The Science behind Preparing and Responding to Pandemic Influenza: The Lessons and Limits of Science

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A strong evidence base provides the foundation for planning and response strategies. Investments in pandemic preparedness included support for research that aided early detection, response, and control of the 2009 influenza A (H1N1) (pH1N1) pandemic. Scientific investigations conducted during the pandemic guided understanding of the virus, disease severity, and epidemiologic risk factors. Field investigations also produced information that strengthened guidance for the use of antivirals, identification of target populations for monovalent pH1N1 vaccine, and refinement of recommendations for social distancing measures. Communication of this evolving evidence base was important to sustaining credibility of public health. Areas where substantial controversy emerged, such as the optimal approach to respiratory protection of healthcare workers, often suffered from gaps in the evidence base. Many aspects of the 2009–2010 pandemic influenza experience provide ongoing opportunities for additional study, which will strengthen plans for future pandemic response as well as control of seasonal influenza.

Pandemics of influenza can cause catastrophic illness and societal disruption and consequently rank high among natural threats that necessitate ongoing public health and medical preparedness efforts. A high degree of uncertainty is intrinsic to pandemic planning and response because of the variability of influenza viruses and wide range of features of previous pandemics. The ability to generalize from patterns of transmission or risk factors for disease observed in seasonal influenza to pandemics is unclear. Because of these uncertainties, having the capacity to gather data quickly and develop a strong evidence base provides the foundation for an effective response. The pH1N1 pandemic provided an opportunity to capitalize on many scientific investments but also illuminated areas in which gaps in available science made the development and implementation of policy difficult.

THE ROLE OF SCIENCE IN PREPARING FOR THE PANDEMIC

The emergence of the H5N1 subtype of influenza A in Hong Kong in 1997 and the subsequent widespread avian epizootic and episodes of highly lethal human H5N1 influenza illness prompted a reinvigoration of governmental efforts to address the threat of a pandemic. In 2005, the US government issued a national strategy to strengthen pandemic preparedness [1] and the Department of Health and Human Services (DHHS) released its Pandemic Influenza Plan [2]. From 2006 to 2009, the US Congress appropriated more than 5.62 billion US dollars to strengthen the US and global preparedness levels [3, 4]. Although a large part of these resources focused on procuring antiviral medicines, expanding vaccine manufacturing capacity, and strengthening the public health infrastructure, investments also included research targeted to improve...
diagnostic tests, treatments, and vaccine development. Several critical investments proved to be of value in time for the 2009 H1N1 pandemic response, whereas other areas, such as new vaccine technology, were not ready for deployment in 2009.

Improving diagnostic tests, including those that could indicate the possibility of novel influenza strains, was intended to speed the detection of the next pandemic. The pH1N1 virus was first detected in a specimen taken from a patient enrolled in a DHHS-funded and Centers for Disease Control and Prevention (CDC)–funded study to evaluate the performance of a point-of-care diagnostic device [5]. In addition, CDC developed and validated a 5-target polymerase chain reaction test method, licensed by the Food and Drug Administration (FDA) in 2008, that provided the foundation for initial surveillance for unsubtypable influenza A strains in public health laboratories across the United States.

Substantial scientific effort during the prepandemic period focused on vaccine development against the H5N1 virus. Studies found that high antigen content was required to elicit adequate responses [6]; dose-sparing could be achieved with the use of adjuvants but not with intradermal administration [7]. These studies guided the procuring and stockpiling of H5N1 vaccine. However, the results of clinical trials of 2009 H1N1 vaccines showed them to have completely different properties than those of H5N1 vaccines [8–10], challenging the relevance of a number of prepandemic planning assumptions, including the potential need for adjuvants.

The available science base also was applied to evaluating potential policies for the use of influenza vaccine during a pandemic. The CDC’s Advisory Committee on Immunization Practices (ACIP) and DHHS’s National Vaccine Advisory Committee reviewed evidence on the disease burden and risk factors for influenza and its complications and produced a framework for prioritizing scarce supplies of pandemic vaccines. The work of these scientific advisory committees was supplemented by input from a national public engagement exercise, which sought citizen deliberation on the best ways to target scarce resources in the setting of a pandemic [11]. Results of this exercise suggested that during a pandemic, in addition to reducing morbidity and mortality, minimizing societal disruption was a socially worthwhile goal of vaccination strategies. The public’s input led to a framework that incorporated protecting critical infrastructure personnel to minimize disruption in the event of a severe pandemic. The public engagement participants also prioritized the vaccination of children and pregnant women. The prepandemic review of priorities for the allocation of scarce vaccine provided a strong foundation to build on when the ACIP convened emergently in July 2009 to make recommendation on vaccine use during the actual pandemic [12].


Scientific investigation was critical to the discovery phase of the pandemic. The recognition of a novel influenza virus in April 2009 relied on the CDC’s genetic characterization of viruses that were confirmed to be influenza A but were not typeable as either seasonal H1N1 or H3N2 [5, 13]. The CDC’s influenza laboratory, which serves as a World Health Organization (WHO) International Influenza Collaborating Center, promptly posted results of genetic sequencing of the new virus to the Internet [13]. On 24 April, researchers in Canada announced confirmation of the same viral sequences from specimens collected from severely ill patients in Mexico. The CDC laboratory scientists rapidly developed reagents and test kits that were specific for the new virus, and following the FDA’s issuance of Emergency Use Authorization for the diagnostic test, shipped reagents to public health laboratories across the United States and worldwide. Availability of reagents and sequence information allowed the rapid expansion of capacity to detect the virus and track the extent and course of the pandemic, as well as facilitating investigations of virulence and pathogenesis, transmission dynamics, occurrence in swine and other species, antigenicity and vaccine development, new diagnostic testing approaches, and antiviral effectiveness.

Public health science was also active in the initial phase of the pandemic. Priorities included prompt characterization of the epidemiologic characteristics and spectrum of disease associated with infection with the virus [14]. Age, underlying medical conditions, and pregnancy were associated with greater risk of either illness or severe outcomes of influenza [14–16]. These findings were rapidly translated into focused guidance to promote prompt empiric antiviral treatment of these patients to reduce influenza complications. Prepandemic studies had shown that treatment was more effective when initiated early [14, 17]. Systematic assessment of the accuracy of rapid diagnostic tests to detect the new virus led to guidance that cautioned clinicians against relying on negative test results when determining the need for antiviral therapy [18].

Other epidemiologic field investigations helped to define the serial interval (or generation time) of infection, the most likely duration of symptoms and of viral shedding, and age-specific attack rates in households [19]. These findings were incorporated into updated guidance on the period of exclusion from school or work following illness and provided corroboration of serologic studies that showed that older adults had some preexisting immunity against the virus [20, 21]. Epidemiologic studies also helped address questions about whether seasonal influenza vaccine had any effect on susceptibility to the pH1N1 virus [22, 23].
The multiple rapid evaluations of the newly emerged virus and the disease it caused proved essential for providing a science base for evolving policy and protocols for early management of the epidemic. They also helped address rumors and myths that threatened public cooperation and public health credibility.

Two critical measures in any epidemic are the disease burden and the trajectory of spread. The course of the 2009 H1N1 pandemic was tracked by multiple seasonal influenza surveillance systems, which were strengthened and expanded in order to address the key information needs of the pandemic [24]. Early in the course of the pandemic, case-based reporting provided the means to receive detailed epidemiologic information from all states about laboratory-confirmed cases. Hospitals were characterized in detail by the Emerging Infections Program network, which provided population-based rates of laboratory-confirmed hospitalizations. Trends in outpatient and emergency department influenza-like illness (ILI) were followed through ILI-net, BioSense, and eventually with other syndromic systems, such as Distribute (IDIS). Virologic surveillance from WHO and the National Respiratory and Enteric Virus Surveillance System (NREVSS) provided invaluable information each week on the particular influenza viruses that were circulating; from late April 2009 through February 2010 these data consistently showed that the pH1N1 strain predominated. Community studies supplemented these systems and provided the foundation for estimates of the burden of cases, hospitalizations, and deaths [25]; these estimates were disseminated periodically by the CDC throughout the fall and winter (http://www.cdc.gov/h1n1flu/estimates_2009_h1n1.htm).

THE INTERVENTIONS: DRUGS, VACCINES, PERSONAL PROTECTIVE EQUIPMENT, AND BEHAVIOR CHANGE

The science base that supports interventions to prevent, treat, or slow the spread of pH1N1 was primarily derived from experience with seasonal influenza. Guidance for the use of antiviral medications during the pandemic was based on evaluations of the effectiveness of these drugs against disease caused by both seasonal and H5N1 viruses, but observational data collected during the pandemic strengthened the evidence that treatment of severe illness with oseltamivir was beneficial, even when initiated more than 48 h after illness onset [26]. A new intravenous neuraminidase inhibitor, Peramivir, was authorized for emergency use during the pandemic, but the scope of follow-up data collected in the context of emergency use is not appropriate or adequate to support its licensure.

The US government policy to use unadjuvanted monovalent 2009 H1N1 vaccine meant that much of the evidence base from trivalent seasonal influenza vaccines was likely to be applicable to the pandemic vaccines. Recommendations for 2009 H1N1 vaccine use were made by the ACIP on the basis of what was known about seasonal influenza and seasonal influenza vaccines and results of surveillance and field investigations conducted during the spring [12]. In the prelude to the vaccine program’s initiation but following issuance of these recommendations, several vaccine clinical trials confirmed that the traditional single 15-μg dose without adjuvant induced strong immune responses in most adults and older children, that 2 doses were required to ensure a high proportion of children <10 years of age would respond, and that short-term reactogenicity was similar to that seen with trivalent seasonal influenza vaccines [8–10]. Despite the monovalent vaccines’ similarity to the trivalent seasonal vaccines, existing safety monitoring methods were augmented to evaluate the safety of 2009 H1N1 monovalent vaccines following their wide-scale use [27]. An independent vaccine safety assessment working group, convened on behalf of the National Vaccine Advisory Committee, was established to determine whether any adverse event signals were attributable to the vaccine. Vaccine safety monitoring used multiple systems; sophisticated statistical techniques facilitated rigorous evaluations of potential safety signals [28]. New methods allowed rapid and near real-time monitoring of vaccine uptake over time to track implementation of vaccination recommendations [29]. Vaccine effectiveness is also being studied, although the precision of final estimates may be limited by relatively late availability of vaccine in relation to disease increases. Because a diversity of implementation approaches were used to deliver monovalent 2009 H1N1 vaccine, it should be possible to develop an evidence base that defines best practices. Retrospective evaluations of school-based vaccination and other strategies are ongoing and will provide lessons learned for future pandemics, as well as seasonal influenza programs.

Behavioral interventions were widely promoted to reduce the spread of pH1N1, particularly in the period before vaccine became available. These interventions included recommendations on covering coughs, washing hands frequently, and staying home from school or work when influenza-like symptoms occurred. Periodic surveys suggest widespread changes in self-reported behaviors. Yet the science base in support of these measures for influenza prevention and control is primarily inferential [30]. The scientific and logistical considerations of studies to evaluate the effectiveness of these measures are complex and challenging, but some evaluations that use seasonal influenza outcomes are in progress.

Because of uncertainty about the virulence and transmissibility of the pH1N1 virus and the lack of widely available vaccine in the beginning of the pandemic, the appropriate use of respiratory protection with N-95 or surgical masks received substantial attention. Gaps in knowledge about the relative importance of airborne versus droplet spread of influenza hampered the development of policy. Review of the topic by a specially convened Institute of Medicine committee concluded
that fit-tested N-95 respirators, or respirators that are demonstrably more effective should be used as one measure in the continuum of safety and infection control efforts to reduce the risk of infection, but that more research was needed to determine the most appropriate means of respiratory protection against pH1N1 [31]. As is often the case, the lack of a strong evidence base meant that substantial controversy surrounded the tradeoffs inherent in the recommendations and CDC’s interim policy.

Another area of controversy was recommendations for the length of time ill people needed to stay home from school or work. Early on, the CDC’s interim guidance suggested a 7 day exclusion period after the onset of symptoms. These recommendations were made at a time when the characteristics of transmission of the pH1N1 virus and the spectrum of disease were not well defined and were based on a conservative assessment of the length of time when shedding of seasonal influenza strains was thought most likely to occur. Additional data about the transmission dynamics of the pH1N1 virus, rapidly assembled from early field investigations, as well as a better understanding of the clinical spectrum of disease, expanded the relevant evidence base [32, 33]. Thus, guidance could be updated to focus on excluding ill persons and generally keeping schools, businesses, universities and other institutions open; updated guidance recommended exclusion for 24 hours after a person becomes afebrile without the use of antipyretics. This guidance on the period of exclusion minimized societal disruption compared to initial recommendations and could be justified by the evolving evidence. Had the clinical spectrum of disease associated with the virus been much more severe, more aggressive recommendations for school dismissal and closure of other institutions and exclusion policies may have been appropriate. Remaining gaps in the science around exclusion policies relate to the ability of persons with asymptomatic infection to transmit and the relationship between the duration of shedding and transmission dynamics.

**COMMUNICATING THE SCIENCE: RISK COMMUNICATION AND UNCERTAINTY**

Communication was an essential element in the response to the 2009 H1N1 pandemic. Numerous investigations were reported as early releases to the Morbidity and Mortality Weekly Report, and critical scientific results, such as the genetic characterization of the novel virus [13], early clinical case series providing information on symptoms and comorbid medical conditions [14], and the excess risk of serious disease occurring among pregnant women [15, 16], were reported promptly by fast-tracked peer review at leading scientific journals.

The CDC and WHO each held frequent press briefings to ensure timely dissemination of new information on the evolving threat and intervention programs. Public health spokespeople relied on the principles of risk communication in media briefings and other outreach sessions. In general, crisis communication principles emphasize a focus on transparency and acknowledging uncertainty, as well as a commitment to frequent updates as new information emerges. Empathy and openness are key components of message delivery and can help sustain credibility of the investigation and response, even when information is limited and there are more questions than answers available. In general, public health experts, scientists, and physicians served as spokespeople for the response, which likely strengthened credibility and public confidence.

A particular challenge in communication about the vaccination program derived from consumer uncertainty regarding the safety of monovalent 2009 H1N1 vaccines. Some myths and rumors circulated widely on the Internet and through viral e-mails claiming unsubstantiated problems associated with vaccination. Although mainstream media generally discredited such claims, alternative media sources perpetuated myths and often used sensationalism to sustain viewer interest. Public health organizations sought to counter these rumors with frequent updates, including factual information about what was being found through safety monitoring [28] and through disseminating tools and information to health care providers and other sources of consumer information.

**DECISION-MAKING WITH IMPERFECT SCIENCE**

Decision-making during any public health crisis is best informed by having a strong evidence-base, but in many situations sufficient evidence cannot be gathered in time for plans that must be urgently implemented if they are to be effective. Anticipation of the types of decisions needed and what new information is most important for developing policy can help prioritize interpandemic research. Much of the pandemic preparedness efforts of the US government before 2009 had addressed a worst case scenario; such planning can acknowledge that interventions can be scaled back if circumstances permit. The features of this pandemic, characterized through surveillance and epidemiologic investigations conducted in the Northern hemisphere during the spring and Southern hemisphere during the summer of 2009, served as the basis for updated public health policies for schools and other institutions and guidance for the vaccination program developed in preparation for the anticipated fall wave. These policies addressed the most likely scenario based on what had been learned about the epidemic’s characteristics to date but also incorporated guidance for a scenario in which the virus or disease patterns were more severe. Rapid assessments of characteristics of disease during the fall surge in illness corroborated that patterns were similar to those identified in the spring. Much is left to be learned regarding the response to the 2009 H1N1 pandemic, such as the identification of most effective strategies...
for delivering vaccine or other countermeasures rapidly to large populations.

Although it is tempting to assume that the world will be free of pandemic influenza for another 30 or 40 years, influenza viruses continue to emerge and continued vigilance is needed. The 2009 pandemic experience provides a unique opportunity to strengthen the scientific evidence to support ongoing influenza preparedness. The occurrence of annual epidemics of seasonal influenza provides a fertile ground for study, and an opportunity to strengthen long-term preparedness while improving control of a common cause of illness and death between pandemics.

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References


