REVIEW ARTICLE

GLOBAL HEALTH

Pandemic Preparedness and Response — Lessons from the H1N1 Influenza of 2009

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A number of viruses have pandemic potential. For example, the coronavirus responsible for the severe acute respiratory syndrome (SARS), which first appeared in southern China in November 2002, caused 8096 cases and 774 deaths in 26 countries before coming to a halt by July 2003 mainly owing to isolation and quarantine.[1] In terms of persistence, versatility, potential severity, and speed of spread, however, few viruses rival influenza virus. Endemic in a number of species, including humans, birds, and pigs, influenza virus causes annual outbreaks punctuated by occasional worldwide pandemics, which are characterized by sustained community spread in multiple regions of the world.

Beyond spread, the degree to which a pandemic is defined according to the severity of the disease, or whether it may be simply described as often producing many illnesses and deaths, remains ambiguous.[2] At its worst, pandemic influenza can be catastrophic: the great influenza pandemic of 1918–1919 is estimated to have infected 500 million persons worldwide and to have killed 50 to 100 million persons.[3] In a typical year of seasonal outbreaks in the Northern and Southern Hemispheres, influenza virus causes as many as 5 million cases of severe illness in humans and 500,000 deaths.[4]

Over the past decade, sporadic cases of severe influenza and deaths in humans have been caused by a number of avian influenza A viruses, including the H5N1 virus, first detected in 1997, and the H7N9 and H10N8 viruses, first reported in 2013. Such sporadic cases may be harbingers of a gathering pandemic, but the likelihood is difficult to judge because it is not known how frequently similar zoonotic episodes occurred silently in the past, when surveillance was more limited, and did not cause pandemics.

The most recent global pandemic was caused by the influenza A (H1N1) strain, which was first detected in North America in 2009 (influenza A[H1N1]pdm09). This event prompted the first activation of provisions under the 2005 International Health Regulations (IHR), which went into effect in 2007.[5] Deliberations that led to the 2005 IHR revisions were shaped by experience in the SARS outbreak of 2003. The regulations delineate the responsibilities of individual countries and the leadership role of the World Health Organization (WHO) in declaring and managing a public health emergency of international concern.

The 2009 H1N1 pandemic presented a public health emergency of uncertain scope, duration, and effect. The experience exposed strengths of the newly implemented IHR as well as a number of deficiencies and defects, including vulnerabilities in global, national, and local public health capacities; limitations of scientific knowledge; difficulties in decision making under conditions of uncertainty; complexities in international cooperation; and challenges in communication among experts, policymakers, and the public.

An interactive timeline of the 2009 H1N1 influenza pandemic is available at NEJM.org

At the request of the WHO, an international committee, which I chaired, reviewed the experience of the pandemic, with special attention given to the function of the 2005 IHR and the performance of the WHO.[6] Since this was the first time that the 2005 IHR was tested in a real-world situation, it was inevitable that aspects of the response to the series of outbreaks and subsequent pandemic could have been improved. Even though there were areas of outstanding performance, such as the timely identification of the pathogen, the development of sensitive and specific diagnostics, and the creation of highly interactive networks of public health officials, the most fundamental conclusion of the committee, which applies today, is not reassuring: "The world is ill prepared to respond to a severe influenza pandemic or to any similarly global, sustained and threatening public-health emergency."[6]

In this article, I focus on lessons from the global response to the 2009 H1N1 pandemic. I identify some of the key successes and shortcomings in the global response, on the basis of the findings and conclusions of the review committee. The article concludes by pointing to steps that can improve global readiness to deal with future pandemics.

TIME COURSE OF THE 2009 H1N1 PANDEMIC

The first laboratory-confirmed cases of H1N1 influenza appeared in Mexico in February and March of 2009. Cases that were detected in California in late March were laboratory-confirmed by mid-April. By the end of April, cases had been reported in a number of U.S. states and in countries on various continents, including Canada, Spain, the United Kingdom, New Zealand, Israel, and Germany. On April 25, invoking its authority under the 2005 IHR, the WHO declared a public health emergency of international concern and convened the emergency committee called for in the regulations. The WHO also established a dedicated internal group to coordinate the response to the widening outbreaks. As of June 9, 2009, a total of 73 countries had reported more than 26,000 laboratory-confirmed cases, and the WHO declared on June 11 that the situation met the criteria for phase 6 — that is, a full-fledged pandemic (Table 1). By the time the pandemic had waned, in August 2010, virtually all countries had reported laboratory-confirmed cases (Fig. 1). An interactive graphic showing the timeline of the 2009 H1N1 pandemic is available with the full text of this article at NEJM.org.

Evidence from the first outbreak in Mexico was alarming. An observational study of 899 hospitalized patients showed that 58 (6.5%) became critically ill, and of those, 41% died.[7] During the course of the pandemic, mortality among children, young adults, and pregnant women was much higher than in a typical influenza season, and there was substantial variation in severity among different regions of the world.[8] In general, older adults fared relatively well, and the total number of influenza-related deaths worldwide (estimated ranges of 123,000 to 203,000 deaths[8] and 105,700 to 395,600 deaths[9]) proved similar to the number in a relatively mild year of seasonal influenza. However, because of the proportionately higher mortality among children and young adults, the severity in terms of years of life lost was greater than in a typical year of seasonal influenza.[10]

2005 INTERNATIONAL HEALTH REGULATIONS

A number of provisions of the 2005 IHR proved helpful in dealing with the 2009 H1N1 pandemic. For example, the 2005 IHR established systematic approaches to surveillance, early-warning systems, and response in member states and promoted technical cooperation and sharing of logistic support. Communication among countries and the WHO was strengthened by the establishment in each member state of National Focal Points — national offices that would be responsible for rapid collection and dissemination of emerging data and guidance.

A static and potentially outdated list of notifiable diseases in previous regulations was replaced by a more flexible flow diagram and decision tool that identified conditions warranting public health action. The 2005 IHR required, for the first time, that member states implementing unilateral measures that interfere with international traffic and trade inform the WHO and that they also provide a public health rationale and scientific justification for those measures. Most important, the 2005 IHR formally assigned to the WHO the authority to declare a public health emergency of international concern and take a leading role in the global response.

Despite these positive features, many member states did not have in place the capacities called for in the IHR, nor were they on a path to meet

Table 1. World Health Organization (WHO) Pandemic-Phase Descriptions and Main Actions According to Phase.

Phase	Estimated Probability of Pandemic	Description	Main Actions in Affected Countries	Main Actions in Nonaffected Countries
1	Uncertain	No animal influenza virus circulating among animals has been reported to cause infection in humans	Developing and implementing national pandemic-influenza preparedness and response plans and harmonizing them with national emergency preparedness and response plans	Same as in affected countries
2	Uncertain	An animal influenza virus circulating in domesticated or wild animals is known to have caused infection in humans and is therefore considered a specific potential pandemic threat	Same as phase 1	Same as phase 1
3	Uncertain	An animal or human–animal influenza reassortant virus has caused sporadic cases or small clusters of disease in people but has not resulted in a level of human-to-human transmission sufficient to sustain community-level outbreaks	Same as phase 1	Same as phase 1
4	Medium to high	Human-to-human transmission of an animal or human–animal influenza reassortant virus that is able to sustain community-level outbreaks has been verified	Rapid containment	Readiness for pandemic response
5	High to certain	The same identified virus has caused sustained community-level outbreaks in at least two countries in one WHO region	Pandemic response: each country implements the actions called for in its national plans	Readiness for imminent pandemic response
6	Pandemic in progress	In addition to the criteria for phase 5, the same virus has caused sustained community-level outbreaks in at least one other country in another WHO region	Same as phase 5	Same as phase 5

their obligations by the 2012 deadline specified in the document. Of the 194 eligible states, 128 (66%) responded to a WHO questionnaire on their state of progress in 2011. Only 58% of the responding member states reported having developed national plans to meet their core capacity requirements, and only 10% claimed to have fully established the capacities called for in the IHR.[6]

The IHR fails to specify a basis for virus sharing and vaccine sharing. This has been partially ameliorated in a framework for pandemic-influenza preparedness, adopted in 2011, that calls on member states to encourage vaccine manufacturers to set aside a fraction of their pandemic-vaccine production for donation and for discounted pricing in developing countries.[11] A glaring gap in the IHR, which has not been remedied, is its lack of enforceable sanctions. For example, if a country fails to explain why it restricted trade or travel, no financial penalties or punitive trade sanctions are called for under the 2005 IHR.

WORLD HEALTH ORGANIZATION

The WHO is an indispensable global resource for leading and coordinating the response to a pandemic. In the 2009 H1N1 pandemic, the WHO had many notable achievements. The organization provided guidance to inform national influenza-preparedness plans, which were in place in 74 countries at the time of the first outbreak in North America, and helped countries monitor their development of IHR core capacities. The WHO Global Influenza Surveillance Network detected, identified, and characterized the virus in a timely manner and monitored the course of the pandemic.

Within 48 hours after the activation of provisions in the 2005 IHR, the WHO convened the first meeting of the emergency committee of experts who would advise the WHO on the status

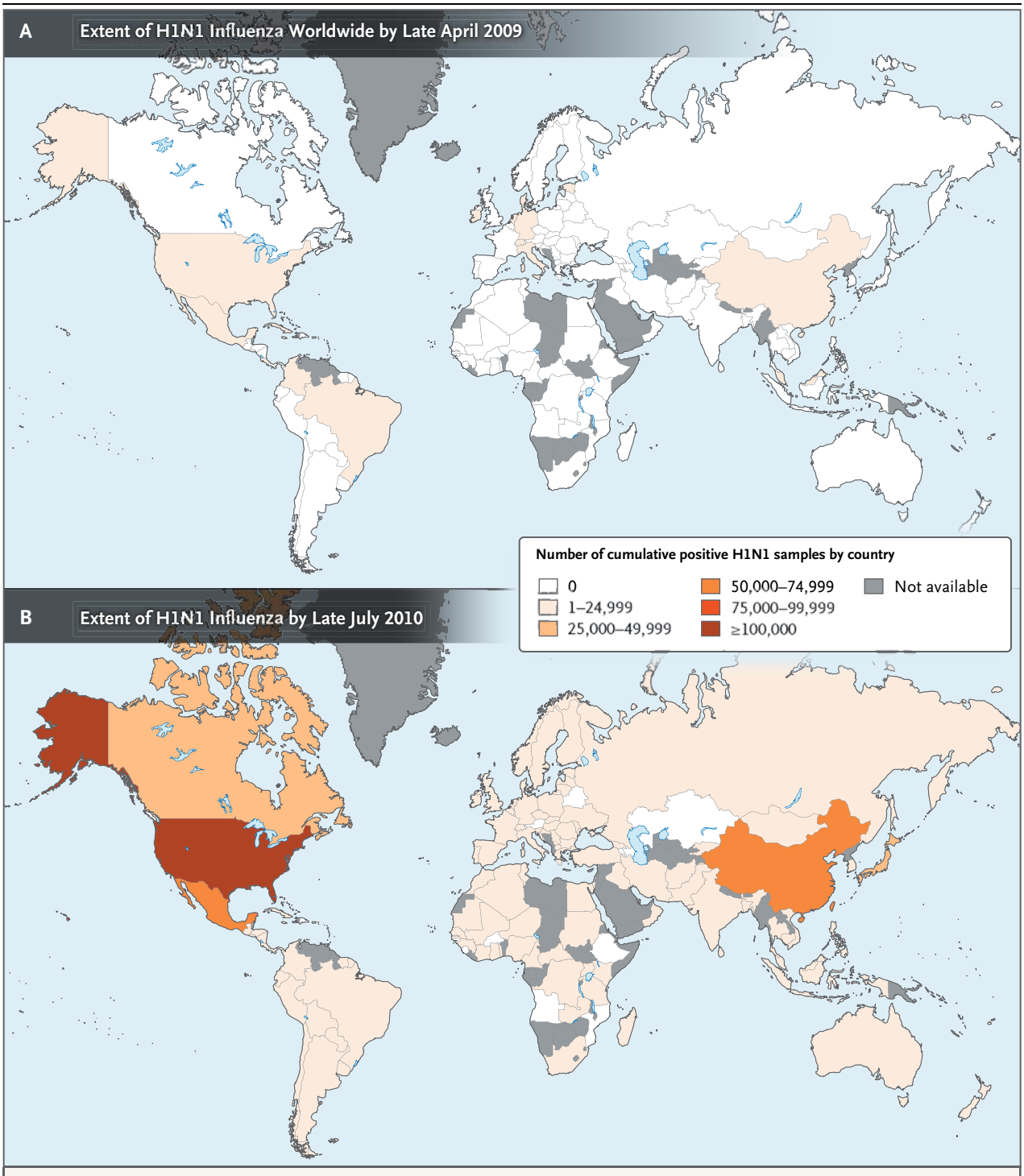

Figure 1. H1N1 Influenza Pandemic.
Data are from the World Health Organization and http://fluNet.org.

of the pandemic. Within 32 days after the WHO had declared a public health emergency of international concern, the first candidate reassortant vaccine viruses were developed, and vaccine seed strains and control reagents were made available within a few weeks. The Strategic Advisory Group of Experts on immunization at the WHO provided early recommendations on vaccine target groups

and dose. The WHO provided prompt and valuable field assistance to affected countries and efficiently distributed more than 3 million courses of antiviral drugs to 72 countries.

Against this backdrop of accomplishment, the WHO confronted systemic difficulties and made a number of missteps in the course of coping with the unfolding pandemic. Although the WHO is the only global agency with legitimate authority to lead the response to a pandemic, it is burdened by a number of structural impediments. First, the WHO is simultaneously the moral voice for health in the world and the servant of its member states, which authorize the overall program and budget. National interests may conflict with a mandate to equitably protect the health of every person on the planet. Second, the budget of the WHO is incommensurate with the scope of its responsibilities. Only approximately one quarter of the budget comes from member-state assessments, and the rest depends on specific project support from countries and foundations. These budget realities and the personnel-management requirements inherent in being a United Nations agency constrain flexibility.

Third, the WHO is better designed to respond to focal, short-term emergencies, such as investigating an outbreak of hemorrhagic fever in sub-Saharan Africa, or to manage a multiyear, steady-state disease-control program than to mount and sustain the kind of intensive, global response that is required to deal with a rapidly unfolding pandemic. Finally, the regional WHO offices are autonomous, with member states of the region responsible for the election of the regional director, budget, and program. Although this system allows for regional variation to suit local conditions, the arrangement limits the ability of the WHO to direct a globally coherent and coordinated response during a global health emergency.

In anticipation of a possible pandemic before 2009, public health authorities had focused on the threat of avian H5N1 influenza, and a signal feature among recognized cases of H5N1 influenza in humans was mortality exceeding 50%.[12] Hence, it was expected that a newly emerging pandemic virus would cause many deaths as well as widespread disease, and the WHO said as much on its website on pandemic preparedness in advance of the 2009 H1N1 pandemic.

The prospects of a pandemic depend on the transmissibility and virulence of the virus and on the susceptibility of the population, which may vary according to age and past exposure to influenza viruses. Although a catastrophic pandemic probably depends on the emergence of a new antigenic type of influenza virus, it does not follow that every newly emerging influenza virus will produce an especially severe burden of influenza. For example, in the 40 years between the mid-1930s and mid-1970s, the 5 years of greatest excess mortality from influenza in the United States were 1937, 1943, 1953, 1957, and 1960, but among these years, only 1957 was marked by a new antigenic type (H2N2), and 1968 (the year when H3N2 appeared) did not rank in the top five for severity.[13] The expectation of a very severe pandemic was understandable in the context of H5N1 but not necessarily for every new antigenic type.

Since the formal criteria for advancing from one phase to the next higher phase in an emerging pandemic were based entirely on the extent of spread and not on severity, this led to public confusion about exactly what the WHO meant by a pandemic. The WHO lacked a consistent, measurable, and understandable depiction of the severity of a pandemic. This situation was problematic because, regardless of the definition of a pandemic, the decisions about response logically depend on both spread and severity. In addition, the defining phase structure that was based on spread was needlessly complex in that it defined more stages than there were differentiated responses, and the structure that seemed suitable for planning proved less suited to operational management.

The weekly requests by the WHO for data were overwhelming for some countries, particularly those with limited epidemiologic and laboratory capacity. As the epidemic progressed, it was not always evident to country officials that the data they submitted were being analyzed and used. Rather than focus on laboratory-confirmed cases, a surveillance model that relied on syndromic surveillance and selective, systematic virologic testing might have been more revealing.[14] Public health officials in some countries, such as the U.K. Health Protection Agency, produced weekly summaries that tracked domestic indicators of influenza spread and severity while noting pertinent global influenza activity, and this approach could hold lessons for other countries as well as for the WHO.[15]

When the WHO convened an expert group, typically for a 1- or 2-day consultation, the prac-

tice of the organization was not to disclose the identities of the experts until the consultation was concluded. Similarly, the WHO kept confidential the identities of emergency-committee members convened under the provisions of the IHR, who would advise the WHO on the status of the emerging pandemic. Although the intent was to shield the experts from commercial or political influences, the effect was to stoke suspicions about the potential links between individual members of the emergency committee and industry.[16] Although the review committee uncovered no evidence of inappropriate influence on the emergency committee, the decision to keep the members' identities secret fostered suspicions about WHO decision making, which were exacerbated by the failure to apply systematic and open procedures for disclosing, recognizing, and managing conflicts of interest. A practice of confidentiality that was arguably fitting for a 1-day consultation was ill-suited to an advisory function that extended over a period of months.

The failure to acknowledge legitimate criticisms, such as inconsistent descriptions of the meaning of a pandemic and the lack of timely and open disclosure of potential conflicts of interest, undermined the ability of the WHO to respond effectively to unfounded criticisms. For example, the WHO was wrongly accused of rushing to declare phase 6, or a full-fledged pandemic, because such action would trigger vaccine orders sought by manufacturers. This kind of suspicion proved hard for the WHO to dispel, despite the fact that the declaration of phase 6 was delayed until the sustained community spread in multiple countries in multiple WHO regions was incontrovertible.

The WHO made a number of operational missteps, including conferring with only a subset of the emergency committee, rather than inviting input from the full group, at a crucial point of deciding to declare progression from phase 4 to phase 5. Throughout the pandemic period, the WHO generated an unmanageable number of documents from multiple technical units within the organization and lacked a cohesive, overarching set of procedures and priorities for producing consistent and timely technical guidance. In addition, after the declaration of phase 6, a time when public awareness of the evolving pandemic was especially important, the WHO chose to diminish proactive communication with the media by discontinuing routine press conferences on the pandemic.

The most serious operational shortcoming, however, was the failure to distribute enough influenza vaccine in a timely way. Ultimately, 78 million doses of vaccine were sent to 77 countries, but mainly long after they would have done the most good. At its root, this reflected a shortfall in global vaccine-production capacity and technical delays due to reliance on viral egg cultures for production, as well as distributional problems. Among the latter were variation among wealthier countries and manufacturers in their willingness to donate vaccine, concerns about liability, complex negotiations over legal agreements with both manufacturers and recipient countries, a lack of procedures to bypass national regulatory requirements for imported vaccine, and limited national and local capacities to transport, store, and administer vaccines. Some recipient countries thought that the WHO did not adequately explain that the liability provisions included in their recipient agreements were the same as the provisions accepted by purchasing countries.

LOOKING AHEAD

In light of these structural impediments and operational deficiencies, the world was very fortunate that the 2009 H1N1 influenza pandemic was not more severe. On the basis of its analysis, the review committee offered 15 recommendations to the WHO and the member states (Table 2). The report and recommendations were endorsed by the member states at the 64th World Health Assembly in May 2011, and the relevant WHO departments incorporated the recommendations into their biennial work plans.[17] Some recommendations, such as improved protocols for vaccine sharing, have been carried out, some are within the power of the WHO to implement, and others depend on the actions and resources of the member states, which have yet to be committed to this purpose.

Beyond institutional, political, and managerial difficulties, the most fundamental constraints on pandemic preparedness are the limits of scientific understanding and technical capacity. Perhaps because only three or four influenza pandemics tend to occur each century, at least in recent centuries, the annals of influ-

enza are filled with overly confident predictions based on insufficient evidence.[18] Studies designed to select for avian-origin viruses that can be transmitted more readily than the original virus in mammalian species (gain-of-function studies) may arguably help predict the pandemic potential of naturally occurring viruses but have raised concerns about the possibilities of intentional misuse and unintended consequences.[19,20] In the current state of scientific knowledge, however, no one can predict with confidence which influenza virus will become dangerous to human health and to what degree. The only way, potentially, to reduce this uncertainty is through a deeper biologic and epidemiologic understanding.

Disease detection, surveillance, and laboratory capacity are improving in many countries. The new techniques of Web-based field reports and analysis of Web-based search patterns can yield valuable intelligence that can give the world a head start on the next emerging pandemic.[21]

In addition to superior surveillance and agreements on virus and vaccine sharing, the world needs better antiviral agents and more effective influenza vaccines, greater production capacity, and faster throughput. One comprehensive assessment showed that the effectiveness of current influenza vaccines in practice is lower than is typically asserted, especially among elderly persons.[22] The traditional methods of influenza-vaccine production, which rely on egg cultures, are often too slow to keep up with a first wave of pandemic spread, and in total, the annual capacity of influenza-vaccine production covers less than one third of the global population.

In early 2013, the Food and Drug Administration approved the first trivalent influenza vaccine produced with the use of recombinant technology,[23] and other production methods are under active research and development. At least four lower-income countries have their own influenza-vaccine manufacturing facilities, and more are on the way. Most important, if research could yield a universal (non–strain-specific), long-lasting, safe, and effective vaccine against influenza, the annual frenzy of action against influenza would be transformed into a proactive, long-term prevention program.[24,25]

In the meantime, influenza outbreaks and pandemics will continue to challenge policymakers and public health leaders to make decisions under conditions of stress and uncertainty.

Table 2. Recommendations of the WHO Review Committee on the Functioning of the 2005 International Health Regulations (IHR) in Relation to the 2009 H1N1 Influenza Pandemic.

Accelerate the implementation of the core capacities required by the IHR
Enhance the WHO Event Information Site*
Reinforce evidence-based decisions on international travel and trade
Ensure necessary authority and resources for all National Focal Points†
Strengthen the internal capacity of the WHO for sustained response
Improve practices for the appointment of an emergency committee
Revise pandemic-preparedness guidance
Develop and apply measures to assess the severity of a pandemic
Streamline the management of guidance documents
Develop and implement a strategic, organization-wide communications policy
Encourage advance agreements for vaccine distribution and delivery
Establish a more extensive public health reserve workforce globally
Create a contingency fund for public health emergencies
Reach an agreement on the sharing of viruses, access to vaccines, and other benefits
Pursue a comprehensive influenza research and evaluation program

* The Event Information Site is a WHO website that, in the event of a pandemic, would serve as an authoritative resource to disseminate reliable, up-to-date, and readily accessible information related to the pandemic.

† National Focal Points are national offices that are responsible for the rapid collection and dissemination of emerging data and guidance.

Pandemics will challenge national authorities and the WHO to function more efficiently and effectively with insufficient resources. Preparation beyond planning, with advance protocols and agreements, the commitment of ready reserves of public health experts and a financial line of credit, and the fulfillment of the IHR requirements can all help. Whenever the next influenza pandemic arises, many more lives may be at risk. By heeding the lessons from the 2009 H1N1 pandemic, the international community will be able to cope more successfully the next time.

The views expressed in this article are those of the author and do not necessarily represent the views of the Institute of Medicine.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

Members of the World Health Organization committee for the review of the 2009 H1N1 pandemic and 2005 International Health Regulations, on whose work this article is largely based, include Preben Aavitsland (Norway), Tjandra Y. Aditama (Indonesia), Silvia Bino (Albania), Eduardo Hage Carmo (Brazil), Martin Cetron (United States), Omar El Menzhi (Morocco), Yuri Fedorov (Russia), Andrew Forsyth (New Zealand), Claudia Gonzalez (Chile), Mohammad Mehdi Gouya (Iran), Amr Mohamed Kandeel (Egypt), Arlene King (Canada), Abdulsalami Nasidi (Nigeria), Paul Odehouri-Koudou (Ivory Coast), Nobuhiko Okabe (Japan), Mahmudur Rahman (Bangladesh), Palliri Ravindran (India), José Ignacio

Santos (Mexico), Palanitina Tupuimatagi Toelupe (Samoa), Patricia Ann Troop (United Kingdom), Kumnuan Ungchusak (Thailand), Kuku Voyi (South Africa), Yu Wang (China), and Sam Zaramba (Uganda). The committee secretariat was led by Nick Drager and included Dominique Metais, Faith McLellan, Mary Chamberland, Nadia Day, Alice Ghent, Sue Horsfall, Janet Kincaid, Phillip Lambach, Linda Larsson, Fabienne Maertens, Joan Ntabadde, Les Olson, Magdalena Rabini, Sarah Ramsay, Mick Reid, Chastine Rodriguez, Alexandra Rosado-Miguel, and Natasha Shapovalova.

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