national governments should continue to be encouraged to increase and sustain their investments in preparedness, there is also a need to explore the availability of financing from nongovernment sources. New models and sources of financing are needed to increase the availability of resources for preparedness.

### **Private Sector**

Beyond the financial sector, there has been acknowledgment in recent years of the need to engage the broader private sector in disease outbreak preparedness activities. A severe respiratory pandemic is likely to devastate economic growth, either directly via trade and travel restrictions or indirectly via high morbidity and mortality and the loss to jobs and industry, such as tourism. Therefore, both out of self-preservation and for reasons of corporate social responsibility, the private sector will need to play a greater role in planning for and responding to such events.

Increasingly, public-private partnerships are being proposed as a model to expand the availability of financial resources for preparedness. The Coalition for Epidemic Preparedness Innovations (CEPI) receives financial contributions from governments and private philanthropists to promote vaccine development for priority pathogens identified in the WHO R&D Blueprint. To date, CEPI intends to invest upwards of \$500 million in candidate vaccines for MERS-CoV, Lassa, Nipah, Rift Valley fever, and chikungunya. CEPI is also making investments in platform technologies with the goal of accelerating development of vaccines for previously unrecognized diseases, such as Disease X. Overall, CEPI has set a \$1 billion fund-raising target.<sup>79</sup> Another example of public-private partnership, the PIP framework, requires industry stakeholders to pay an annual contribution, of which 70% is used by WHO solely on influenza preparedness activities.<sup>80</sup>

Still more initiatives are required to mobilize financial support to enhance preparedness systems. Identifying new sources of funding for both national preparedness strengthening and research and development of vaccines, diagnostics, and treatments for high-priority diseases is greatly needed.

Governments have historically viewed the private sector as a potential source of support for public sector–led operations, including in-kind donations and purchases of equipment, supplies, or medical countermeasures. But the private sector has additional capabilities and expertise that can be tapped to support preparedness efforts.<sup>50</sup> The unique expertise and services of several industries deserve special attention. The first is the pharmaceutical industry, which plays a key role in the research, development, and manufacture of medical countermeasures. The second is the airlines, transportation, and logistics/shipping industries, which can ensure the transfer of medical personnel and equipment for scaling up operations. The third is the medical supply industry, which would also be of high global importance in a pandemic and contribute to R&D and manufacturing of MCMs. And fourth is the global communications sector—both those who provide the hardware and software around communications, as well as those who are global leaders in delivering content and helping to serve public information needs.

Despite its potential, private sector involvement to date has been haphazard and mostly limited to the response phase of a disease outbreak. A key challenge is the lack of advance communication and coordination between public and private actors, which is needed to clarify the appropriate roles, responsibilities, and expectations of each during an epidemic or pandemic. The Private Sector Roundtable and a variety of efforts at the World Economic Forum around private-sector engagement in preparedness and response are notable exceptions in which global business has been leading or participating in the development of new partnerships and potential solutions with WHO and governments.<sup>50, 81</sup>

The partnership between government and the private sector will be most effective if defined and agreed on well in advance of an event. The ad hoc inclusion of private sector services into a health response could conceivably hinder a response in that it could risk public suspicion of private sector involvement for monetary or financial gain. Prenegotiated partnerships and/or memoranda of understanding that transparently define the nature and extent of private-sector involvement are needed.

Private-sector organizations can also meaningfully contribute to preparedness by preparing continuity plans to ensure their continued operations in the event of a potential pandemic.<sup>82</sup> Many communities rely on such organizations to provide essential services. Therefore, these organizations can also serve as extensions of government health response by educating their employees, families, and surrounding communities about recommended protective actions and planning to provide support for employees who become ill.



## **Security**

The potential for deliberate release of a high-impact respiratory pathogen provides a clear case of an instance when engagement with the security sector is required. However, the need to involve security in disease outbreak preparedness is not limited to deliberate events. The ongoing outbreak of Ebola in the Democratic Republic of Congo has also underscored the importance of having robust partnerships between health and security. Generally, a national or international security sector will include military, law enforcement, and intelligence agencies.

Militaries may have a mandate and well-defined protocols for disaster relief operations, but their experience in disease preparedness and response may be limited. National militaries may have experience in medical countermeasure research and development, transport elements, military health or other surveillance programs, or other initiatives that may prove relevant to outbreak preparedness and response.

Challenges that could prevent or complicate engagement from the security sector include a possible lack of experience with biological or health-related emergency response in a given country's security agencies; a mutual lack of understanding regarding the needs of the response and potential assets that could be brought to bear; a lack of training, equipment, or buy-in from military personnel; and the possibility that security sector involvement could, if improperly implemented, be at cross-purposes with efforts to provide communities with public health or medical interventions.<sup>83,84</sup> On balance, in many countries the security sector could bring valuable expertise and assets to bear, both in terms of preparing for high-impact respiratory pathogens and in the response and in medical countermeasure research and development. Countries should seek to find mechanisms to incorporate the security sector, while planning on avoiding the possible complications of this kind of engagement.

## **Surveillance, Monitoring, and Assessment Systems**

### **Surveillance Capabilities**

Reviews of past events have revealed limitations in global and national surveillance capabilities. Current systems vary widely in their quality, and many under-resourced settings do not have surveillance systems that could adequately serve those purposes. Furthermore, existing surveillance systems are highly fragmented and local, with data that cannot easily be pooled and analyzed to direct a large-scale response. Enhancing (and, in some under-resourced settings, implementing) surveillance systems would improve capabilities to prevent, detect, and respond to an event from a high-impact respiratory pathogen. A commonly cited limitation is insufficient availability of laboratory testing.<sup>85</sup> Laboratory information is essential for ensuring the availability of accurate and actionable surveil-

lance. In addition to assessing the availability of laboratories that can perform diagnostic testing, countries must also consider the capacity of laboratories to handle testing in the event that there is a large surge in demand. While laboratory networks and surveillance mechanisms including GISRS, FluNet, and WHO Collaborating Centers are vital components of current surveillance capacities, efforts should be made to further strengthen these mechanisms and improve laboratory testing.

Surveillance capacity as measured by the JEE tool requires syndromic surveillance for 3 core syndromes (including severe acute respiratory syndrome) and regular analysis and reporting of surveillance data. Of the countries for which data is available, the average surveillance score is 3.3 out of 5 on the JEE, which suggests that there is room for strengthening the capacity of many countries to detect and monitor outbreaks.<sup>86</sup>

During large-scale events involving a respiratory pathogen, it will be critically important that countries and the international community have ready access to information to support decision making about how best to respond. A key question that is likely to emerge right away is how severe the event is in terms of health impacts (eg, percent ill, percent of cases resulting in death or severe outcomes). As demonstrated in the 2009 influenza pandemic, the answers to these questions are likely not readily available in traditional public health surveillance systems. Health officials should identify additional data sources that may provide insights to these questions and make plans for accessing and analyzing them.<sup>87</sup> To enable this, countries should invest in developing surveillance systems that produce timely, accurate, and highly resolved data that can be easily analyzed and shared. Specific diagnostic information would be of great importance, and countries should have plans for the development or uptake of diagnostic tests. In an event involving a novel pathogen, PCR-based tests are likely to be the first to be available to aid in diagnosis and confirmation. In preparation for this, national public health laboratories and large commercial laboratories should develop a concept-of-operations for how to distribute test kits rapidly to relevant clinical sites and laboratories in areas affected by the outbreak.

In instances in which demand exceeds capacity at available laboratories, policies for testing may change. For example, during the 2009 influenza pandemic, public health laboratories stopped confirming individual cases of influenza once transmission became widespread.<sup>88</sup> Such changes in testing procedures would require pre-event planning to determine criteria for testing and communication about planned protocol changes with clinicians, public health practitioners, and the public.

The information needs and sharing that may occur during deliberate events may vary greatly from a naturally occurring event. For example, there will be a need to assess the risk of subsequent attack—a consideration that is likely to be central in discussions about

how to utilize medical countermeasures. It has also been identified that there are insufficient mechanisms to enable rapid information sharing across sectors during a deliberate event response.<sup>37</sup>

Additional gains could be made by further developing modeling capabilities to enable the modeling of surveillance data to gain insights into its anticipated trajectory and potential future impacts of an event, as well as modeling around possible response strategies. Modeling can support public health decision making in a number of ways, including planning and comparing interventions, forecasting the trajectory of the epidemic, and simulating risk scenarios.<sup>89</sup> Models can also transform diverse data streams into a mathematical representation of an outbreak that is more structured and informative than the input data individually. In order to be as useful as possible, modeling capabilities should be implemented in advance of an emergency and closely integrated with the public health decision-making team to facilitate rapid analyses and decision-making cycles. Decision makers also must be informed in advance about the expected limitations of modeling approaches and how uncertainties about existing data may affect model predictions.

### **Detection Capabilities and Diagnostics**

In the event of a novel outbreak of a high-impact respiratory pathogen, early detection of the event through regular diagnostic testing may not be possible. Routine tests may not properly identify novel diseases. In these circumstances, clinical recognition that something is not normal and rapid reporting of this to appropriate public health authorities would be critical for enlisting the right specialized diagnostic expertise and for mounting a rapid response. In higher-resource countries, specialized diagnostic tools or approaches could be used in efforts to make a rapid initial, pathogen-specific diagnosis of the first patients, with the time to specific diagnosis depending on the pathogen, the samples, the period between recognition of a clinical anomaly, and the initiation of testing. In lower resource settings, or in healthcare settings where clinical anomalies might not be easily evident, it might take substantially longer to initiate the proper testing for a novel pathogen. In those settings, regional, national, or international laboratories might need to be engaged to make an initial specific pathogen diagnosis.

Once a pathogen responsible for an emerging epidemic or pandemic is definitively identified as the etiology, the use of diagnostic tools would switch. Diagnostics would no longer be needed for detection, but instead they would be needed for event management. In this latter phase, diagnostics become an important tool in event characterization (determining who is affected, who is at risk of severe outcomes) and in clinical management of patients to optimize treatment and to reduce transmission through proper isolation.

In the clinical realm, in a high-resource setting, the approach to a novel diagnosis would be expected to begin with initial confirmation using research-related molecular diagnostics, then would evolve to clinical syndromic surveillance with post facto laboratory confirmation, eventual testing at reference laboratories and major commercial laboratories, and, finally, to widely disseminated diagnostic testing strategies. These processes may be facilitated via pre-established processes to authorize emergency use for nonapproved tests and with national laboratories and public health authorities distributing materials (such as primers) to qualified parties. However, this process is often not seamless nor rapid. In settings without well-developed regulatory frameworks, the process would be more uncertain and depend on local expertise, resources, plans, and perhaps international assistance.

With a truly unknown respiratory viral pathogen, initial cases would fail to produce a diagnosis by conventional means, leading to more sophisticated testing, including next-generation sequencing, to identify any clue as to what type of microbe is present and what characterizes it (ie, what viral family it is most closely linked to). In countries with access to such testing, as the diagnostic test is perfected and the etiologic agent better characterized, the development of serological tests to identify past infections as well as simplified molecular diagnostics (and in some cases point-of-care molecular testing) would occur.<sup>90</sup> These tests might first be available at national public health labs and may or may not diffuse to local health centers. Limitations would include technical ability as well the availability of materials for the construction of testing, such as nucleic acid primers. In the context of a novel respiratory pathogen, many cases would be diagnosed using clinical scoring criteria, with or without eventual laboratory confirmation.

In the event of a deliberate release of a pathogen, the first recognition is likely also to occur following recognition of an anomaly (or anomalies) in the clinical sector, where sick patients are turning up for treatment, with similar processes and challenges to diagnostics as noted above. In addition to clinical diagnostics, assessments of where pathogens may have contaminated the environment could be important for law enforcement activities and efforts at attribution, if there is information available that made such assessments feasible. If these assessments were feasible, then this information could help with determining the scope of initial exposures and determining where there might be environmental contamination.

Technological advances are needed to modernize our diagnostic capabilities to become faster and nimbler at the onset of outbreaks, particularly around novel pathogens. Diagnostic tools are required in settings beyond centralized laboratories. Microfluidic devices and other “lab on a chip” devices still in development have the potential to improve diagnostic capacity across a range of settings, shorten the timeline to diagnosis, and ulti-

mately trigger a cascade of other actions needed to isolate and characterize the pathogen.<sup>91</sup> The window for detection for respiratory pathogens would be very short before transmission may become widespread. As such, the development of these sentinel tools can provide the early detection and warning needed to get ahead of an outbreak.

### **Outbreak Investigation and Response**

An epidemiologic investigation and the accompanying response are the backbone of outbreak control. As seen currently in the DRC Ebola outbreak, efforts to complete contact tracing in that setting are challenging but critically valuable. Contact tracing is highly effective for outbreaks that are mildly to moderately transmissible and of a modest scope. For high-impact respiratory pathogens, contact tracing would quickly become infeasible. It is very difficult to identify contacts when all who may have been in the general vicinity of a case may be at risk. Furthermore, as the number of potential contacts grows, the resources required to monitor those people quickly would become overwhelming. A 2011 assessment of the economic burden of measles outbreaks, for example, found that each case of measles generated many dozens or even hundreds of contacts, requiring thousands of personnel hours to manage.<sup>92</sup> New technologies—for example, those making use of location data or push notifications from mobile phones—could conceivably be leveraged to extend the utility of contact tracing for highly transmissible events, though this should be considered an open research question at this point. Absent widespread availability and effectiveness of such technologies, in the event of a large-scale respiratory outbreak, other nonpharmaceutical interventions (detailed below) may be more practical, though they are likely to be less effective.

### **Health Systems and Infrastructure, Health Services, and Clinical Management**

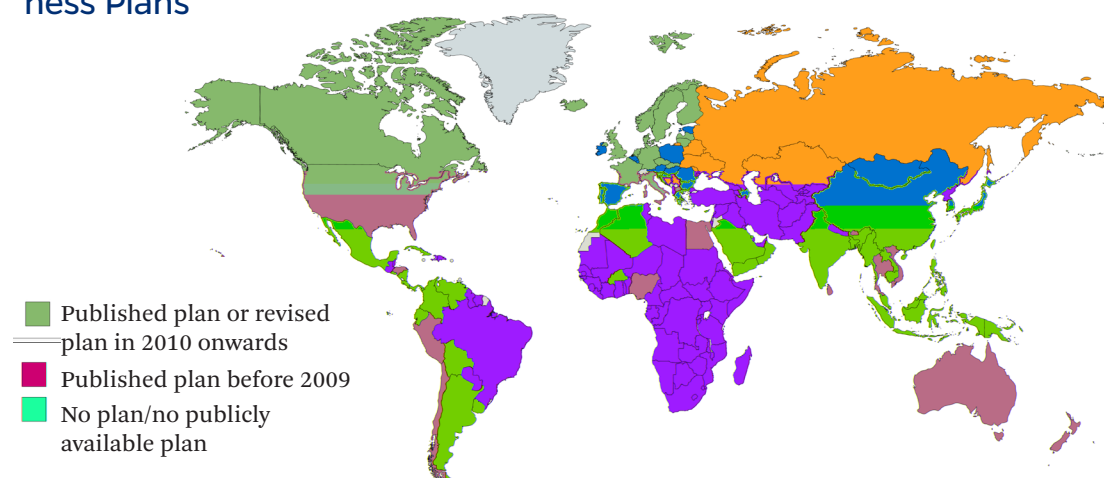
Widespread transmission of a high-impact respiratory pathogen would cause a surge of patients seeking care that would challenge even the most well-prepared health system. As a result, victims of a large-scale outbreak in settings with weak health systems would likely die at a higher rate than would be otherwise expected, due to lack of available modern medical care. Individuals who need to use the overburdened healthcare system for routine care during an outbreak would also likely suffer elevated morbidity and mortality, as available health resources are shifted to the emerging outbreak. As seen in [Box 6](#), absolute mortality estimates for a high-impact respiratory pathogen are much greater today than they were in past decades, which highlights the strain that health systems would be under.

Unprepared or under-resourced health systems could make matters worse by exacerbating disease transmission through nosocomial spread and the inability to promptly

diagnose and render care. During the 2003 SARS epidemic, transmission in healthcare settings played a prominent role, accounting for 72% and 55% of presumed and confirmed cases in Toronto and Taiwan, respectively.<sup>93</sup> During the 2013-2016 West Africa Ebola epidemic, healthcare workers were 21 to 32 times more likely than the general public to get infected with Ebola, which had a severe impact on the affected countries' already-depleted healthcare workforce.<sup>94</sup> The provision of routine medical care also suffered setbacks, with an estimated 50% reduction in access to healthcare services during the epidemic, including care for other infectious diseases such as HIV, tuberculosis, and malaria.<sup>95</sup> The ongoing Ebola outbreak in the Democratic Republic of Congo (DRC) has also seen substantial nosocomial spread to healthcare workers, accounting for approximately 6% of all cases.<sup>96</sup>

International initiatives have aimed to improve health system preparedness and response for outbreaks and pandemics of respiratory diseases, focusing largely on influenza, but global preparedness for a high-impact respiratory pathogen event remains inadequate. One of the strategic objectives of the 2019-2030 WHO Global Influenza Strategy is to “strengthen pandemic preparedness and response for influenza,” and it includes numerous health system-related efforts, including national planning and exercises; building stockpiling capacities; procurement, deployment, and administration of vaccines, treatments, and supplies; and multisectoral collaboration.<sup>54</sup> Not every country, however, has developed influenza preparedness plans. WHO reports that only 32 countries developed or revised plans after the 2009 H1N1 pandemic, and 99 countries still have no influenza plan that is publicly available (see Figure 3).<sup>71,97</sup> Despite these initiatives, preparedness for high-impact respiratory disease outbreaks such as influenza remains dependent on political will and sustainable human and financial resources, and, thus, varies from nation to nation.

**Figure 3: Global Map Identifying Countries with National Influenza Preparedness Plans**



\*Data extracted from WHO Strategic Partnership Portal



Early in a pandemic, isolation of the sick will be critically important to limiting further spread, but most hospitals around the world have very limited isolation capacity, particularly for airborne pathogens, and likely only a fraction of what would be needed in a large outbreak. To adequately prepare for and respond to outbreaks of respiratory pathogens, health facilities would need to increase their capacity for large-scale isolation of patients with highly transmissible respiratory diseases.

While a small number of facilities have dedicated units for the isolation of high-impact infectious disease patients (eg, high-level isolation units), this capacity is very limited, and all facilities need to plan for less resource-intensive yet effective isolation strategies to handle larger patient volume. These include converting regular patient care units into isolation units or cohorting patients who are similarly infected. Plans for just-in-time care or triage facilities (eg, tents or other alternative care facilities) could also provide additional space during emergencies. Once an epidemic is under way, healthcare workers would need to be able to rapidly identify those in need of isolation. Training and education would be required to ensure that frontline healthcare workers, particularly those staffing emergency departments, were fully aware of the emerging epidemic and capable of implementing travel, exposure risk, and symptom screening in order to identify and isolate suspected cases.

Surge capacity planning is another key issue. A large influx of patients during a respiratory pandemic would require additional staff and supplies. Healthcare workers would need to be trained in appropriate infection prevention and control practices, including personal protective equipment (PPE) donning and doffing, and appropriate hand hygiene. The availability of essential basic supplies and equipment must also be included in global planning efforts. There is a severe maldistribution of medical supplies between countries and health systems around the world, and a dedicated effort is needed to determine how low- and middle-income countries would maintain access to critical supplies (eg, masks, respirators, gloves, gowns, IV fluid bags, medical gases) during a large-scale respiratory disease outbreak. Plans to ensure access to other critical logistics and infrastructure—including clean water, electricity, data and telecommunications, and waste management and other sanitation services—during a severe pandemic need to be made.



## Box 6: What Would the 1918 Influenza Pandemic Look Like Today?

In the worst pandemic in recorded history, the 1918 influenza pandemic, the novel virus infected approximately one-third of the global population over a period of 2 years, ultimately leading to 50 to 100 million deaths worldwide. One might imagine that the death rate would be lower today due to the advent of modern medical equipment and procedures that did not exist in 1918, but the global population is now approximately 4 times greater than in 1918. This growth, however, is disproportionately higher in low- and middle-income countries, often the ones with developing health systems. Many—predominantly in Africa, Southeast Asia, Latin America, and the Middle East—have experienced population growths of 1,000% or more since 1918. Crowded urban areas provide prime conditions for the spread of respiratory diseases, and urbanization is increasing globally, including the emergence of 47 “mega-cities” (populations over 10 million). By comparison, London was the world’s largest city in 1918, at approximately 5 million people. Additionally, global travel has increased by orders of magnitude compared to 1918. Even then, shipping and population movement (including World War I) played an important role in global spread of the disease, but today, humans can fly anywhere in the world in less than 1 incubation period, meaning that global transmission can be expected to be even faster.

In 1918, the global case fatality ratio is estimated to have been 2.5%, but it was considerably greater in low- and middle-income countries, with some estimates exceeding 10%. Today, some high-income countries would be expected to fare much better because of modern health care, but the case fatality in countries with limited access to healthcare could be as bad as or worse than 1918. Simple arithmetic would suggest the possibility of 100 to 400 million deaths if a 1918-like pandemic were to occur today, but unprepared or under-resourced health systems could further exacerbate disease transmission through nosocomial spread and an inability to promptly diagnose and render care, a particular concern for developing health systems. During the 2003 SARS epidemic, 72% and 55% of presumed and confirmed cases in Toronto and Taiwan, respectively, occurred as a result of healthcare transmission. A similar nosocomial outbreak in which healthcare facilities became amplifiers of the epidemic, this time of MERS, happened in South Korea in 2015.

## Community Engagement

Community engagement entails the collaboration of affected and at-risk populations with policymakers and practitioners in the generation, implementation, and evaluation of measures to safeguard public health and safety.<sup>98</sup> When genuinely operating within a community engagement framework, authorities see themselves as working *with*, rather than *on behalf of* potentially endangered people, and they accord community members both respect and responsibility as actors who have influence over their own well-being.<sup>46,99</sup> Community engagement—comprised of dialogue, power sharing, collaborative decision making, and combined actions among a community, its providers, and its leaders—can strengthen readiness, response, and recovery in the case of a potential high-impact respiratory pathogen outbreak.<sup>100</sup> Once fully engaged in larger systems of disease outbreak planning and consequence management, for instance, community members can offer ideas and insights that enable public health interventions and clinical care to be more culturally competent, attuned to local conditions, and socially acceptable.<sup>46</sup> In addition to their intellectual contributions, the community offers the power of many hands—for example, backfilling depleted responder workforces, complementing care in the formal health sector with care in the home, and standing up mutual aid networks for ill and/or confined people and their families.<sup>100</sup> Lastly, beyond the community’s practical offerings are its moral and ethical ones: Leaders faced with extreme conditions and stark choices can elicit community values and views on—and thus secure broader support for—for

instance, the allocation of scarce life-saving resources, the alteration of burial practices to accommodate mass casualties, and the appropriateness of research on novel countermeasures in emergency conditions.<sup>101</sup>

Treatment of community engagement in the high-level reviews and reports cited earlier ranges from specific mention as a core capacity in health security to silence on the topic altogether. Some recent health security reports and reviews strongly advocate community engagement as a “core function when managing a health emergency.”<sup>4,44,46-48</sup> Helping prompt such a stance is recognition that “community engagement ultimately made the difference” in the countries most affected by the H1N1 and H5N1 outbreaks,<sup>47</sup> and that greater efforts to understand, and to earn the cooperation of wary villagers who resisted care and containment measures, could have reduced the impacts of the West Africa Ebola outbreak.

For previously unaware audiences, the West Africa Ebola outbreak concretized the benefits of community engagement when practiced—and the adverse effects when neglected. The West Africa Ebola outbreak experiences—including community rejection of public health interventions and the deaths of several health workers and journalists in Guinea in September 2014—brought an immediacy and urgency to the importance of having the trust and help of affected communities during a high-impact infectious disease outbreak.<sup>18,42,44,47</sup> As discerned through Ebola successes and failures, the positive effects of community engagement include creating bridges, open dialogue, and mutual understanding among clinical trial participants, communities, and investigators, thus furthering research;<sup>102</sup> achieving collective behavior change, such as alterations in burial practices, social gatherings, and healing practices, through cultural sensitivity and joint problem solving, thus interrupting disaster transmission; and enhancing the cultural competency of health workers seeking to bring the benefits of evidence-based care and infection control.

Social science—the study of collective human behavior and beliefs within their larger historical, political, and economic contexts—is emerging as critical to fully informed health security policy and practice. As some key reports and reviews argue, social scientists—knowledgeable about human interactions, economic exchanges, political ideologies, religious beliefs, value systems, and historic context—complement those thought leaders who have more typically informed disease outbreak preparedness and health security efforts, including medical, epidemiological, governmental, financial, and operational experts.<sup>43,44,46</sup>

## Risk Communication

WHO and other public health organizations have developed updated guidelines for emergency risk communication that are applicable to highly transmissible respiratory diseases. Yet, communication with the public, partners, and intermediaries as well as between key organizational stakeholders continues to be an important area for strengthening preparedness. Without strong, accurate communication efforts, no amount of planning, intervention, or response is likely to be highly effective in the response to a pandemic involving a high-impact respiratory pathogen.

In *Communicating Risk in Public Health Emergencies*, a WHO guideline for emergency risk communication policy and practice, a well-reasoned and evidence-based approach to risk communication has been developed.<sup>103</sup> Nonetheless, experience with recent outbreaks, such as Ebola, indicate that further improvement is still needed in the actual *implementation* of these and other state-of-the-art guidelines.<sup>104,105</sup> Although risk communication is featured in the Joint External Evaluation tool,<sup>66</sup> high-level reports and reviews for global response organizations show a need for greater commitment to prioritizing risk communication to the public and trusted partners as a key response element in its own right, rather than as an ancillary component of other public health efforts. Many of the high-level reports reviewed for this study acknowledged the importance of risk communication, but relatively few described clear strategies, approaches, or priorities with respect to communication with the public.

As countries strive to apply leading-edge recommendations for risk communication in the context of more localized, naturally occurring outbreaks, they should also recognize the added complexities with a global outbreak from a high-impact respiratory pathogen—one that could arise naturally or from a lab accident or a deliberate attack. These contextual elements—for example, the whole world is at risk, how do we attribute where this came from, who is to blame—will likely complicate crisis and emergency risk communication. Apart from having to employ effective public education to dampen people's impulses to shun affected individuals or groups during the outbreak for fear of disease, for example, authorities may also need to provide frequent updates on any investigation into the outbreak's origins and advise against lashing out against others who “look like” they may have spread the disease (in the event of a naturally occurring pandemic) or those who might be presumed perpetrators (in the case of a biological attack).<sup>106,107</sup> In the case of a newly emergent pathogen for which novel countermeasures are urgently produced, a host of risk communication dilemmas may arise—for example, how to inform peoples' choices about uptake when they fear a seemingly “rushed” drug or vaccine, how to elicit public confidence in decisions about the allocation of a very scarce life-saving countermeasure, and how to avert the uptake of fraudulent, life-threatening alternatives when access to the real beneficial countermeasure is impossible.<sup>108</sup>

## **Communication with the Public**

One of the goals of public health communicators is to successfully engage with the public to increase understanding of risks and investment in protective activities. Effective communication with members of the public will enable informed decisions and responses that are more supportive of vital public health activities. It includes timely, understandable, and transparent communications that link to protective actions and self-efficacy. However, communication efforts with members of the public are not always easy and may require changes in current approaches. The US CDC has developed Crisis and Emergency Risk Communication (CERC) training and tools that can provide public health organizations with the foundational principles and practices of crisis and risk communication with the public.<sup>103,105</sup> Communication and the establishment of trusted lines of communication between the community and public health is a vital component of effective public health response.

## **Partners/Intermediary Groups**

Risk communication also includes communication with and through intermediaries such as trusted on-the-ground partners and the news media in order to leverage their capacity as amplifiers of appropriate risk and protective action messages.<sup>109</sup> Although there are many fundamental differences between these different groups, they both act as message mediators and require dedicated time and effort to build relationships and partnerships over time. By proactively widening and reinforcing partnerships with community, faith-based, and healthcare organizations, public health communicators have a ready conduit in future disease outbreaks. Furthermore, these trusted partners may also act as advocates during times when public trust in public health is low and misinformation is rampant. Similarly, established and strong relationships with the news media can help to ensure the right messages get to members of the public.

## **Communication Between Response Groups, Governments, and Other Stakeholders**

Communication between the private and public sectors is a vital component of an effective outbreak response to enable collaborative and noncontradictory efforts and produce consistent risk messages to the public.<sup>58</sup> Collaboration and communication between private and public sectors has been highlighted in multiple reports and reviews as a key area in need of improvement.

## **Medical Countermeasures and Pharmaceutical Interventions**

The availability of safe and effective medical countermeasures (MCMs) will greatly enhance our abilities to respond to a high-impact respiratory pathogen. During such events involving high-impact respiratory pathogens, the availability of MCMs (ie, vaccines,

therapeutics, diagnostics, and other medical supplies such as personal protective equipment, or PPE) represent our best opportunities to limit morbidity, mortality, and disease transmission. Vaccination is the single most effective pharmaceutical intervention and would likely be the preferred MCM in a high-impact respiratory pathogen outbreak because it can typically prevent infection in individuals and limit transmission in populations. Antivirals and other therapeutics like monoclonal antibodies, if available to treat the ill, might be of great clinical value, and, in some cases, if there were sufficient supplies of these products (seemingly unlikely in most places under current conditions), they could serve as prophylactic agents. PPE, including masks and respirators, would also play a critical role in infection prevention and control, particularly if no vaccine or therapeutics are immediately available.<sup>110</sup>

The ability of MCMs to alter the course of a high-impact respiratory pathogen would depend on the effectiveness, timeliness, and efficiency of a complex system that starts at basic discovery and ends at the treatment or prevention of illness (see Table 2). In between, national and local governments, academic institutions, the pharmaceutical industry, and the private sector would need to move products through early and advanced development and the regulatory process, the manufacturing and finishing processes, and the distribution and dispensing systems needed to administer countermeasures to people who need them. From an MCM perspective, global capacity to respond to pandemic influenza is likely to be far stronger than it would be for any other novel high-impact respiratory pathogen, given that annual epidemics of seasonal influenza create a sustainable market for vaccines and antivirals that may be able to be adapted for use in the event that a pandemic strain emerges. However, even in that case, very few countries have the capability to develop and distribute MCMs in time to have an epidemiologically meaningful impact on the course of a pandemic. For example, in 2009, the peak of the H1N1 influenza pandemic passed before a vaccine was widely available.

**Table 2: Making and Using Drugs and Vaccines**

<b>Activities*</b>	<b>Primary Actor</b>
Basic discovery	Academia and industry
Early development	Academia & industry
Advanced development	Industry
Manufacturing and production	Industry
Distribution	Public or private logistics
Dispensing or administration	Public health; health care; pharmacies; perhaps community organizations? Perhaps self-administration, if future technologies and approaches allow?

\*Sources of funding for these activities comes predominantly from governments, foundations, international organizations, and industry.

If the high-impact respiratory pathogen is not influenza, then the prospects around MCM development would be far more dire, as MCMs are likely to be much less far along in development—if in development at all. In the case that an existing vaccine candidate has been developed (eg, perhaps a coronavirus vaccine for an existing coronavirus could be used with some value for a novel coronavirus that causes high-impact respiratory outbreak), there is likely to be no surge manufacturing plan or capacity. If the pathogen is completely novel and there is no existing research base—what WHO refers to as a Disease X scenario—there is no alternative but to start with fundamental science and then advance MCMs through the development pipeline as quickly as possible.

Given existing approaches, technologies, and policies, vaccine development takes an estimated 15 years and costs approximately \$1.4 billion ([see Box 7](#)).<sup>111-114</sup> Attempts at developing vaccines against respiratory pathogens such as SARS coronavirus have been slow. Technical barriers at the discovery and R&D phases of development or market failures can be rate limiting.

Once a candidate drug or vaccine has been developed, it must then go through clinical trials to test for safety and efficacy. However, as was demonstrated in the 2014-2016 Ebola epidemic in West Africa, trials in the midst of an outbreak will be logistically and ethically challenging. Moreover, many countries maintain their own paradigm for pharmaceutical regulation and have not put in place policies for emergency use of medical countermeasures that may not have full regulatory approval. These complexities could slow international MCM deployment, which could impede efforts to control a severe disease outbreak. During the 2009 influenza pandemic, according to former US Ebola Response Coordinator Ron Klain, “thousands of doses of vaccine sat in warehouses because of a lack of an internationally accepted process to approve and administer it, and to compensate individuals who might be harmed by it.”<sup>115</sup>

In current conditions, manufacturing would be a critical bottleneck in the MCM response to a novel respiratory pathogen. The bulk of our manufacturing capacity for vaccines exists in a handful of large pharmaceutical companies in only a few countries. Further, those companies have optimized their manufacturing output based on the projected demand for their products, which means there is very little surge capacity in the system. Companies would be faced with taking commercial vaccine production offline in order to accommodate vaccine for the new pathogen. Also, manufacturers may face political pressure to produce vaccine for their home country before exporting to the rest of the world. This could mean that only a few countries have access to MCMs until manufacturing could be significantly expanded, which could be months or even years.



Even if an adequate supply of MCMs could be assured, for example, from preestablished stockpiles, dispensing and administration of vaccines, drugs, and other MCMs would be a significant challenge. Many countries currently do not have the capacity to accept large amounts of MCMs much less rapidly administer them en masse. Points of dispensing (PODs), mass vaccination campaigns, and other extraordinary public health measures would need to be taken to achieve population-level protection.

What is needed, but is not currently possible, is the capability to get MCMs from discovery to mass administration within a few months. This would include very rapid identification of drug or vaccine targets, development of the drug or vaccine itself, safety and efficacy testing and regulatory approval, manufacturing at a global scale and ensuring MCM quality, sharing MCMs equitably throughout the population, and mass dispensing and administration. With this in mind, investment in next-generation approaches to MCM research, development, manufacturing, dispensing, and administration will be critical to creating an effective response capacity globally. CEPI is an important new global organization whose purpose is to develop vaccine candidates for diseases with epidemic potential. CEPI has engaged many vaccine development companies in this work to date. Even if CEPI succeeds as is hoped, a system will need to be built around it for creating rapid development pathways for dealing with novel, fast-moving threats; for rapid clinical testing; and for mass manufacturing of products once they are shown to be effective and safe.<sup>116</sup>

Platform technologies have been called for as a means of accelerating vaccine development for pandemic preparedness. We define a platform technology as one employing an “underlying, nearly identical mechanism, device, delivery vector, or cell line . . . for multiple target vaccines.”<sup>117,118</sup> The chief potential advantages to this approach would be to save time and cost by building on systems that are already proven effective and to rely on systems in an emergency that have been shown to work. Nucleic acid vaccines, for example, are readily adapted for new targets by simply changing the nucleotide sequence; manufacture and its attendant safety testing is simplified because these vaccines could be considered “chemicals” and, like the manufacture of small-molecule chemical MCMs, may not need extensive batch testing once the manufacturing processes are established.

Flexible manufacturing offers another approach for expediting the development of MCMs. Technologies for flexible manufacturing include single-use components for all stages of manufacture (production, processing, and fill-and-finish), modular factory design, portable modular manufacturing, and continuous processing. Some of these techniques are already in widespread use; others are in development. These technologies can be used in combination with platform vaccine technologies, which would allow multiple candidate vaccines using the same platform to be manufactured at the same site.



Another advance that could make scale-up of drugs and vaccines more feasible in events involving a high-impact respiratory pathogen is the strategy of distributed manufacturing. Traditional manufacturing processes often bring together, assemble, and process materials in centrally located sites, and the products are then distributed out to the customer. However, in the future it is possible to envision distributed manufacturing, in which the final products are assembled and distributed from sites closer to the final customers. A vision for distributed manufacturing posits that much of the supply chain can be supplied digitally. Decentralized, small-scale production facilities, biokits, mini-labs, or 3D printers could enable widespread production of MCMs at local outlets (eg, local manufacturing centers, pharmacies, or hospitals). Globally distributed manufacturing could provide products for areas that currently lack the capacity to produce MCMs. These approaches could lead to more equitable coverage during a crisis and allow remote and at-risk populations to receive MCMs more quickly. If local outlets routinely used distributed manufacturing to produce drugs for normal use, these units could provide emergency capacity during an event involving a high-impact respiratory pathogen.

Globally distributed manufacturing could also have the virtues of being less susceptible to single point failures, either by accident or deliberate disruption, and less vulnerable to trade disruptions than conventional manufacturing. While distributed manufacturing would still rely on international trade for raw materials, it would reduce reliance on a small number of critical manufacturing nodes. In contrast, today's biopharmaceutical industry relies on centralized production in relatively few countries. Higher-income countries would likely be able to benefit from this strategy earlier, but donors and international organizations could assist in helping lower-income countries, individually or as regional or partner groups, also develop these capacities.

While healthcare workers in a pandemic would require and be comfortable using PPE, specifically masks and respirators, providing masks for the public to limit risk of transmission would be a greater challenge. Widespread use of masks and respirators by the public would be complicated by the challenges of proper fit, the costs, and the inability of the supply chain to provide masks at that scale.<sup>119</sup> The same mask suppliers would be besieged by countries and healthcare facilities around the world. If there were limited availability of masks and respirators in a given country (which would be highly probable), they would need to be prioritized for health facilities to provide protection for healthcare workers and increase infection prevention and control measures. Beyond this, in the public setting, there is very little available information that studies the effectiveness of masks outside of health facilities. Additional research into the development of easy-to-use, effective, and reusable masks for wider use should be considered.

## Box 7: The Economics of Medical Countermeasure Development

The development of medical countermeasures against emerging infectious disease threats faces several unique challenges. Pharmaceutical companies, both publicly traded and privately owned, generally make investment decisions based on potential market size and revenue potential, as well as the ease of the regulatory approval pathway. Emerging infectious disease outbreaks lack predictability in terms of their nature, size, location, frequency, and duration. The revenue streams a company may realize from an emerging infectious disease countermeasure are uncertain, as many of these events occur in low-resource settings in which there is little to no ability to purchase such products, increasing the risk that a firm may not achieve a return on investment. In addition, there are opportunity costs incurred for not pursuing more lucrative activities that compete for the same financial, personnel, and manufacturing resources. In essence, there is no commercial market for the majority of emerging infectious disease countermeasures.

It is also important to understand that the global pharmaceutical industry as a whole is represented by fewer players (as companies have increasingly relied on mergers to acquire new research), and fewer new drugs are in development (as research and development costs have risen along with competition from generic drugs). Development of novel drugs that serve previously unmet needs is particularly sluggish. In the United States, which has the largest pharmaceutical market in the world, only 13% of new drugs approved between 2005 and 2016 were novel drug products.<sup>120</sup>

In light of these realities, it is necessary to consider different avenues for promoting research and development of medical countermeasures for respiratory transmissible diseases with pandemic potential. Regulatory, policy, tax, and direct financial incentives have all been used at various times and could be pursued further to encourage R&D investment by industry. When structured appropriately, tax incentives can entice companies to develop drugs eligible for these inducements. For example, as a consequence of the Orphan Drug Designation program, which provided federal tax incentives to encourage development of drugs for rare diseases affecting fewer than 200,000 people annually, the number of claims by companies for this tax credit increased 5-fold between 2005 and 2014 in the United States.<sup>120</sup> The promise of expedited regulatory review can also positively influence industry R&D investment, especially if companies are permitted to apply expedited review “vouchers” to any drug in their development pipeline or sell the vouchers to other companies.

Direct incentives, such as milestone payments given to a company at various designated stages when the company develops a needed MCM, can also be effective. Direct incentives have been used successfully both at the national and now international levels. CEPI, a global partnership among public, private, philanthropic, and civil society organizations, has created financial pull incentives to bring multiple candidate vaccines for certain emerging infectious diseases through an intermediate (phase IIb) level of development. By stopping at a specific development level and pursuing further development as threat analyses change, a layered-security approach to threats could be pursued in a less costly manner versus full-development through licensure.

Policy and regulatory approaches of countries, especially those relating to intellectual property rights, can be tremendously influential on investment decisions by the private sector. Regulations that predictably protect the intellectual property rights of companies provide an incentive for investments in innovation, facilitate exports to other countries in need, and can lead to technology transfer to importing countries. Research and development of MCMs is a long-term, uncertain, and extremely expensive endeavor. (Some estimate an average of 15 years and US\$1.4 billion.<sup>120</sup>) Robust and transparent regulatory and policy regimes, as well as political stability, can help to minimize investment risk for the private sector.

## Nonpharmaceutical Interventions

As has been demonstrated in recent events such as Ebola and 2009 H1N1 pandemic, national governments and responding agencies may seek to employ nonpharmaceutical interventions (NPIs) in disease outbreaks, either in coordination with available medical countermeasures or, in the absence of developed vaccines and therapeutics, as the primary measure to prevent or slow down disease spread. NPIs principally aim to limit the degree to which exposure to ongoing infectious disease threats can occur, both at the individual and community levels.

The degree to which NPI measures will be effective at preventing or limiting transmission of high-impact respiratory pathogens is uncertain and will largely depend on the context, timing, and epidemiology of the outbreak. In addition, the range of NPIs that might be called for in response to a high-impact respiratory pandemic ([see Box 8](#) for the most commonly considered) all differ considerably in terms of objectives, feasibility, costs, downside consequence, and evidence. In determining whether and how to implement NPIs, countries must assess each proposed measure on the following dimensions:<sup>121</sup>

1. **Epidemiologic assessment:** Do available data or experience suggest a specific NPI will work to prevent or slow transmission in a meaningful way?
2. **Logistical assessment:** Is the particular NPI measure feasible given available resources?
3. **Social, economic, and political assessment:** What are the possible unintended adverse societal consequences of a particular NPI?

### Box 8: Definitions of NPI

While NPIs cover a variety of measures, those that might be most likely to be considered or called for in the setting of a pandemic caused by a high-impact respiratory pathogen include: travel restrictions, movement restrictions, quarantine, and social distancing.

**Travel restrictions** refer to enforceable limitations on travel but should not be confused with travel alerts or notices, which provide information for travelers on ongoing health events.

**Movement restrictions** are measures implemented to prevent or limit contact between infectious individuals and susceptible populations, ranging from limits on how or where an individual can travel to full quarantine.

**Quarantine** is a separation of potentially infectious individuals from susceptible populations. It is often confused with isolation, which refers to separating individuals known to be transmissible (typically implemented in a health facility). Though isolation is routinely used in healthcare and public health practice, the use of quarantine is rare and has been controversial.

**Social distancing** covers an array of measures aimed at reducing contact between members of the community that could potentially result in disease transmission, including closing schools, canceling mass gatherings, facilitating remote- or tele-working, and suspending mass transit operations.

A multitude of factors will likely determine how effective NPIs will be, such as the size and geographical range of the outbreak, the specific pathogen, the timing of the outbreak, and the country of occurrence. For example, studies have found that travel restrictions would be less effective once a disease has spread to multiple geographic areas or been introduced to large cities. Additionally, studies show that travel restrictions may have some impact for mild to moderately transmissible pathogens (such as SARS).<sup>122</sup> For highly transmissible pathogens, travel restrictions may only slightly delay the epidemic peak, and the total number of cases would ultimately experience no significant change.<sup>123</sup> While travel restrictions would be unlikely to prevent or substantially slow regional or international transmission of infectious diseases, these measures are commonly used by countries in response to international outbreaks.<sup>10,123-127</sup> In recent events such as the 2009 influenza A H1N1 and Ebola in West Africa, many countries implemented travel restrictions, despite evidence that such measures would likely not help. In some instances, these measures have hindered international efforts to contain disease spread.<sup>128</sup>

In the context of a high-impact respiratory pathogen, quarantine may be the least likely NPI to be effective in controlling the spread due to high transmissibility. To implement effective quarantine measures, it would need to be possible to accurately evaluate an individual's exposure, which would be difficult to do for a respiratory pathogen because of the ease of widespread transmission from infected individuals. Quarantine measures will be least effective for pathogens that are highly transmissible, have short incubation periods, and spread through true airborne mechanisms, as opposed to droplets. As with travel restrictions, quarantine appears to delay the introduction of highly transmissible diseases but not prevent their spread entirely. Quarantine measures also appear more effective with pathogens that had a longer incubation period, such as measles, compared to those with shorter incubation periods, such as influenza.<sup>123</sup> Experiences with quarantine during the West Africa Ebola epidemic highlight the added difficulty of implementing such measures on a large scale, which would only be more difficult in the case of a highly transmissible respiratory disease.<sup>129</sup>

NPIs often require addressing additional considerations or challenges to implement. For example, quarantine requires strict adherence to be effective, so it works best when government has a track record of successful implementation. Quarantine also requires a high level of public cooperation and adherence. Quarantine measures also require a high level of public cooperation and adherence. Quarantine measures also require a high level of public cooperation and adherence.

Monitoring and enforcing some of these NPI measures would be quite difficult if not impossible, due to the inability to fully monitor large communities and address noncompliance issues. In pandemic conditions when leaders are under great pressure to act, NPIs could be employed in inappropriate circumstances or have serious secondary or tertiary consequences that could themselves hinder outbreak response efforts. For example, travel restrictions could potentially hinder response efforts, as they could slow or prevent the transportation of personnel or materials. They would place additional economic burdens on the affected country, as the restrictions could hamper or stop their ability to trade. The disruption of normal activities such as schools closing may result in children congregating elsewhere, thus making social distancing efforts irrelevant. Quarantine efforts could be highly disruptive to societies and economies if they are implemented for prolonged periods.<sup>121</sup> In the response to government efforts to quarantine apartment complexes in Hong Kong during the SARS response, inhabitants of those buildings fled before authorities arrived, increasing risk of spread and driving the disease underground.<sup>130</sup>

NPIs would be highly likely to be considered or used by countries during a high-impact disease outbreak for a number of reasons. If there are no available medical countermeasures, NPIs may be viewed as the primary intervention to contain and control the event. NPIs such as travel restrictions have also been employed by countries as a political or social measure to abate fear rather than a necessary public health measure. While national public health guidelines generally recommend NPIs during an outbreak to limit contact frequency between individuals and to decrease the potential risk of spread of respiratory pathogens, there is a broad lack of evidence of efficacy and a lack of understanding about secondary adverse impacts. It is necessary to further study the effectiveness of NPIs in a variety of contexts to ensure that they are employed properly with a strong evidence base, and that the value of taking any specific NPI intervention in a particular pandemic setting is not outweighed by the potential harm. It is important to communicate to political leaders the absence of evidence surrounding many NPI interventions and the adverse consequences that may follow them.

## **Accidental Release and Biosafety**

Biosafety encompasses lab infrastructure, PPE, and laboratory protocols; these are the tools and practices designed to protect laboratory workers and the environment from infection escaping from the laboratory. Laboratory-acquired infections (LAIs) occur from occupational exposures to pathogens to those working in a laboratory. LAIs not only affect the health of the individual researcher but also pose a risk to the broader public health, as LAIs are a mechanism for accidental release of pathogens into the environment. This is especially troubling when the pathogen in question is not endemic to the area or when

there are few or no countermeasures or treatments. And it would be of potentially extraordinary consequence, even pandemic consequence, if a lab infection with a high-impact respiratory pathogen led to human spread outside the laboratory.

Good biosafety practices substantially lower the risk of a pathogen escaping the laboratory via contaminated clothing, items, or skin, and they seek to ensure pathogens are contained during transportation. The 2 most widely used resources for biosafety are WHO's *Laboratory Biosafety Manual* and the US CDC's *Biosafety in Microbiological and Biomedical Laboratories* (BMBL) handbook.<sup>131,132</sup> These documents outline how to categorize risk groups for pathogens, which then determines which biosafety precautions are necessary for working with that agent. The JEE tool also includes a section on biosafety and biosecurity, including minimum requirements of strong biosafety systems.<sup>66</sup> These requirements primarily focus on training and a whole-government approach to handling biosafety and biosecurity.

There are 2 different approaches to biosafety in laboratories, one relying primarily on infrastructure, such as biological safety cabinets, and the second primarily emphasizing PPE. Each national government is responsible for promoting a particular approach, which will determine both how resources are allocated for biosafety and what protocols are used in a laboratory in that nation. Many pathogens that spread via respiratory transmission or aerosols would be considered a Risk Group 3, which requires a Biosafety Level 3 laboratory. In a country that prioritizes engineering controls, laboratory staff may not be required to wear respirators while working in a laboratory that houses these easily aerosolized pathogens. When relying on engineering controls, regular maintenance of laboratory equipment, such as biological safety cabinets and venting systems, is vital to prevent the accidental release of a laboratory organism. In a country that emphasizes PPE, any personnel entering a laboratory space that works with such agents will have to wear respiratory protection and be trained regularly in appropriate biosafety procedures.

Biosafety has often been perceived as not sufficiently important to afford resources necessary for training, oversight, equipment, standards, and other mechanisms to protect the laboratorians' and the public's health. This has happened in lower-income countries but also in high-income countries. It has been demonstrated repeatedly that accidents—whether in biomedical laboratories or in other highly technical spaces—can cause significant political and social problems, often with lasting consequences to research and operations. These events are believed to be considerably underreported due to lack of reporting mechanisms and potential consequences to the researchers or research institution. There are no widely accepted international biosafety norms or national model programs for countries that permit research labs to do experimental work on high-impact respiratory pathogens. There is a need to agree on and strengthen norms surrounding



oversight and approval of research around novel high-impact respiratory pathogens, laboratory accident reporting, biosafety instruction, accreditation, and requirements for biosafety oversight, and these steps require funding and political commitment.

## **Deliberate Use and Biosecurity**

When considering the possibility of a deliberate release of a novel high-impact respiratory pathogen, the exact properties of the pathogen and its transmission dynamics would be uncertain, ranging from synthesis of a known virus to the creation of an engineered strain with highly unexpected properties. Deliberate release scenarios are more complex than natural epidemics because they would be initiated by an attacker who chose where and how to attack for a purpose.<sup>133</sup> The objectives of such an attack would have an impact on the outcomes of the event above and beyond the properties of the pathogen itself in the sense of where and how the pathogen was disseminated.

Deviation from a natural pattern would be expected even if no engineered or altered traits had been introduced into the pathogen. For example, its release might be coordinated across locations and timepoints, such that traditional outbreak response efforts could become misguided or overwhelmed. Risk would not be determined solely by epidemiology and exposure risks. Higher doses of pathogens could create more fulminant manifestations of a disease. Deliberate attacks might also target the emergency responses and critical services that a country would use to respond to the resulting epidemic. Countries and international organizations should not assume that preparedness for a naturally occurring outbreak equates to preparedness for a deliberate release event. Special attention should be given to plan and prepare for such deliberate events.

Earlier national and international experience with biological weapons and bioterrorism predates the synthetic biology revolution. Over the past decade, technology has made it increasingly straightforward to alter the genetics of a pathogen. Some RNA viruses may particularly lend themselves to natural pandemic spread,<sup>15</sup> but they are currently hard to engineer, particularly with trans genes.<sup>134</sup> It is reasonable to predict that the barriers to such engineering will decrease in the future. Rapid advances in synthetic biology capabilities, such as nucleic acid synthesis, increase the possibility that pathogens could be engineered to meet specific objectives of a sophisticated attacker.

Advances in synthetic biology capabilities have driven innovation in the life sciences and created novel capabilities and novel risks. One such capability is nucleic acid synthesis, which has enabled the creation of new therapeutics. However, one research team demonstrated the possibility of utilizing this technology to create the horsepox virus (closely related to smallpox) from scratch.<sup>135</sup> Although these were leading researchers with good



intentions, their published results demonstrated the mechanism for creating orthopox virus without accessing the 2 known highly restrictive smallpox reserves in Russia and the United States.

To prevent the misuse of synthesis technologies, an industry organization called the International Gene Synthesis Consortium (IGSC) has developed shared practices for the screening of sequences and of customers, and IGSC companies comprise 80% of the total gene synthesis market. However, to date, only the United States has guidance for screening of gene synthesis products, and no country actively encourages their research institutions and researchers to preferentially use the services of IGSC companies or other companies that perform screening.

The BWC is the oldest international treaty that bans an entire class of weapons. Of importance in this regard, the United Nations Secretary-General's Mechanism (UNSGM) provides an international body of evidence to determine whether a deliberate event has occurred. The UNSGM is convened at the Secretary-General's discretion. While this capability exists on the international level, and its effectiveness is often called into question, there are few similar mechanisms for reporting at lower levels of government or private industry.<sup>136,137</sup> It is often unclear how suspicions of a crime can be reported by a life sciences practitioner. In many cases, law enforcement would not have the biological research knowledge to appropriately evaluate concerns, which would discourage reporting. To counteract that, law enforcement agents and life scientists need to cultivate stronger relationships with each other so that suspicious activity may be reported and potential crimes prevented. Intelligence officials also need a better understanding of biological risks to enhance prevention. Communication, data sharing, outreach, and coordination are key capabilities for a country to be able to manage an effective response to any fast-moving epidemic. This is even more important in the case of a directed release scenario in which one can presume that the attacker will be deliberately eroding such capabilities as part of a broader objective.

It may be possible to provide partial deterrence of deliberate events by establishing attribution tools and methods that would support the potential identification of the responsible actor. Even if such capability is underdeveloped, the potential for attribution may change the perceived risk of developing and deploying such a weapon for some actors. Not all deliberate use cases are equally subject to deterrence, because some motivations may outweigh concerns of being identified. Effective deterrence would require that a potential actor is aware of attribution capabilities and persuaded that governments or the international community would respond to the attack.

In recent times there has been growing attention to deliberate use scenarios, including tabletop and simulation exercises, to provide lessons and recommendations for responding to a deliberate biological event. While many exercises call for the strengthening of the UNSGM and the identification of the organizations that would be involved in any aspect of a response, including the public health response and investigation and attribution, there is still a leadership deficit. Of particular note, a tabletop exercise hosted by the Nuclear Threat Initiative, Georgetown University, and the Center for Global Development at the 2019 Munich Security Conference called for the establishment of a “permanent facilitator and/or unit [within the UN] devoted to coordinating the response to deliberate, high-impact, or unusual biological events.”<sup>37</sup> While the increasing interest in preparing for a deliberate event is positive, these exercises highlight the lack of current preparedness for such an event.

## CONCLUSIONS: STRENGTHENING PREPAREDNESS FOR A HIGH-IMPACT RESPIRATORY PATHOGEN PANDEMIC

### 1. Countries should build up their national core public health capacities.

Countries should continue to build and improve core public health capacities across the globe. While these capacities cannot fully prepare countries or the international community for high-impact respiratory pandemic events, they provide fundamental structure, planning, and workforce for outbreak detection and response and are critical underpinnings for additional capacities that are needed. Member States should continue to endorse JEE assessments and to ensure that WHO has the resources it needs to continue to play a coordinating role. Those countries that have not yet agreed to take part in JEEs should be encouraged by WHO and pressured by allies to do so. But the JEEs should be viewed as only the start of a process that is ultimately meant to result in improvements being made. Once countries identify gaps in their core capacities, it is essential that they commit to addressing them. Countries should then develop, cost, and finance national action plans to improve their core capacities and conduct exercises to test the extent to which capacities will function as planned during emergencies. Special attention should be paid to ensuring action plans are sustainable and the national and regional financial mechanisms used are maintainable over a number of years. This will ultimately require national resources, in addition to donor funding that may be available.

As countries work to develop core public health capacities in fulfillment of their domestic and IHR obligations, it is important that they evaluate the functionality of these capacities. Risk-specific exercises (eg, pandemic influenza, Ebola) and after-action reports following actual events are important for examining how capacities worked or are likely to work, and the results from these evaluations should be compared to JEEs and national action plans. Results should be used to update, modify, or enhance ongoing capacity development efforts.

Countries and WHO should continue to work to ensure that core capacity strengthening is viewed as a matter of priority by leaders. National budgets should reflect a commitment to capacity development. Donors should work with countries to address remaining shortfalls and to incentivize additional national investments. Member countries and WHO should support and actively participate in initiatives, such as the Global Health Security Agenda and the Alliance for Health Security, which help to normalize national and multinational actions to strengthen core capacities provide a convening platform for national leaders to maintain momentum toward IHR capacity building and to share lessons learned.

Data will be essential to motivate political leaders and measure progress. Additional sources of data should be sought by WHO and the GPMB that could provide ongoing assessment of global progress towards IHR capacity development, particularly in light of the current JEE timetable, which will likely require 5 or more years before countries can undergo a second JEE. The World Bank has suggested that the development of preparedness indices could help fill this gap.

## **2. National and global surveillance capacities should be improved, with a focus on helping improve the management of epidemic response.**

Even the most robust public health surveillance systems are unlikely on their own to provide sufficient information to inform the wide range of decisions that would need to occur during an epidemic or pandemic response. A key limitation in national and international surveillance systems will be their inability to fully monitor the impact of events and to support real-time decision making about the availability and mobilization of resources needed to help control the spread. Lack of fast data exchange between health facilities and public health in most countries would slow or limit understanding of key aspects of the epidemic, including what percentage of cases develop severe illness or die, what populations are proving most at risk of the disease and at risk for dying, and how healthcare systems are coping with caring for the sick. Data from the private sector will also be an important part of the full picture needed to understand the near-term impacts of events and identify and monitor availability of resources that are needed (eg, medical supplies) to support the response.

If a pandemic were initiated by a deliberate event, countries and the international community would need to have in place agreements about what information needs to be shared. To answer questions about the source of an attack and the risks of subsequent ones will likely require data found outside of the health sector. This process may be quite challenging, because nations' security concerns may limit the degree to which affected and nonaffected countries are willing to share information.

Regardless of whether a high-impact respiratory pathogen occurs as the result of nature, accident, or deliberate use, there is great need for new surveillance technologies. Where appropriate and feasible, countries, philanthropies, and other international organizations should continue to encourage the uptake of molecular diagnostic testing for respiratory pathogen nucleic acids—specifically, simple, point-of-care, multiplex devices. Additionally, the development and increased use of new diagnostic tools, particularly those that can be used outside of traditional laboratories, could increase the capacity and

speed with which highly specific surveillance data become available. The development and fielding of technologies that could facilitate tracking of patients on a large scale would help to improve preparedness for outbreaks, epidemics, and the early stages of a pandemic.

### **3. Frameworks for sample and benefit sharing need to be developed that apply to high-impact respiratory pathogens beyond influenza.**

The PIP framework represents a milestone arrangement among WHO Member States, public health, industry, and other stakeholders by promoting access to influenza viral samples and epidemiologic data and ensuring that the benefits derived from samples and information are more equitably distributed around the globe. The framework is based on the principle of reciprocity and mutual interests, such that governments and industry all benefit from the agreement. Participation in the PIP framework has also strengthened the global network of influenza surveillance, including laboratory capacity building, the GISRS surveillance system, and national influenza centers. Despite general agreement on the principles of the framework, implementation has come under criticism by some for slow cross-border coordination, legal restrictions, and other impediments that limit the speed of viral sample sharing. It remains to be seen whether the PIP framework will remain relevant if countries do not conform by continuing to share specimens and if partnership contributions, including vaccines and other MCMs, from industry are not delivered to countries during emergencies in a timely manner. Ongoing issues surrounding advances in biotechnology (ie, sharing genetic sequencing data as a substitute for the physical virus) and the public health implications of the Nagoya Protocol to the CBD will also need to be addressed.

There are also serious questions over the continued adherence to the framework during a high-impact influenza pandemic. In such an event, the slightest delay in sample sharing can potentially translate to significant global harm. Countries may be tempted to withhold samples in return for financial gain or other reward, while manufacturers may be pressured by national governments to reserve vaccines and diagnostic tools for domestic use. Pharmaceutical and diagnostic industry leaders will need to continue to participate via annual partnership contributions and follow through on their commitments to provide a percentage of product to PIP countries. Physical specimens and genetic sequencing data, will need to be shared promptly with developers. Yet, it is also the case that even with the PIP framework in place, the global quantity of medical countermeasures that can be produced quickly would fall short of the anticipated global demand during a severe pandemic influenza.

A significant concern is that the PIP framework and accompanying surveillance systems and capacity-building measures have focused solely on pandemic influenza. While some of these capacity-building measures (eg, laboratory capacity) are cross-cutting, other high-impact respiratory pathogens have not received a commensurate level of international attention, focus, and resources, despite their potential to cause significant harm. Difficult past experience in transferring Zika and Ebola virus specimens across borders have underscored continued challenges in countries' abilities and/or willingness to sharing specimens in the middle of a crisis. Delays of this kind would have even greater consequences for a high-impact respiratory pathogen, such as a novel coronavirus. As the bilateral negotiations during the H1N1 pandemic in 2009 revealed, these negotiations are often fraught and time-consuming and unsuitable to carry out during an emergency.

Pre-event negotiations could facilitate the rapid sharing of samples and epidemiologic data when a deadly new strain emerges, as well as the subsequent distribution of benefits across the globe, potentially saving millions of lives. More pre-event planning and negotiations are needed on the part of WHO Member States, public health, and industry to develop and prepare contractual agreements on the fundamental questions of access and benefit sharing for noninfluenza pathogens. It remains to be seen whether such a framework (or frameworks) should be modeled on PIP or whether an alternative mechanism is required. Frameworks will need to take into account the emergence of a broad range of respiratory pathogens with high-impact potential. Frameworks should be based on the principle of reciprocity and mutually reinforcing interests and conducted in collaboration with WHO Member States, industry, and civil society.

#### **4. Countries and WHO need to assess and improve health systems' readiness for infectious disease emergencies.**

To adequately prepare for and respond to outbreaks and pandemics of respiratory diseases, countries should assess the readiness of health facilities to effectively treat patients with a transmissible disease with high case fatalities. Health facilities would play a central role in mitigating or amplifying disease spread during communicable disease emergencies, but they have not been central to national efforts to develop core capacities to detect and respond to infectious disease emergencies. While the JEE provides for countries a well-defined list to assess the availability of core capacities, there has not been a similar international effort to define and evaluate the capacities for national health systems, and facilities need to respond to health emergencies, particularly infectious disease emergencies. WHO should work with member countries to develop a corresponding assessment tool for health systems and facilities, so that countries have a means of assessing the readiness of the broader health sector for infectious disease emergen-

cies. These efforts should be aligned with countries' ongoing work to undergo JEEs and to advance universal health coverage and to improve the quality of care that is delivered at health facilities.

WHO should lead an expert-informed process to develop technical guidance to inform the clinical management of patients with highly contagious respiratory diseases during a severe outbreak. This guidance should include recommended PPE, treatment courses, disinfection guidelines, and personnel training. Additionally, health systems may need guidance for allocating scarce resources, such as mechanical ventilators and medications, if the demand exceeds available supply. Given differences in countries' health systems, this guidance may need to be tiered for low-, medium-, and high-resource settings.

Countries should work to establish mechanisms for bi-directional information exchange between frontline healthcare providers directly treating patients and experts at external organizations, such as a national center for disease control or public health institute, who can provide critical subject matter expertise and guidance. Countries wishing to access additional clinical expertise should explore the feasibility of plugging into international networks. For example, the WHO Emerging Diseases Clinical Assessment and Response Network provides subject matter expertise—including from WHO, NGOs, and academic institutions—to frontline providers for the clinical management of patients with emerging infectious diseases. The success of these types of networks depends on the existence of mechanisms for frontline healthcare providers to relay clinical information to subject matter experts, and for those experts to quickly gather, analyze, and compile relevant information from multiple sources to devise best practices. National and/or international systems would be needed to turn this into clinical guidance that could be broadly disseminated to frontline providers and public health practitioners.

Partnerships between public health officials and healthcare leaders should not be established ad hoc during a crisis but should be routine in advance of future emergencies. An incident command/incident management system (ICS/IMS) should be established at local, state/provincial, and national levels to help broadly coordinate a response. Additionally, emergency operations centers (EOCs) at national and local levels would be needed to coordinate efforts between public health and health services delivery organizations, and ideally these plans should be trained and exercised routinely.

Countries should plan for the possibility of there being interruptions in the availability of essential basic supplies and equipment. Health facilities would need plans for continuing operations in the event that supplies are no longer available from their primary sources. Countries with sufficient resources should consider establishing stockpiles of critical or



high-volume products, including at the facility, local, regional, and national levels. These stockpiles would ideally include not only basic supplies, such as IV tubing and fluid, but also disease-specific supplies, such as PPE (eg, gloves, surgical masks, N95 respirators, powered air-purifying respirators, or PAPRs), and medical countermeasures (eg, antivirals, antibiotics, vaccines). These stockpiles would help to ensure that facilities are self-sustaining during a protracted public health emergency. Other critical logistics and infrastructure—including plans for maintaining access to critical medical gases (eg, oxygen, nitrogen), clean water, electricity, data and telecommunications, and sanitation services during a widespread pandemic—should be ensured or developed. Global or regional stockpiles with operational plans for deployment and sharing may be needed to assist countries that are unable to afford or maintain individual stockpiles.

## **5. Countries and international health authorities should more fully incorporate community engagement and social science in preparedness.**

International guidelines should be developed that demonstrate specific clear use cases for community engagement in the context of a potential high-impact respiratory pathogen outbreak. A rich library exists of general guidance on community engagement as well as its applications to specific public health issues, including Ebola and Zika outbreak management. Despite that, community engagement is underappreciated as a core health security capability. To operationalize what many still consider to be an intangible or vague objective, WHO should develop guidance—via a multidisciplinary consultation and drawing on WHO’s CEQ model—that illustrates concrete use cases for community engagement before, during, and after a potential severe outbreak of a high-impact respiratory pathogen, including reduction of an outbreak’s social and economic—and not just health—effects.

Community engagement has been recognized as a vital part of disease outbreak response efforts, a sentiment that was strengthened after the 2014-2016 Ebola outbreak in West Africa. However, little has been done to implement community engagement into national preparedness planning and mechanisms. Building trust within communities takes time but is necessary to strengthen the response effort. If initial outreach and engagement occurs before a disease outbreak, relationships that are built and strengthened could be leveraged during response efforts, which could in turn mitigate community resistance and other factors that may hinder or complicate a response. By ensuring local stakeholders are involved in decision making and preparedness planning, countries can develop more inclusive plans over which community leaders can take ownership. The kind of community engagement used to help prepare for smaller outbreaks or expected

disease events could also be used to help plan for and consider larger ones like pandemics with high-impact respiratory pathogens. This way, community engagement efforts could be put to routine benefit.

When designing or refining systems to prevent, detect, respond to, and recover from major outbreaks, social scientists should be consulted on potential community-level chokepoints and sites for cooperation. National health authorities and multilateral health organizations should develop and utilize their social science research capacities further. Attuned to social context, using people-centered methodologies, and leveraging in-depth knowledge of specific communities and regions, social scientists can serve as important advisors on and enablers of community engagement in the context of a high-impact infectious disease outbreak. Local cultural beliefs and practices were often presented as barriers to the swift, effective control of the Ebola outbreak in West Africa. Yet, community engagement exercises specific to pandemic influenza planning have also shown how cultural values (eg, Maori concepts of solidarity, neighborliness, mutual aid) can be leveraged for greater preparedness. Social scientists, and anthropologists in particular, can help with meaningful reframing of public health objectives in locally relevant terms and practices.

## **6. Countries and WHO should develop and exercise plans for risk communication during high-impact respiratory events.**

Risk communication should continue to be prioritized as an important response element on par with other public health efforts. WHO should establish a standing communications advisory committee to elevate both the prioritization of and the capacity to implement timely, accurate, and effective communication. Risk and crisis communication with the public and key partners should be included as a key component of infectious disease response, on equal footing with other response components such as medical surge, medical countermeasure development/manufacturing/distribution, and surveillance. By acknowledging the need for and prioritizing risk communication early, other aspects of the response will likely encounter fewer barriers and challenges.

Dedicated efforts to build public trust in local public health workforces and collaborations with influential partners before, during, and after crises should be made. Public trust is an essential component of effective communication. Yet, this is not something that can be delivered “just-in-time.” WHO has noted the importance of public trust and community engagement, and it should keep moving forward on this with a commitment to long-term building of public trust and partnerships. Partnerships with well-respected community members who are able to engage with other local residents in culturally

competent ways can also be critical for facilitating effective response activities. These communication channels and relationships must be set up ahead of an emergency in order to be effective communication conduits during a crisis. Communication during the response to a high-impact respiratory pandemic would be affected by the way that communication works during smaller, more routine responses.

Communication frameworks and practices to use distributive information networks should be modernized, moving beyond a command and control model. Communication has changed rapidly in the past decade, toward a more decentralized and distributive process of transferring information and ideas. International public health response has struggled to evolve to fit an environment of rapid exchange of information, misinformation, and disinformation. In order to be truly effective in global public health response, WHO will need to keep up with shifting communication approaches and technologies, to embrace new ways and trends around communication. WHO will likely need to commit significant resources and political capital to invest in these leading-edge communication technologies and approaches.

## **7. R&D aimed at rapid vaccine development for novel threats and distributed surge manufacturing should be a top global pandemic planning priority.**

### **MCM Research and Development**

There are a range of promising approaches to accelerate rapid vaccine development that should be concomitantly pursued and funded, given the uncertainty in knowing which might bring the most important leaps forward. Traditional vaccine development through big pharma and biotech companies will continue for now to be the backbone of the field. Organizations like CEPI will help to accelerate the development process for vaccines that have already been identified as priorities by WHO. Nucleic acid (RNA and DNA)-based vaccines are widely seen as highly promising and potentially rapid vaccine development pathways, though they have not yet broken through with licensed products. In addition, advancements in non-nucleic acid-based platform technologies offer some hope of improving the speed with which vaccines for novel pandemic threats are developed and should be expanded. Contemporary advances in sequencing and structure function analysis—aided by AI and big data analytic approaches—are yielding improvements in both speed and precision of immunological design and should be supported. Similar gains are evident in the antimicrobial arena; as machine learning enters the drug discovery field, approaches to identifying appropriate targets for microbial control are shortening the times to leads and subsequent sensitivity and specificity studies. Academic institutions, national governments, the biopharmaceutical industry, international organizations, and

other stakeholders should be fully engaged in this effort, and accelerating vaccine development for rapid creation of a vaccine in the setting of a novel high-impact respiratory pathogen should be seen as an explicit, organized, highly funded top global goal.

### **Distribution and Dispensing**

Mass vaccination strategies should be developed and put in place to increase immediate access. Once a safe and effective vaccine has been developed and is ready to be manufactured at scale, approaches to delivering and administering MCMs will also need to scale, and scale rapidly. A standing collaboration among international organizations, national governments, and the private sector will be needed in order to enable and coordinate global distribution to ensure maximal effectiveness and equitable access. In addition, the uptake of novel, needle-free administration technologies, specifically those that enable either simplified or, potentially, self-administration, should be a priority to improve our collective ability to administer these countermeasures in clinically relevant timeframes. For example, several different routes of administration, including the oral, nasal, patch, and intradermal routes, offer the potential for both more robust immune responses and the ability to more rapidly achieve population-level coverage.

Industry, national regulatory bodies, public health authorities, and other stakeholders should invest in and promote the use of technologies that enable a rapid, streamlined approach to the administration of MCMs. Furthermore, WHO should encourage and support the creation of a public-private partnership dedicated to planning for and executing the prioritization and distribution of MCMs in a severe outbreak.

### **Surge Manufacturing in Crisis**

National and international regulatory requirements need to be prepared and coordinated to enable rapid production of MCMs. Many countries maintain their own paradigm for pharmaceutical regulation, and significant regulatory challenges are associated with deconflicting the regulatory processes across countries. In addition, many countries lack tools to limit manufacturer liability during a crisis. These complexities will slow international MCM deployment and thereby impede efforts to control an outbreak as it begins to spread around the world.

WHO helps coordinate activities across the essential regulatory bodies, including the FDA, the National Institute for Biological Standards and Control in the UK, and the Therapeutic Goods Administration in Australia. This coordination covers, for example, standardization of vaccine reagents that can be used across jurisdictions. While this cooperation is critical, regulatory differences across borders still delay MCM deployment during major outbreaks now and would in a pandemic given current conditions. A number of adaptations could be put in place to reduce the time to approval. For example, agencies

should consider regulating some platform technologies by platform, rather than by product. The relevant regulatory bodies, global authorization agencies, and public and private manufacturers should develop and exercise response plans. In addition, national regulatory agencies should establish mechanisms dedicated to decreasing timelines associated with regulatory requirements for MCMs in emergencies, while continuing to ensure safety and efficacy. WHO, industry, national regulatory bodies, and other stakeholders should work together to enable and radically increase MCM surge production and access globally through localized distributed manufacturing. Given the current geographic disparities in where such production and manufacturing efforts are conducted, access and benefit-sharing agreements will be needed.

### **Other Research and Development**

During an event involving a high-impact respiratory pathogen, there will be a critical need to conduct research to inform the response. Clinical research is needed to inform the development of medical countermeasures and to understand what medical interventions are likely to improve survival. There has been important progress in facilitating the conduct of emergency clinical trials, though more work needs to be done to prepare to do them in very difficult conditions and rapidly. Operational research is also needed to inform public health response questions, such as, “What intervention and communication strategies work best to limit transmission?” The absence of dedicated mechanisms to facilitate operational research during outbreak responses can result in a failure to consistently and systematically collect and analyze the valuable, ephemeral data that are crucial for improving outbreak response. During a public health crisis, limited public health and healthcare resources must be dedicated to performing response activities rather than conducting research efforts. Therefore, additional resources and pre-event planning will be needed to ensure that high-priority research can be conducted without impeding response efforts. WHO, member countries, and philanthropies should develop dedicated resources and plans for the conduct of operational research during outbreaks, epidemics, and pandemics. Pre-identified networks of researchers could help facilitate and prioritize research that is conducted.

## **8. Frameworks and plans articulating the evidence and role for nonpharmaceutical interventions need to be established.**

In contagious disease emergencies, particularly those for which MCMs are not available, countries will be inclined to use NPIs to limit spread. Guidelines from public health authorities such as WHO exist regarding the use of NPIs, but they do not provide sufficient information to guide the appropriate use of these measures. There is a need to explicitly identify in which contexts NPIs should be used, in which contexts they should

not be pursued, and what the negative consequences of use may be. There is great diversity of outbreaks, from the pathogen to the geographic setting, size, and epidemiologic characterization, and specific NPIs might work in one setting but fail in another. This would be particularly true in the midst of a high-impact respiratory pandemic, given that a number of potential NPIs would not logically be of any value for containment in those conditions. Countries and international organizations need to better analyze the potential value and impact of NPIs, determine where a particular NPI would be effective, and conclude in which contexts they are likely do more harm than good. NPIs would have a greater likelihood of being implemented effectively if they were well analyzed ahead of time than if considered ad hoc in the midst of a crisis.

Public health authorities should provide this risk/benefit analysis regarding NPIs to decision makers before NPIs are initiated in a crisis. During an emerging outbreak with a novel pathogen for which no medical countermeasures will exist, countries may need external guidance regarding the implementation of NPIs to contain or slow the outbreak. WHO should retain the capacity to rapidly provide this critical guidance, driven by scientific evidence where it exists. In some cases, implementation of some NPIs, such as travel restrictions and quarantine, might be pursued for social or political purposes by political leaders, rather than pursued because of public health evidence. WHO should rapidly and clearly articulate its opposition to inappropriate NPIs, especially when they threaten public health response activities.

Many NPIs, particularly those falling under social distancing, require support and acceptance by the public. As these measures inherently limit civil liberties by restricting individuals' movements, assembly, and social interaction, they can be a source of substantial opposition from affected individuals and populations. Providing strong evidenced-backed reasoning for the necessity of NPIs, including the predicted impact they will have in containing the outbreak, will be all the more crucial. WHO and national leaders will play a principal role in implementing NPIs and communicating the role and necessity of these measures to the public; therefore, they should collect and disseminate research to support their decision to use NPIs.

## **9. National governments should strengthen biosafety around high-impact respiratory pathogens.**

Biosafety needs to become a national-level political priority, particularly for countries that are funding research with the potential to result in accidents with pathogens that could initiate high-impact respiratory pandemics. All nations should be advised to adopt national-level comprehensive biosafety norms for research involving high-impact respi-



ratory pathogens. Countries that fund such research should have oversight systems in place that consider the risks and benefits of this kind of work, and they should have maximally stringent biosafety requirements for any laboratory that is allowed to pursue this type of research. WHO should develop stronger interest and capability in monitoring this kind of research and advising member nations about the risks and benefits surrounding it.

## **10. National governments need to prepare for the deliberate use of a respiratory pathogen.**

Any attacker that successfully deploys a bioweapon (as opposed to conventional weapons) should be presumed to have substantial biological scientific abilities, particularly if it is discovered that the pathogen has been engineered. If a bioweapon is used that causes a high-impact respiratory epidemic or pandemic, that would suggest a great degree of capability and sophistication in the attacker. Such an attacker might try to improve the chance of success by deploying the bioweapon simultaneously in multiple locations. It may be that such an attack is done without claiming responsibility, or without public notification that a release has occurred. Widespread dissemination of a bioweapon could overwhelm traditional outbreak surveillance and control efforts.

In the event of a rapidly moving respiratory epidemic or pandemic, governments, either on their own or with the help of other countries of WHO, would need to be able to quickly employ polymerase-chain reaction (PCR) and whole genome sequencing (WGS) of the pathogen, whether the epidemic was caused naturally or deliberately. These kinds of rapid diagnostics have been increasingly used to diagnose respiratory viral infections and so are increasingly familiar tools for diagnosing this class of diseases. WGS could additionally provide indications of whether the pathogen was engineered if it differs significantly from known wild-type forms in existing genetic databases like NCBI BLAST.

Countries should also support the adoption of synthesis screening approaches intended to identify research on high-impact respiratory pathogens. Such screening approaches should identify orthopox synthesis efforts, for example, and flag them for national authorities to review. Synthesis of coronaviruses and novel influenza strains should also require special review of the proposed work and the proposed buyer before approval. The US government provides guidance on synthesis screening. It is not a perfect approach for preventing the illicit synthesis of high-impact respiratory pathogens, because it focuses on the US select agent list, which does not necessarily include the viral components of greatest concern for this problem. More R&D and informatics will be needed to improve screening strategies for high-impact respiratory pathogens, but the US model provides a good start for now.



By building ties between law enforcement and the life sciences community, countries can foster connections between these 2 disparate sectors in anticipation of a deliberate event. Since it takes a significant amount of effort, skill, tacit knowledge, and laboratory equipment to develop a viable bioweapon, reporting by life scientists should be considered one of the first lines of defense against a deliberate event. Life scientists working in high-containment or government laboratories are often required to undergo dual-use research of concern (DURC) training; however, there are very few reporting mechanisms through which a concerned scientist can report the activities of a colleague to a superior without being worried about risking his or her career. There are even fewer clear mechanisms to connect the science and law enforcement communities if a scientist has substantial concerns that someone in her or his community is pursuing bioweapons development. A first step to cultivating this relationship is to create an appropriate and accessible method for life scientists and public health practitioners to report these kinds of concerns. In the United States, special investigators are trained to respond to bioweapons concerns that are reported to them. The framework of this program could be modified to suit different government structures.

Finally, a deliberate release event that results in a pandemic spread of a respiratory pathogen would require a high level of sophisticated coordination to bring the outbreak under control. One or 2 governments could not accomplish this effort without working in close concert with other governments and international organizations.

## REFERENCES

1. Schoch-Spana M. "Hospital's full-up": the 1918 influenza pandemic. *Public Health Rep.* 2001;116(Suppl 2):32-33.
2. Byerly CR. The U.S. military and the influenza pandemic of 1918-1919. *Public Health Rep.* 2010;125(Suppl 3):82-91.
3. Barry J. *The Great Influenza: The Story of the Deadliest Pandemic in History*. New York: Penguin Group; 2004.
4. Snyder MR, Ravi SJ. 1818, 1918, 2018: two centuries of pandemics. *Health Secur.* 2018;16(6):410-415.
5. World Bank says flu pandemic could cost \$3 trillion. CIDRAP. October 17, 2008. <http://www.cidrap.umn.edu/news-perspective/2008/10/world-bank-says-flu-pandemic-could-cost-3-trillion>. Accessed May 22, 2019.
6. World Bank Group. 2014-2015 West Africa Ebola Crisis: Impact Update. May 10, 2016. <http://www.worldbank.org/en/topic/macroeconomics/publication/2014-2015-west-africa-ebola-crisis-impact-update>. Accessed June 13, 2019.
7. International Working Group for Financing Preparedness. *From Panic and Neglect to Investing in Health Security: Financing Pandemic Preparedness at a National Level*. Washington, DC: World Bank; 2017. <http://pubdocs.worldbank.org/en/890291523304595565/FINAL-3t-5b70DQJBR-BL-C-cesse-Ma.73,2dcgZJBR>

18. World Health Organization. Implementation of the International Health Regulations (2005): Report of the Review Committee on the Role of the International Health Regulations (2005) in the Ebola Outbreak and Response. Geneva: World Health Organization; 2016. [http://apps.who.int/gb/ebwha/pdf\\_files/WHA69/A69\\_21-en.pdf?ua=1](http://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_21-en.pdf?ua=1). Accessed May 24, 2019.
19. World Health Organization. Implementation of the International Health Regulations (2005): Report of the Review Committee on the Functioning of the International Health Regulations (2005) in relation to Pandemic (H1N1) 2009. Geneva: World Health Organization; 2011. [https://apps.who.int/iris/bitstream/handle/10665/3350/A64\\_10-en.pdf?sequence=1&isAllowed=y](https://apps.who.int/iris/bitstream/handle/10665/3350/A64_10-en.pdf?sequence=1&isAllowed=y). Accessed May 24, 2019.
20. World Health Organization. List of Blueprint priority diseases. <http://www.who.int/blueprint/priority-diseases/en/>. Accessed June 13, 2019.
21. Johns Hopkins Center for Health Security. Clade X Pandemic Exercise: Implications of Clade X for National Policy. Baltimore, MD: Johns Hopkins Center for Health Security; 2018. [http://www.centerforhealthsecurity.org/our-work/events/2018\\_clade\\_x\\_exercise/about-clade-x](http://www.centerforhealthsecurity.org/our-work/events/2018_clade_x_exercise/about-clade-x). Accessed June 13, 2019.
22. Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza. Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. *N Engl J Med*. 2010;362(18):1708-1719.
23. Adalja AA. Biothreat agents and emerging infectious disease in the emergency department. *Emerg Med Clin North Am*. 2018;36(4):823-834.
24. Paules C, Subbarao K. Influenza. *Lancet*. 2017;390(10095):697-708.
25. Fraser C, Riley S, Anderson RM, Ferguson NM. Factors that make an infectious disease outbreak controllable. *Proc Natl Acad Sci U S A*. 2004;101(16):6146-6151.
26. Pulliam JR, Dushoff J. Ability to replicate in the cytoplasm predicts zoonotic transmission of livestock viruses. *J Infect Dis*. 2009;199(4):565-568.
27. Centers for Diseases Control and Prevention. Vaccine for measles. Last reviewed June 13, 2019. <https://www.cdc.gov/measles/vaccination.html>. Accessed June 18, 2019.
28. Perry R. Measles. In: Heymann DL, ed. *Control of Communicable Diseases Manual*. 20th ed. Washington, DC: American Public Health Association; 2015:389-397.
29. World Health Organization. Measles. May 9, 2019. <https://www.who.int/news-room/fact-sheets/detail/measles>. Accessed June 3, 2019.
30. Wallace G, Leroy Z. Measles. In: Hamborsky J, Kroger A, Wolfe S, eds. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 13th ed. Washington, DC: Centers for Disease Control and Prevention, Public Health Foundation; 2015. <https://www.cdc.gov/vaccines/pubs/pinkbook/meas.html#diagnosis>. Accessed June 3, 2019.
31. Naim HY. Measles virus. *Hum Vaccin Immunother*. 2015;11(1):21-26.
32. McClure CC, Cataldi JR, O'Leary ST. Vaccine hesitancy: where we are and where we are going. *Clin Ther*. 2017;39(8):1550-1562.
33. Omer SB, Bednarczyk R. Measles was eliminated. But we can't be sure it'll stay that way. *Washington Post*. February 11, 2019. <https://www.washingtonpost.com/outlook/2019/02/11/measles-was-eliminated-we-cant-be-sure-itll-stay-that-way/>. Accessed June 3, 2019.
34. Boseley S. Measles cases up 300% worldwide in 2019, says WHO. *Guardian*. April 15, 2019. <https://www.theguardian.com/society/2019/apr/15/measles-cases-up-300-worldwide-2019-says-who-vaccination>. Accessed June 13, 2019.
35. Lamb E. Understand the measles outbreak with this one weird number. *Scientific American*. January 31, 2015. <https://blogs.scientificamerican.com/roots-of-unity/understand-the-measles-outbreak-with-this-one-weird-number/>. Accessed 3 June 2019.
36. Belser JA, Tumpey TM. The 1918 flu, 100 years later. *Science*. 2018;359(6373):255.

37. Cameron E, Katz R, Konyndyk J, Nalabandian M. *A Spreading Plague: Lessons and Recommendations for Responding to a Deliberate Biological Event*. Washington, DC: Nuclear Threat Initiative; Georgetown University; Center for Global Development; June 2019. [https://media.nti.org/documents/NTI\\_Paper\\_A\\_Spreading\\_Plague\\_FINAL\\_061119.pdf](https://media.nti.org/documents/NTI_Paper_A_Spreading_Plague_FINAL_061119.pdf). Accessed June 15, 2019.
38. Davtyan M, Brown B, Folayan MO. Addressing Ebola-related stigma: lessons learned from HIV/AIDS. *Glob Health Action*. 2014;7:26058.
39. Samari G. Islamophobia and public health in the United States. *Am J Public Health*. 2016;106(11):1920-1925.
40. United Nations Security Council. Peace and security. <https://www.un.org/securitycouncil/>. Accessed June 13, 2019.
41. Hsu YC, Chen YL, Wei HN, Yang YW, Chen YH. Risk and outbreak communication: lessons from Taiwan's experiences in the post-SARS era. *Health Secur*. 2017;15(2):165-169.
42. Moon S, Sridhar D, Pate MA, et al. Will Ebola change the game? Ten essential reforms before the next pandemic. The report of the Harvard-LSHTM Independent Panel on the Global Response to Ebola. *Lancet*. 2015;386(10009):2204-2221.
43. European Parliament Committee on Development. Report on the Ebola crisis: the long-term lessons and how to strengthen health systems in developing countries to prevent future crises. Brussels, Belgium: European Parliament; 2015. [http://www.europarl.europa.eu/doceo/document/A-8-2015-0281\\_EN.html](http://www.europarl.europa.eu/doceo/document/A-8-2015-0281_EN.html). Accessed June 19, 2019.
44. World Health Organization. *Report of the Ebola Interim Assessment Panel*. Geneva: World Health Organization; 2015. <https://www.who.int/csr/resources/publications/ebola/report-by-panel.pdf?ua=1>. Accessed May 24, 2019.
45. World Health Organization. *Main Operational Lessons Learnt from the WHO Pandemic Influenza A(H1N1) Vaccine Deployment Initiative*. Geneva: World Health Organization; 2010. [https://apps.who.int/iris/bitstream/handle/10665/44711/9789241564342\\_eng.pdf?sequence=1&isAllowed=y](https://apps.who.int/iris/bitstream/handle/10665/44711/9789241564342_eng.pdf?sequence=1&isAllowed=y). Accessed May 24, 2019.
46. National Academy of Medicine; Commission on a Global Health Risk Framework for the Future. *The Neglected Dimension of Global Security: A Framework to Counter Infectious Disease Crises*. Washington, DC: National Academies Press; 2016.
47. United Nations. *Protecting Humanity from Future Health Crises: Report of the High-Level Panel on the Global Response to Health Crises*. January 25, 2016. [https://www.un.org/ga/search/view\\_doc.asp?symbol=A/70/723](https://www.un.org/ga/search/view_doc.asp?symbol=A/70/723). Accessed May 24, 2019.
48. United Nations. Report of the Global Health Crises Task Force. June 22, 2017. [https://www.un.org/ga/search/view\\_doc.asp?symbol=A/72/113](https://www.un.org/ga/search/view_doc.asp?symbol=A/72/113). Accessed May 24, 2019.
49. World Health Organization. Report of the Independent Oversight and Advisory Committee for the WHO Health Emergencies Programme. Geneva: World Health Organization; 2017. [https://www.un.org/en/pdfs/A70\\_8-en.IOAC.pdf](https://www.un.org/en/pdfs/A70_8-en.IOAC.pdf). Accessed May 24, 2019.
50. World Economic Forum. *Managing the Risk and Impact of Future Epidemics: Options for Public-Private Cooperation*. 2015. [http://www3.weforum.org/docs/WEF\\_Managing\\_Risk\\_Epidemics\\_report\\_2015.pdf](http://www3.weforum.org/docs/WEF_Managing_Risk_Epidemics_report_2015.pdf). Accessed May 24, 2019.
51. International Vaccines Task Force. *Money & Microbes: Strengthening Clinical Research Capacity to Prevent Epidemics*. Washington, DC: World Bank; 2018. <http://documents.worldbank.org/curated/en/120551526675250202/pdf/126338-REVISED-27231-IVTF-Report-reduced.pdf>. Accessed May 24, 2019.
52. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Global Health; Forum on Microbial Threats. *Exploring Lessons Learned from a Century of Outbreaks: Readiness for 2030: Proceedings of a Workshop*. Washington, DC: National Academies Press; 2019.

53. World Health Organization. *Pandemic Influenza Preparedness Framework for the Sharing of Influenza Viruses and Access to Vaccines and Other Benefits*. Geneva: World Health Organization; 2011. [https://apps.who.int/iris/bitstream/handle/10665/44796/9789241503082\\_eng.pdf?sequence=1](https://apps.who.int/iris/bitstream/handle/10665/44796/9789241503082_eng.pdf?sequence=1). Accessed 24 May 2019.
54. World Health Organization. *Global Influenza Strategy*. Geneva: World Health Organization; 2019. <https://apps.who.int/iris/bitstream/handle/10665/311184/9789241515320-eng.pdf?ua=1>. Accessed May 24, 2019.
55. World Health Organization. *Review of the Pandemic Influenza Preparedness Framework for the Sharing of Influenza Viruses and Access to Vaccines and Other Benefits: Report of the 2016 Pandemic Influenza Preparedness Framework Review Group*. Geneva: World Health Organization; 2016. [https://www.who.int/influenza/pip/2016-review/ADVANCE\\_EB140\\_PIPReview.pdf](https://www.who.int/influenza/pip/2016-review/ADVANCE_EB140_PIPReview.pdf). Accessed June 19, 2019.
56. World Health Organization. *International Health Regulations (2005)*. 3d ed. Geneva: World Health Organization; 2017. <https://www.who.int/ihr/publications/9789241580496/en/>. Accessed May 23, 2019.
57. Bardosh K, de Vries D, Stellmach D, et al. *Towards People-Centred Epidemic Preparedness and Response: From Knowledge to Action*. London: Wellcome Trust; undated. <http://www.glopid-r.org/wp-content/uploads/2019/07/towards-people-centered-epidemic-preparedness-and-response-report.pdf>. Accessed June 13, 2019.
58. Konyndyk J. *Struggling with Scale: Ebola's Lessons for the Next Pandemic*. Center for Global Development. Washington, DC: Center for Global Development; 2019. <https://www.cgdev.org/sites/default/files/struggling-scale-ebolas-lessons-next-pandemic.pdf>. Accessed June 13, 2019.
59. Independent Commission on Multilateralism. *Global Pandemics and Global Public Health*. New York: International Peace Institute; 2017. <https://www.ipinst.org/wp-content/uploads/2017/10/Global-Pandemics-and-Global-Public-Health1.pdf>. Accessed May 24, 2019.
60. World Health Organization. *Report of the WHO Pandemic Influenza A(H1N1) Vaccine Deployment Initiative*. Geneva: World Health Organization; 2012. [https://www.who.int/influenza\\_vaccines\\_plan/resources/h1n1\\_deployment\\_report.pdf](https://www.who.int/influenza_vaccines_plan/resources/h1n1_deployment_report.pdf). Accessed June 19, 2019.
61. World Health Organization. The ten years of the Global Action Plan for Influenza Vaccines: report to the Director-General from the GAP Advisory Group. Geneva: World Health Organization; 2016. [https://www.who.int/influenza/GAP\\_AG\\_report\\_to\\_WHO\\_DG.pdf?ua=1](https://www.who.int/influenza/GAP_AG_report_to_WHO_DG.pdf?ua=1). Accessed June 19, 2019.
62. Burci GL, Quirin J. Implementation of the International Health Regulations (2005): recent developments at the World Health Organization. *ASIL Insights*. September 25, 2018;22(13). <https://www.asil.org/insights/volume/22/issue/13/implementation-international-health-regulations-2005-recent-developments>. Accessed June 14, 2019.
63. Kluge H, Martín-Moreno JM, Emiroglu N, et al. Strengthening global health security by embedding the International Health Regulations requirements into national health systems. *BMJ Glob Health*. 2018;3(Suppl 1):e000656.
64. Ijaz K, Kasowski E, Arthur RR, Angulo FJ, Dowell SF. International Health Regulations—what gets measured gets done. *Emerg Infect Dis*. 2012;18(7):1054-1057.
65. World Health Organization. *Joint External Evaluation Tool*. 2d ed. Geneva: World Health Organization; 2018. [https://www.who.int/ihr/publications/WHO\\_HSE\\_GCR\\_2018\\_2/en/](https://www.who.int/ihr/publications/WHO_HSE_GCR_2018_2/en/). Accessed May 23, 2019.
66. World Health Organization. Joint External Evaluation (JEE) mission reports. <http://www.who.int/ihr/procedures/mission-reports/en/>. Accessed June 13, 2019.
67. World Health Organization. *Public Health Response to Biological and Chemical Weapons: WHO Guidance*. Geneva: WHO; 2004. <https://www.who.int/csr/delibepidemics/biochemguide/en/>. Accessed June 13, 2019.
68. United Nations Office at Geneva. About the Biological Weapons Convention. [https://www.unog.ch/80256EE600585943/\(httpPages\)/77CF2516DDC5DCF5C1257E520032EF67?OpenDocument](https://www.unog.ch/80256EE600585943/(httpPages)/77CF2516DDC5DCF5C1257E520032EF67?OpenDocument). Accessed June 13, 2019.



69. World Health Organization. *Pandemic Influenza Preparedness Framework. Annual Progress Report. 1 January-31 December 2018*. Geneva: WHO; 2019. <https://apps.who.int/iris/bitstream/handle/10665/311901/WHO-WHE-IHM-PIP-2019.1-eng.pdf?ua=1>. Accessed June 13, 2019.
70. PIVI. The Partnership for Influenza Vaccine Introduction. <https://pivipartners.org/>. Accessed June 13, 2019.
71. World Health Organization. Strategic Partnership for International Health Regulations (2005) and Health Security (SPH). About influenza. <https://extranet.who.int/sph/influenza-plan>. Accessed June 13, 2019.
72. World Health Organization. Global Influenza Surveillance and Response System (GISRS). [http://www.who.int/influenza/gisrs\\_laboratory/en/](http://www.who.int/influenza/gisrs_laboratory/en/). Accessed June 14, 2019.
73. World Health Organization. WHO's new Health Emergencies Programme. <http://www.who.int/features/qa/health-emergencies-programme/en/>. Accessed June 14, 2019.
74. World Health Organization. *Emergency Response Framework*. Geneva: World Health Organization; 2017. <https://www.who.int/hac/about/erf/en/>. Accessed May 23, 2019.
75. Fidler DP. Negotiating equitable access to influenza vaccines: global health diplomacy and the controversies surrounding avian influenza H5N1 and pandemic influenza H1N1. *PLoS Med*. 2010;7(5):e1000247.
76. World Health Organization. *Report of the WHO Pandemic Influenza A(H1N1) Vaccine Deployment Initiative*. Geneva: World Health Organization; 2012. [https://www.who.int/influenza\\_vaccines\\_plan/resources/h1n1\\_deployment\\_report.pdf](https://www.who.int/influenza_vaccines_plan/resources/h1n1_deployment_report.pdf). Accessed June 19, 2019.
77. Food and Agriculture Organization of the United Nations; World Organisation for Animal Health; World Health Organization. *Taking a Multisectoral, One Health Approach: A Tripartite Guide to Addressing Zoonotic Diseases in Countries*. Geneva: WHO, FAO, OIE; 2019. [http://www.oie.int/fileadmin/Home/eng/Media\\_Center/docs/EN\\_TripartiteZoonosesGuide\\_webversion.pdf](http://www.oie.int/fileadmin/Home/eng/Media_Center/docs/EN_TripartiteZoonosesGuide_webversion.pdf). Accessed June 14, 2019.
78. Berger KM, Wood JLN, Jenkins B, et al. Policy and science for global health security: shaping the course of international health. *Trop Med Infect Dis*. 2019;4(2).
79. Ravi SJ, Snyder MR, Rivers C. Review of international efforts to strengthen the global outbreak response system since the 2014-16 West Africa Ebola epidemic. *Health Policy Plan*. 2019;34(1):47-54.
80. World Health Organization. *Pandemic Influenza Preparedness Framework: Partnership Contribution High-Level Implementation Plan I. Final Report 2014-2017*. Geneva: WHO; 2018. <https://apps.who.int/iris/bitstream/handle/10665/276211/WHO-WHE-IHM-PIP-2018.3-eng.pdf?ua=1>. Accessed June 14, 2019.
81. Smiley S. The Private Sector RoundTable and global health. July 18, 2016. <https://borgenproject.org/private-sector-roundtable/>. Accessed June 14, 2019.
82. World Health Organization. *Whole-of-Society Pandemic Readiness: WHO Guidelines for Pandemic Preparedness and Response in the Non-health Sector*. Geneva: Global Influenza Programme; 2009. [https://www.who.int/influenza/preparedness/pandemic/2009-0808\\_wos\\_pandemic\\_readiness\\_final.pdf](https://www.who.int/influenza/preparedness/pandemic/2009-0808_wos_pandemic_readiness_final.pdf). Accessed June 14, 2019.
83. Thomson N, Littlejohn M, Strathdee SA, et al. Harnessing synergies at the interface of public health and the security sector. *Lancet*. 2019;393(10168):207-209.
84. Michaud J, Moss K, Licina D, et al. Militaries and global health: peace, conflict, and disaster response. *Lancet*. 2019;393(10168):276-286.
85. Onyebujoh PC, Thirumala AK, Ndiokubwayo, J. Integrating laboratory networks, surveillance systems and public health institutes in Africa. *Afr J Lab Med*. 2016;5(3):431.
86. Resolve to Save Lives, Prevent Epidemics. Resources. <https://preventepidemics.org/resources/>. Accessed June 13, 2019.
87. Toner ES, Nuzzo JB, Watson M, et al. Biosurveillance where it happens: state and local capabilities and needs. *Biosecur Bioterror*. 2011;9(4):321-330.



88. World Health Organization. Changes in reporting requirements for pandemic (H1N1) 2009 virus infection. July 16, 2009. [https://www.who.int/csr/disease/swineflu/notes/h1n1\\_surveillance\\_20090710/en/](https://www.who.int/csr/disease/swineflu/notes/h1n1_surveillance_20090710/en/) Accessed June 14, 2019.
89. Lofgren ET, Halloran ME, Rivers CM, et al. Opinion: mathematical models: a key tool for outbreak response. *Proc Natl Acad Sci U S A*. 2014;111(51):18095-18096.
90. Haussig JM, Targosz A, Engelhart S, et al. Feasibility study for the use of self-collected nasal swabs to identify pathogens among participants of a population-based surveillance system for acute respiratory infections (GrippeWeb-Plus)—Germany, 2016. *Influenza Other Respir Viruses*. 2019 Mar 29. <https://onlinelibrary.wiley.com/doi/epdf/10.1111/irv.12644>. Accessed May 21, 2019.
91. Watson C, Sell TK, Watson M, et al. *Technologies to Address Global Catastrophic Biological Risks*. Baltimore, MD: Johns Hopkins Center for Health Security; 2018. [http://www.centerforhealthsecurity.org/our-work/pubs\\_archive/pubs-pdfs/2018/181009-gcbr-tech-report.pdf](http://www.centerforhealthsecurity.org/our-work/pubs_archive/pubs-pdfs/2018/181009-gcbr-tech-report.pdf). Accessed June 14, 2019.
92. Ortega-Sanchez IR, Vijayaraghavan M, Barskey AE, Wallace GS. The economic burden of sixteen measles outbreaks on United States public health departments in 2011. *Vaccine*. 2014;32(11):1311-1317.
93. McDonald LC, Simor AE, Su IJ, et al. SARS in healthcare facilities, Toronto and Taiwan. *Emerg Infect Dis*. 2004;10(5):777-781.
94. World Health Organization. Ebola health worker infections. <https://www.who.int/features/ebola/health-care-worker/en/>. Accessed June 13, 2019.
95. Parpia AS, Ndeffo-Mbah ML, Wenzel NS, Galvani AP. Effects of response to 2014-2015 Ebola outbreak on deaths from malaria, HIV/AIDS, and tuberculosis, West Africa. *Emerg Infect Dis*. 2016;22(3):433-441.
96. World Health Organization, Regional Office for Africa. *Ebola virus disease: Democratic Republic of Congo, External Situation Report 41*. May 14, 2019. [https://apps.who.int/iris/bitstream/handle/10665/312376/SITREP\\_EVD\\_DRC\\_20190514-eng.pdf](https://apps.who.int/iris/bitstream/handle/10665/312376/SITREP_EVD_DRC_20190514-eng.pdf). Accessed June 13, 2019.
97. World Health Organization. *Global Influenza Programme: Essential Steps for Developing or Updating a National Pandemic Influenza Preparedness Plan*. 2018. <https://apps.who.int/iris/bitstream/handle/10665/272253/WHO-WHE-IHM-GIP-2018.1-eng.pdf?ua=1>. Accessed June 13, 2019.
98. Murphy FG, ed. *Community Engagement, Organization, and Development for Public Health Practice*. New York: Springer Publishing Company; 2013.
99. Marston C, Hinton R, Kean S, et al. Community participation for transformative action on women's, children's and adolescents' health. *Bull World Health Organ*. 2016;94(5):376-382.
100. Schoch-Spana M, Franco C, Nuzzo JB, Usenza C; Working Group on Community Engagement in Health Emergency Planning. Community engagement: leadership tool for catastrophic health events. *Biosecur Bioterror* 2007;5(1):8-25.
101. World Health Organization. *Ethical Considerations in Developing a Public Health Response to Pandemic Influenza*. Geneva: WHO; 2007. [https://www.who.int/csr/resources/publications/WHO\\_CDS\\_EPR\\_GIP\\_2007\\_2c.pdf](https://www.who.int/csr/resources/publications/WHO_CDS_EPR_GIP_2007_2c.pdf). Accessed June 19, 2019
102. Smout EM, Enria L, Mooney L, et al. Implementing a novel community engagement system during a clinical trial of a candidate Ebola vaccine within an outbreak setting. *Int J Infect Dis*. 2016;45(Suppl 1):191.
103. World Health Organization. *Communicating Risk in Public Health Emergencies*. Geneva: WHO; 2017. <https://apps.who.int/iris/bitstream/handle/10665/259807/9789241550208-eng.pdf;jsessionid=CBDACFC88F583B7651C9A2A0933A539F?sequence=2>. Accessed May 23, 2019.
104. Vinck P, Pham PN, Bindu KK, Bedford J, Nilles EJ. Institutional trust and misinformation in the response to the 2018-19 Ebola outbreak in North Kivu, DR Congo: a population-based survey. *Lancet Infect Dis*. 2019;19(5):529-536.
105. Centers for Disease Control and Prevention. Crisis and Emergency Risk Communication (CERC). Last reviewed January 23, 2018. <https://emergency.cdc.gov/cerc/>. Accessed May 23, 2019.

106. Person B, Sy F, Holton K, Govert B, Liang A; National Center for Infectious Diseases/SARS Community Outreach Team. Fear and stigma: the epidemic within the SARS outbreak. *Emerg Infect Dis.* 2004;10(2):358-363.
107. Working Group on “Governance Dilemmas” in Bioterrorism Response. Leading during bioattacks and epidemics with the public’s trust and help. *Biosecur Bioterror.* 2004;2(1):25-40.
108. Schoch-Spana M, Brunson E, Chandler H, et al. Recommendations on how to manage anticipated communication dilemmas involving medical countermeasures in an emergency. *Public Health Rep.* 2018;133(4):366-378.
109. Covello VT. Best practices in public health risk and crisis communication. *J Health Commun.* 2003;8(Suppl 1):5-8.
110. Rambhia KJ, Watson M, Sell TK, Waldhorn R, Toner E. Mass vaccination for the 2009 H1N1 pandemic: approaches, challenges, and recommendations. *Biosecur Bioterror.* 2010;8(4):321-330.
111. Gouglas D, Thanh Le T, Henderson K, et al. Estimating the cost of vaccine development against epidemic infectious diseases: a cost minimisation study. *Lancet Glob Health.* 2018;6(12):e1386-e1396.
112. Pronker ES, Weenen TC, Commandeur HR, Osterhaus AD, Claassen HJ. The gold industry standard for risk and cost of drug and vaccine development revisited. *Vaccine.* 2011;29(35):5846-5849.
113. Plotkin SA, Mahmoud AA, Farrar J. Establishing a global vaccine-development fund. *N Engl J Med.* 2015;373(4):297-300.
114. DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: new estimates of R&D costs. *J Health Econ.* 2016;47:20-33.
115. Klain R. Confronting the pandemic threat. *Democracy.* March 14, 2016. <https://democracyjournal.org/magazine/40/confronting-the-pandemic-threat/>. Accessed June 14, 2019.
116. CEPI. New vaccines for a safer world. <https://cepi.net/>. Accessed June 14, 2019.
117. Charlton Hume HK, Lua LHL. Platform technologies for modern vaccine manufacturing. *Vaccine.* 2017;35(35 Pt A):4480-4485.
118. Adalja AA, Watson M, Cicero A, Inglesby T. *Vaccine Platforms: State of the Field and Looming Challenges.* Baltimore, MD: Johns Hopkins Center for Health Security; 2019. [http://www.centerforhealthsecurity.org/our-work/pubs\\_archive/pubs-pdfs/2019/190423-OPP-platform-report.pdf](http://www.centerforhealthsecurity.org/our-work/pubs_archive/pubs-pdfs/2019/190423-OPP-platform-report.pdf). Accessed June 19, 2019.
119. Centers for Disease Control and Prevention. Interim guidance for the use of masks to control seasonal influenza virus transmission. Last reviewed March 5, 2019. <https://www.cdc.gov/flu/professionals/infectioncontrol/maskguidance.htm>. Accessed May 23, 2019.
120. United States Government Accountability Office. *Drug Industry: Profits, Research and Development Spending, and Merger and Acquisition Deals.* Washington, DC: GAO; 2017. <https://www.gao.gov/assets/690/688472.pdf>. Accessed June 16, 2019.
121. Inglesby T, Nuzzo J, O’Toole T, Henderson D. Disease mitigation measures in the control of pandemic influenza. *Biosecur Bioterror.* 2006;4(4):366-375.
122. Camitz M, Liljeros F. The effect of travel restrictions on the spread of a moderately contagious disease. *BMC Med.* 2006;4:32.
123. Mateus ALP, Otete HE, Beck CR, Dolan GP, Nguyen-Van-Tam JS. Effectiveness of travel restrictions in the rapid containment of human influenza: a systematic review. *Bull World Health Organ.* 2014;92(12):868-880D.
124. Poletto C, Gomes MF, Pastore y Piontti A, et al. Assessing the impact of travel restrictions on international spread of the 2014 West African Ebola epidemic. *Euro Surveill.* 2014;19(42):20936.
125. Belluz J, Hoffman S. Why travel bans will only make the Ebola epidemic worse. *Vox.* October 17, 2014. <https://www.vox.com/2014/10/13/6964633/travel-ban-airport-screening-ebola-outbreak-virus/in/5740388>. Accessed May 23, 2019.

126. Berman R. Democrats vs. Obama on an Ebola travel ban. *Atlantic*. October 21, 2014. <https://www.theatlantic.com/politics/archive/2014/10/democrats-defy-obama-in-favor-of-ebola-travel-ban/381712/>. Accessed May 23, 2019.
127. Mundasad S. Travel ban to Ebola affected countries, UK officials say. *BBC News*. August 28, 2014. <https://www.bbc.com/news/health-28966419>. Accessed May 23, 2019.
128. Pattani R. Unsanctioned travel restrictions related to Ebola unravel the global social contract. *CMAJ*. 2015;187(3):166–167.
129. Sell TK, Shearer MP, Meyer D, et al. Public health resilience checklist for high-consequence infectious diseases—informed by the domestic Ebola response in the United States. *J Public Health Manag Pract*. 2018;24(6):510-508.
130. Crampton T. As SARS rages, Hong Kong orders a quarantine. *New York Times*. April 1, 2003. <https://www.nytimes.com/2003/04/01/news/as-sars-rages-hong-kong-orders-a-quarantine.html>. Accessed June 17, 2019.
131. World Health Organization. *Laboratory Biosafety Manual*. 3d ed. Geneva: World Health Organization; 2004. [https://www.who.int/csr/resources/publications/biosafety/WHO\\_CDS\\_CSR\\_LYO\\_2004\\_11/en/](https://www.who.int/csr/resources/publications/biosafety/WHO_CDS_CSR_LYO_2004_11/en/). Accessed June 19, 2019.
132. Wilson DE, Chosewood LC. *Biosafety in Microbiological and Biomedical Laboratories*. 5th ed. Washington, DC: US Department of Health and Human Services; 2009. <https://www.cdc.gov/labs/pdf/CDC-BiosafetyMicrobiologicalBiomedicalLaboratories-2009-P.PDF>. Accessed June 19, 2019.
133. Morgan MJ. The origins of the new terrorism. Carlisle, PA: US Army War College; 2004. <https://apps.dtic.mil/dtic/tr/fulltext/u2/a597084.pdf>
134. Spronken MI, Short KR, Herfst S, et al. Optimisations and challenges involved in the creation of various bioluminescent and fluorescent influenza A virus strains for in vitro and in vivo applications. *PLoS One*. 2015;10(8):e0133888.
135. Noyce RS, Lederman S, Evans DH. Construction of an infectious horsepox virus vaccine from chemically synthesized DNA fragments. *PLoS One*. 2018;13(1):e0188453.
136. United Nations Office at Geneva. The Biological Weapons Convention. [https://www.unog.ch/80256EE600585943/\(httpPages\)/04FBBDD6315AC720C1257180004B1B2F?OpenDocument](https://www.unog.ch/80256EE600585943/(httpPages)/04FBBDD6315AC720C1257180004B1B2F?OpenDocument). Accessed June 17, 2019.
137. United Nations Office for Disarmament Affairs. Secretary-General's mechanism for investigation of alleged use of chemical and biological weapons. <https://www.un.org/disarmament/wmd/secretary-general-mechanism/>. Accessed June 17, 2019.



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