Influenza Pandemic Preparedness Plan for the United States

Peter A. Patriarca and Nancy J. Cox

In preparation for the next influenza pandemic, a comprehensive and action-oriented plan is presently under development that focuses on six major areas: (1) improvements in ongoing virologic and disease-based surveillance systems; (2) vaccination of high-priority target groups, and, given sufficient vaccine supplies, the entire US population; (3) liability programs for vaccine manufacturers and health care providers; (4) research to improve detection of new variants and to accelerate the availability of existing and novel vaccines and antiviral agents; (5) integrated, multicomponent communication systems for rapid information dissemination and exchange; and (6) emergency preparedness plans to provide for adequate medical care and maintenance of essential community services. The sudden and unpredictable emergence of pandemic influenza and its potential for causing severe health and social consequences dictate the need for close collaboration among a wide variety of organizations in both the public and private sectors.

Influenza viruses are well known for their ability to cause sudden, pervasive infection in all age groups on a global scale, due in part to their unusual genomic properties. Rapid rates of evolution in the genes that encode the major antigenic determinants of the virus—the hemagglutinin (HA) and neuraminidase (NA) surface proteins—have led to the emergence of annual influenza epidemics of varying severity, resulting in ~750,000 excess deaths in the United States since 1958 during interpandemic periods [1–5]. Segmentation of the genome has led to periodic “antigenic shifts” of the HA and NA, primarily through reassortment of gene segments between human and avian or swine influenza viruses during chance coinfections, which can result in the sudden and unpredictable emergence of pandemic influenza [4–7]. Recent evidence also suggests that pandemics may be caused by transmission of nonhuman viruses to humans without reassortment [8, 9]. Three pandemics have occurred during the past century alone, one of which—the infamous “Spanish flu” of 1918—was responsible for >20 million deaths worldwide, primarily in young adults [10]. Although mortality rates associated with the more recent pandemics of 1957 (A/Asia [H2N2]) and 1968 (A/Hong Kong [H3N2]) were reduced in part by antibiotic therapy for secondary bacterial infections and more aggressive supportive care [3, 4, 7], both pandemics were associated with high rates of morbidity and social disruption, with combined economic losses of ~$32 billion (in 1995 dollars) [2–4, 7].

To prepare for the next influenza pandemic, an event considered by most experts to be inevitable [6], public health officials from around the world have begun to devise strategies by which influenza-related morbidity, mortality, and social disruption might be reduced [11, 12]. This process was revisited in the United States in 1993, when the federal government convened a panel of experts from the public and private sectors to review the initial plan developed in 1978 and to assess the nation’s current capacity to respond to the next pandemic [13]. The panel not only considered tasks specifically related to the pandemic itself but also those aimed at reducing the cumulative toll of influenza during the current interpandemic period. This report summarizes major areas discussed by the panel and provides a preview of a comprehensive influenza pandemic preparedness plan for the United States that is presently under development.

Precepts and Assumptions

Before considering priority activities that would allow the United States to better cope with the next pandemic, the panel developed the following series of precepts and assumptions to guide the planning process.

The plan must be considered from the outset as a national, and not federal, effort, with broad and active participation by a wide variety of governmental and nongovernmental organizations at the national, state, and local levels. Meetings and discussions to date have included representatives from 15 different federal agencies; 24 medical, public health, volunteer, and trade organizations; 5 national advisory committees; various consumer groups; the World Health Organization; and ministries or departments of health from a number of foreign countries. Extensive input from the pharmaceutical industry has also been actively solicited to address and overcome a series of problems that emerged during the 1976 swine influenza vaccination program [14].
The overriding objective of the plan should remain consonant with the principal influenza-related goal of the US Public Health Service: to reduce influenza-related mortality [1]. However, the plan should also place strong emphasis on strategies to reduce morbidity, social disruption, and economic losses, important hallmarks of previous pandemics.

Criteria for declaring that a pandemic exists must be carefully defined. In addition to exhibiting a major shift in its antigenic makeup (“pandemic alert”), the putative pandemic strain must also demonstrate the capacity for multifocal outbreaks in geographically dispersed populations before a “pandemic” is formally declared.

The key prevention strategy to reduce pandemic-associated morbidity and mortality will be the implementation of mass vaccination programs. It should be assumed from the outset that every individual will be susceptible to the pandemic strain and that vaccination of the entire US population will be warranted and recommended. This strategy may have to be modified, however, depending on the availability of sufficient numbers of doses of vaccine and the outcome of special studies examining the clinical and epidemiologic features of disease; such studies should be conducted as soon as possible after the detection of a variant that exhibits an antigenic shift. For example, if older age groups appear to be less susceptible to infection because of prior exposure and immunity, vaccination of younger age groups may be considered a higher priority.

While it can be assumed that substantial financial and human resources will be made available by the US Congress once a pandemic has been declared, support for interpandemic activities will likely remain relatively limited. Thus, it is critical to (1) stress the importance of ongoing activities related to the detection and control of new variants of influenza virus, regardless of the potential for such variants to cause pandemic disease; (2) strengthen the current infrastructure for surveillance, vaccination, and other essential “core” activities at the state and local levels; and (3) identify important gaps in existing activities that will require special actions now to ensure that the United States will be adequately equipped to respond to the next pandemic. Key elements of the plan must also be carefully and continuously integrated with ongoing related initiatives, such as emerging infections [15, 16], adult immunization [17], and emergency preparedness for acts of biologic terrorism [18].

**Priority Areas and Action Steps**

*Early detection and warning.* Timely recognition of new variants of type A influenza viruses must remain the cornerstone of pandemic preparedness. Virologic surveillance has improved considerably during the past 2 decades, increasing the potential for early detection of new antigenic variants and the development of suitable candidate strains for vaccine production. This success has resulted largely from gradual expansion of the World Health Organization global surveillance network, along with the development and use of more sophisticated and powerful laboratory techniques and transfer of knowledge and technology to national laboratories around the world [19]. Efforts are now underway to expand surveillance efforts in China, the country from which pandemic variants such as A/Asian/57 (H2N2) and A/Hong Kong/68 (H3N2) appear to have emerged [6, 7, 20]. There is also growing circumstantial evidence that China may serve as an important source of “drifted” strains, as evidenced by the more recent detection of variants such as A/Beijing/89 (H3N2), A/Beijing/92 (H3N2), and A/Nanchang/95 (H3N2) [1, 19]. Thus, expansion of virologic surveillance in China should also improve the likelihood of correct matches between vaccine and wild strains during interpandemic periods.

*Influenza vaccine development, production, and availability.* Domestic influenza vaccine production has increased dramatically to ~70 million doses annually in recent years [1, 21], a level at which immunization of the entire population with a monovalent (pandemic strain) vaccine can be considered a feasible goal. However, current production techniques rely on the availability of large numbers of embryonated eggs, which could limit production outside the normal influenza vaccine manufacturing cycle (typically January–August). Moreover, even under optimal current conditions, ~6–8 months would be needed from the time a pandemic variant is detected until tens of millions of doses of vaccine would be available for use. In view of these limitations, the development of alternative vaccines, use of cell substrates other than eggs, further improvements in high-growth reassortants used in vaccine production, and the development of more rapid methods to reliably assign potency (HA content) to bulk vaccines should remain high priorities [22]. Progress in these areas will also have a significant impact on vaccine production and availability during interpandemic periods.

*Vaccine utilization and coverage.* Before 1987, annual influenza vaccination coverage among the elderly in the United States rarely exceeded 25%, due in part to misconceptions about benefits and risks, missed opportunities for vaccination, and marked declines in publicly funded programs at the national, state, and local levels [2]. Annual vaccination coverage has increased markedly since that time—to ~50%–55% in persons age ≥65 years in 1993 [21]—due to improved information and education programs sponsored by the public and private sectors, reimbursement by Medicare for vaccination of the elderly, increased assumption of responsibility on the part of the private sector in vaccine delivery efforts, and improved perceptions about the benefits of annual vaccination as a consequence of repeated demonstrations of cost-effectiveness [23–26]. Despite these improvements in coverage, substantially greater efforts are needed to reach the estimated 25 million high-risk individuals who have never received influenza vaccine, many of whom are non-Hispanic blacks [21]. Of perhaps equal priority should be raising immunization coverage with pneumococcal vaccine, in view of the importance of pneumococcal pneumonia as a secondary complication of influenza [1–4]. The recent emergence of antibiotic-resistant strains of *Streptococcus pneumoniae* and obstacles that may preclude
large-scale pneumococcal vaccination programs in the midst of an influenza pandemic further underscore the need to raise pneumococcal vaccine coverage levels far above the 29% estimated for high-risk patients in 1993 [21].

Influenza vaccination programs conducted during the next pandemic will pose a series of difficulties over and above those associated with the interpandemic period. These include expansion of the target population to nontraditional groups, such as healthy children and adults; the need for immunization of tens of millions of persons within as short a time frame as possible; the ability to rapidly allocate and reallocate potentially limited supplies of influenza vaccine to individuals at highest risk of severe illness; determining the extent to which the United States must respond to requests for influenza vaccine from foreign countries; and the development of an equitable program to provide liability coverage for manufacturers and vaccine providers. These and other issues remain the focus of intense discussion and negotiation.

Chemoprophylaxis and therapy. Although widespread use of currently licensed antiviral agents—amantadine and rimantadine—would seem to represent a reasonable strategy for both prophylaxis and therapy of type A influenza during a pandemic—particularly when temporary shortages of influenza vaccine may exist—closer scrutiny of this approach suggests that it may not be feasible. Prophylaxis of even 10% of the US population for a 2-week period would require ~700 million doses, an amount far exceeding the current production capacity of US manufacturers. The potential for long-term stockpiling of the two drugs has also been considered but does not appear to be feasible due to a short dating period, limitations in the availability of raw materials for drug synthesis, and other factors. In addition, the provision of adequate liability coverage for drug manufacturers and health care providers seems problematic due to the relatively vague nature of reported side effects of these two drugs [1]. Thus, barring the discovery of more readily synthesized compounds, the use of antiviral agents during a pandemic, at least for the foreseeable future, will likely be based on a carefully devised contingency plan that balances the needs for national security and maintenance of essential community services (e.g., law enforcement and firefighting capability) with the prevention or mitigation of severe disease in high-risk patients.

Emergency preparedness. An important hallmark of influenza pandemics has been their ability to cause major disruption of routine medical services. As infection sweeps through the population, it first leads to an increase in respiratory illnesses, followed by increases in pneumonias and other infection-related complications, and then deaths [3, 4, 7]. Each of these events compromises the ability of medical facilities to provide adequate care, especially when health care providers themselves frequently become exposed and infected. Experience with the Spanish flu pandemic in 1918 also illustrates the enormous potential of influenza for causing acute social disruption on a scale similar to or even greater than that caused by other natural disasters, but on a much wider geographic scale [10].

In an effort to cope with community disruption and increased demand for medical services on a national scale, contingency plans for dealing with such emergencies are being developed in advance of the pandemic at the national, state, and local levels. Such plans are being devised under the rubric of the Federal Response Plan (for Public Law 93-288, as amended), in which the US Public Health Service (Office of Emergency Preparedness) serves as the lead for emergency support functions listed under “Health and Medical Response” [27]. Other elements of the Federal Response Plan, including “Response and Recovery” and “State and Local Preparedness,” will be coordinated by the Federal Emergency Management Agency (FEMA) through its regional offices, as well as state and county offices of emergency services. The Federal Interagency Committee on Emergency Medical Services, through its Disaster Subcommittee, will also assist in improving coordination between emergency medical and disaster program activities. A vast, multicomponent communications system must also be developed to provide public health officials, practitioners, the media, and the general public with accurate and timely information throughout the course of the pandemic.

Influenza-related research. Most federal funds available for influenza research are provided principally through the National Institutes of Health in the form of grant support for basic scientists to study fundamental issues related to the genetics, molecular biology, and immunology of influenza viruses and infection. While it is essential to continue this support, a new and more focused program of applied research is needed to fill important gaps that would have a more direct and immediate impact on influenza prevention and control. Preliminary priorities for such a program include improved methods for the detection of new variants of influenza viruses, the development and preliminary testing of prototype vaccines potentially containing the H2, H4, and H7 HA subtypes [8], mechanisms to accelerate manufacturing processes for conventional inactivated influenza virus vaccines, and further development of novel antiviral agents and alternative vaccines. These and other priorities were the principle focus for the meeting summarized in this issue of the Journal, and readers should refer to other articles in this supplement for further information.

Summary

During the 20-year period following the most recent pandemic alert, a long progression of scientific, technologic, social, and political developments have made a comprehensive plan for confronting the next influenza pandemic a high priority for the US Public Health Service, the Department of Defense, and other federal agencies. These developments have not only included advancements in our knowledge and understanding of influenza per se but have also included far greater attention to the more general problem of emerging infectious diseases; greater attention to preventive medical services, including adult immunization; greater interest, awareness, and active participation by the private sector and public at large in a wide variety.
of public health issues; and unprecedented international cooperation, collaboration, and communication. These and other important developments have laid the foundation for far greater progress in preventing and controlling influenza in the United States and also provide the framework for the development of a contemporary, comprehensive, and action-oriented plan, the principal elements of which remain under active discussion and evolution.

Comments and suggestions regarding the pandemic plan or any of its components are encouraged and should be referred in writing to the authors.

Acknowledgments

The authors gratefully acknowledge the many contributions of the Federal Interagency Working Group and its consultants (listed in alphabetical order) during the planning process: Nancy H. Arden (CDC); Joseph M. Baldi (formerly with the National Vaccine Program Office [NVPO], Department of Health and Human Services [HHS]); William H. Bancroft (Department of Defense [DoD]); David Benor (Office of General Counsel, Office of The Assistant Secretary for Health, HHS); Leo Bosner (FEMA); Joel G. Breman (NVPO, HHS); Joseph Chin (Health Care Financing Administration [HCFA]); David S. Fedson (formerly with the University of Virginia School of Medicine, Charlottesville); Kathleen F. Gensheimer (State Department of Health, Maine); Charles M. Helms (University of Iowa College of Medicine, Iowa City); Charles H. Hoke (DoD); Dominick A. Iacuzio (NIH); Robert Jevic (Office of Emergency Preparedness, HHS); William S. Jordan, Jr. (formerly with NVPO, HHS); Edwin D. Kilbourne (New York Medical College, Valhalla); Roland A. Levandowski (US Food and Drug Administration [FDA]); Marshall McBean (formerly with HCFA); Kristin L. Nichol (VA Medical Center, Minneapolis); M. Louis Offen (Health Resources Services Administration); Stephen C. Schoenbaum (Harvard Community Health Plan of New England, Providence, RI); Raymond A. Strikas (CDC); and Michael S. Williams (formerly of FDA).

References