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.[101]

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."[4,44,46-48] 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,[47] 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.[18,42,44,47] 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;[102] 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.[43,44,46]

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.[103] 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.[104,105] Although risk communication is featured in the Joint External Evaluation tool,[66] 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).[106,107] 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.[108]

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.[103,105] 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.[109] 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.[58] 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.[110]

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

Activities*	**Primary Actor**
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).[111-114] 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."[115]

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.[116]

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."[117,118] 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, minilabs, 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.[119] 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.[120]

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.[120] 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.[120]) 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:[121]

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).[122] 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.[123] 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.[10,123-127] 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.[128]

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.[123] 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.[129]

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 trusting relationship with the public. Quarantine and other movement restrictions also involve legal and ethical considerations and should be supported by available evidence to prevent undue burden on affected individuals. The government must have both the legal authority to quarantine individuals and the operational ability to enforce quarantine orders. Other considerations when quarantine is being considered include the responsibility for ensuring the safety of affected individuals that are quarantined and providing medical, communication, and legal services as well as food, shelter, and other necessary supplies.

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.[121] 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.[130]

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.[131,132] 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.[66] 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.[133] 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,[15] but they are currently hard to engineer, particularly with trans genes.[134] 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.[135] 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.[136,137] 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."[37] 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 biosaftey 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 NBCI 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 coronavirues 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.

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