Influenza is an acute disease characterized by cough, coryza, fever, pharyngitis, headache, myalgia, and malaise, which can often lead to life-threatening complications in elderly persons and in persons with chronic medical conditions. The disease probably has existed for >2000 years [1]. The etiologic agent of influenza was finally discovered in 1933, and it was the first human respiratory virus to be isolated and characterized [2]. Influenza viruses are negative-stranded RNA viruses that have been classified taxonomically as orthomyxoviruses; they are grouped into 3 major types (A, B, and C), and type A is further divided into multiple subtypes [1]. The remarkable variation of influenza strains, particularly of type A, and their ability to cause annual epidemics of respiratory illness of varying intensity and severity continue to be the focus of intense investigation. Influenza is responsible annually for an illness attack rate of 10%–20%, an average of 20,000 excess deaths, 114,000 hospitalizations, and $1 billion to $3 billion in direct costs for medical care in the United States [3].

In addition to causing annual epidemics, type A influenza viruses have periodically caused sudden, pervasive infection in all age groups on a global scale. Such “pandemics” are believed to have occurred for at least 300 years at unpredictable intervals; they are caused by “shifts” of the major antigenic determinants of the virus—that is, the hemagglutinin and neuraminidase surface proteins [1]. Such “antigenic shifts” may result from exchange (reassortment) of gene segments between human and avian or swine influenza viruses or from direct transmission of nonhuman viruses to humans.

Three pandemics have occurred during the past century alone. The first and most severe, the infamous “Spanish flu” of 1918–1919, was responsible for >20 million deaths worldwide and >500,000 deaths in the United States, primarily among young adults [4]. Mortality associated with the more recent pandemics of 1957 (due to A/Asia [H2N2]; responsible for 69,800 deaths) and 1968 (due to A/Hong Kong [H3N2]; responsible for 33,800 deaths) was confined primarily to elderly and chronically ill persons, and its severity was reduced, in part, by administration of antibiotic therapy for secondary bacterial infections and by more-aggressive supportive care [5]. However, the numbers of deaths in both pandemics were higher than normal for annual influenza epidemics in younger age groups [5]. Both pandemics were associated with high rates of morbidity and social disruption, and combined economic losses were ∼$32 billion (in 1995 dollars) [6].

Given these historical precedents, the current epidemiologic and ecologic circumstances, and the present level of understanding of influenza viruses and influenza infection, it is reasonable to assume that additional pandemics will occur. In any future pandemic, deaths, hospitalizations, and direct costs are still expected to be substantial. Social disruption, interruption
of commerce, school closings, and public unrest are likely when many people are ill at the same time. Assuming an attack rate of 15%–35% for the United States (higher than usual for influenza epidemics but similar to the rates for previous pandemics) and the absence of any intervention, it is estimated that the number of deaths will range from 89,000 to 207,000, the number of hospitalizations will range from 314,000 to 734,000, and the direct costs will range from $71 billion to $166 billion [7]. During the past 2 decades, hospitals have vastly reduced staffing levels and minimized inventory, which can be expected to limit the capacity of the health care industry to handle care for a sudden surge of inpatients [8].

However, it is also possible that the next pandemic will be relatively less severe. For example, the A/H1N1 viruses that reappeared in 1977 (although the outbreak was not considered a pandemic) produced relatively mild disease, compared with A/H3N2 viruses [4]. The pandemic plan of the World Health Organization (WHO) notes that “contingency plans should deal with various attack rates: 10% would be stressful for the community, 25% would disrupt community services and stress hospital and medical care facilities, 50% would be disastrous” [9, p. 22].

Therefore, given the wide range of possibilities, planning to prepare for the next pandemic must emphasize rapid initial assessment of disease impact and must ensure that there is the capability for flexible response to differing levels of disease. In addition, pandemic planning in the United States must take into account the worldwide impact of pandemic influenza. The WHO notes that “many countries lack sufficient resources to prepare appropriately for [a pandemic]” [9, p. 30] and that “WHO expects that important issues will emerge that will require continued international consultation to resolve. Examples of likely issues are differing policies in neighboring countries, and inequity of vaccine availability between rich and poor countries. The exchange of national or regional pandemic preparedness plans is highly encouraged, in order to harmonize the response regionally” [9, p. 32]. Accordingly, since the early 1990s, public health officials from around the world, including the United States, have considered strategies to reduce influenza-related morbidity, mortality, and social disruption. This report reviews the major concepts described in the current influenza pandemic preparedness plan under revision in the United States and updates a previous report [6].

GOAL AND OBJECTIVES

The goal of the US national pandemic influenza action response plan is to limit the impact of an influenza pandemic by (1) limiting the burden of disease (i.e., morbidity and mortality); (2) minimizing social disruption caused by the pandemic; and (3) reducing economic losses attributable to the pandemic. The objectives and priority areas are listed below and in table 1; some of these priority areas are discussed in detail below.

Objective 1: Strengthen national and global capabilities for virologic and disease surveillance with a view to increasing the likelihood of early detection of influenza and effective tracking of its spread in the population. Timely recognition of new variants of influenza has improved considerably during the past several decades, thus increasing the chance that the strains in inactivated vaccines can be updated. Success in this area has resulted largely from continuous efforts to expand the global surveillance network, from the application of more sophisticated and powerful laboratory techniques, and from the global transfer of technology via aggressive training programs and distribution of standardized reagents. Disease-based surveillance systems have failed to improve at the same pace, however, partly because public health officials and the general public no longer perceive influenza as a major threat and partly because resources available for surveillance at the state and local levels gradually eroded in the 1980s and 1990s.

A number of studies [6] have documented the emergence, in China, of pandemic strains of influenza viruses, which apparently arose from genetic reassortment of human and animal viruses. There is also growing circumstantial evidence that China often serves as an important source of variants that have resulted from antigenic drift, which frequently cause epidemic disease during interpandemic periods. These observations prompted the Centers for Disease Control and Prevention (CDC) to support a national influenza surveillance system in China to increase the number of influenza isolates available to the CDC and the WHO network for analysis. This system began with 6 surveillance sites in 1989 and has provided invaluable data for tracking the origination and spread of new variants. Additional sites are being set up by the Chinese Ministry of Health and the WHO in populated areas of China, and especially in south China, where agricultural practices that permit close contact between human and animal populations may increase the probability of coinfections with different influenza A virus subtypes. Expansion of virologic surveillance in China should improve the frequency of correct matches between vaccine and wild strains during interpandemic periods. An active surveillance program in Hong Kong led to identification of the A/H5N1 virus that caused extensive poultry mortality and 6 human deaths in 1997 [10].

Objective 2: Improve national readiness to respond to a potential or actual influenza pandemic. To meet this objective, 8 priorities can be identified.

1. Assist state and local officials in their efforts to develop state and local preparedness plans.
2. Provide clinical guidelines for the community regarding the management of pandemic influenza.
3. The hallmark of large-scale influenza epidemics and pan-
demics has been their ability to cause major disruption of routine medical and community services. The A/H3N2 Sydney virus epidemic in Los Angeles in 1997–1998 occurred in an area that had seen a 17% reduction in the number of hospital beds since 1991, and the epidemic was responsible, in part, for a 61% increase in the number of hours that local emergency departments were required to divert patients to other facilities (C. Glaser, personal communication). In addition, the recent 22 cases of bioterrorism-related anthrax demonstrated how widespread disruption can be caused by only a small number of severe but unexpected and not well understood cases of illness in only a few geographic areas and by the need to offer antibiotic and vaccination prophylaxis to thousands of possibly exposed persons [11, 12].

As the influenza virus moves through the population, it leads to increases in the number of cases of respiratory illness, then to increases in the number of cases of pneumonia and other infection-related complications, and finally to increases in the number of deaths. Each of these events strains the ability of routine community medical services to provide adequate care, especially because providers themselves frequently are exposed and become infected. Experience with the Spanish flu pandemic in 1918–1919 also illustrates the enormous potential of influenza for causing acute social disruption on a scale similar to or even greater than that of other natural disasters.

Implementation of “generic” control measures traditionally used for infectious agents should be considered, especially in the context of potential vaccine shortages. However, because the novel influenza virus will likely be introduced multiple times in multiple locations throughout the United States, it is unlikely that transmission can be substantially contained by targeting surveillance and vaccination efforts to a limited number of sites (e.g., large metropolitan areas). Moreover, classical measures designed to reduce the risk of introduction and transmission of some infectious agents, such as clinical screening and quarantine at ports of entry, are not likely to be effective because of the large percentage of persons who will have clinically inapparent infection or nonspecific respiratory illness. Large-scale use of face masks during the 1918–1919 pandemic had no appreciable effect on community spread. Despite these and other impediments, ancillary control measures may limit, at least to some degree, the speed with which novel influenza viruses sweep through the population. Two of the most likely scenarios would be temporary closure of schools and day care centers, because of the important role of children as vectors of infection in prior pandemics, along with cancellation of nonessential public events at which large numbers of people might congregate in enclosed spaces. These and other potential scenarios require further discussion among national, state, and local health officials, along with criteria by which such measures

Table 1. Influenza pandemic preparedness plan objectives and priority areas.

| Objective 1: Strengthen national and global capabilities for virologic and disease surveillance with a view to increasing the likelihood of early detection of influenza and effective tracking of its spread in the population |
| Assist state and local officials in their efforts to develop state and local preparedness plans |
| Provide clinical guidelines for the community regarding the management of pandemic influenza |
| Create and institutionalize protocols for decision making with regard to the scope, timing, and coordination of responses by components of the Department of Health and Human Services, including protocols for interactions with other agencies of the federal government (e.g., the Federal Emergency Management Agency and the Department of Defense) and interactions with state and local governments, the news media, and other private entities |
| Develop flexible contingency plans for the procurement of vaccines and antiviral drugs |
| Develop flexible contingency plans to reduce potential liability risks to pharmaceutical manufacturers and health care workers and to provide compensation to individuals who experience vaccine- or drug-induced injury |
| Develop flexible contingency plans, in collaboration with state and local officials, to identify those population groups that should receive highest priority for access to vaccine and/or antiviral drugs |
| Collaborate with the international community on pandemic preparedness and planning |
| Identify and secure the resources necessary for an effective response |

Objective 2: Improve national readiness to respond to a potential or actual influenza pandemic

| Work with relevant public and private entities to ensure adequate health care capacity across the nation |
| Foster a strong, sustained basic and applied research program targeted at pandemic influenza |
| Promote the implementation of adult immunization programs (especially those involving influenza and pneumococcal vaccine) and improve vaccination coverage for high-risk groups |
| Develop communication networks and protocols for prompt dissemination of information to public health officials, health care providers, legislators, the news media, and the general public |
| Develop flexible contingency plans to reduce potential liability risks to pharmaceutical manufacturers and health care workers and to provide compensation to individuals who experience vaccine- or drug-induced injury |
| Develop flexible contingency plans, in collaboration with state and local officials, to identify those population groups that should receive highest priority for access to vaccine and/or antiviral drugs |
| Collaborate with the international community on pandemic preparedness and planning |
| Identify and secure the resources necessary for an effective response |

Objective 3: Strengthen influenza-related public health practices, infrastructure, and research

| Work with relevant public and private entities to ensure adequate health care capacity across the nation |
| Create and institutionalize protocols for decision making with regard to the scope, timing, and coordination of responses by components of the Department of Health and Human Services, including protocols for interactions with other agencies of the federal government (e.g., the Federal Emergency Management Agency and the Department of Defense) and interactions with state and local governments, the news media, and other private entities |
| Develop flexible contingency plans for the procurement of vaccines and antiviral drugs |
| Develop flexible contingency plans to reduce potential liability risks to pharmaceutical manufacturers and health care workers and to provide compensation to individuals who experience vaccine- or drug-induced injury |
| Develop flexible contingency plans, in collaboration with state and local officials, to identify those population groups that should receive highest priority for access to vaccine and/or antiviral drugs |
| Collaborate with the international community on pandemic preparedness and planning |
| Identify and secure the resources necessary for an effective response |
might be implemented, monitored, and stopped during the phases of a pandemic in the United States.

To cope with community disruption and increased demand for medical services that is national in scale and virtually simultaneous, it is essential that contingency plans for dealing with such emergencies be developed at the national, state, and local levels in advance of the pandemic. Guidelines for proper triage and treatment of patients with influenza-related illness and contingency plans for identifying additional personnel for essential medical and community services will be especially important. Draft guidelines have been created by a federal working group and are being widely reviewed by federal advisory committee members and consultants to assist health care institutions in maximizing staffed beds and resources available during an influenza pandemic. The greatest challenge for health care facilities is expected to be the management of high numbers of patients with reduced numbers of professional, ancillary, and housekeeping staff. Many hospitals already have protocols for periods when the number of patients is high and have emergency preparedness plans that can be adapted to pandemic planning.

A community-wide coordinated response will be essential; communities and health care organizations will need to have in place special guidelines for medical care in nontraditional settings. Plans should be updated, with special consideration given to the following factors: (1) reducing health care staff absenteeism during a pandemic; (2) ensuring expeditious patient discharge from hospitals; (3) ensuring that emergency departments are prepared for high patient volume; (4) reviewing policies for admission to hospitals and for scheduling of elective procedures and considering how and when to implement contingency plans, such as limitations on elective admissions and surgery; (5) planning for the limited availability and increased need for allocation of equipment and supplies (such as respirators, gurneys, and supply carts) within health care facilities and for potential disruption in the normal delivery of supplies and repair services during the pandemic; and (6) developing, in advance, patient-isolation plans for use during a pandemic.

Existing "generic" emergency preparedness plans can provide the overall framework for many of these activities, but at least some modifications will be needed in a pandemic because of its sudden, widespread, and potentially severe nature. The Department of Health and Human Services' Office of Emergency Preparedness will assume leadership at the national level to coordinate the responses of the US Public Health Service related to health and medical needs and can also call upon other governmental resources (i.e., the state Offices of Emergency Services and the National Emergency Management Association) and nongovernmental resources as needed. Other elements of emergency management at the national level, if required, can be coordinated by the Federal Emergency Management Agency through its system of regional offices and local contacts. These issues are similar to those confronted in planning for biological and chemical terrorism, and influenza pandemic preparedness planning can benefit from those efforts [13, 14].

3. Create and institutionalize protocols for decision making with regard to the scope, timing, and coordination of responses by components of the Department of Health and Human Services, including protocols for interactions with other agencies of the federal government (e.g., the Federal Emergency Management Agency and the Department of Defense) and interactions with state and local governments, the news media, and other private entities.

Proposed definitions of the phases of a pandemic and suggested responses by WHO and national government agencies are discussed in the WHO pandemic plan [9]. It has been proposed that US government pandemic action plan responses should be similar in nature, and these are presently under review.

4. Develop flexible contingency plans for the procurement of vaccines and antiviral drugs.

5. Develop flexible contingency plans to reduce potential liability risks to pharmaceutical manufacturers and health care workers and to provide compensation to individuals who experience vaccine- or drug-induced injury.

6. Develop flexible contingency plans, in collaboration with state and local officials, to identify those population groups that should receive highest priority for access to vaccine and/or antiviral drugs.

7. Collaborate with the international community on pandemic preparedness and planning.

8. Identify and secure the resources necessary for an effective response.

Objective 3: Strengthen influenza-related public health practices, infrastructure, and research. To meet this objective, 5 priorities can be identified.

1. Promote the implementation of adult immunization programs (especially those involving influenza and pneumococcal vaccine) and improve vaccination coverage for high-risk groups.

In recent decades, influenza vaccination programs have seen modest successes. Before 1989, vaccination coverage among elderly persons only rarely exceeded 25%, due in part to the continued misconception that influenza is a mild illness, apprehension about vaccine-associated adverse events, concern about the degree and longevity of protection after vaccination, missed opportunities for vaccination by health care providers, and marked declines in publicly funded programs at the state and local levels. Fortunately, influenza vaccination coverage increased markedly during the 1990s—to ~67% of persons aged ≥65 years in 1999—largely due to improved information and
education programs initiated by the public and private sectors, reimbursement by Medicare for annual vaccination of elderly persons, increased vaccine delivery efforts by the private sector, and improved perception and repeated demonstration of the effectiveness of annual vaccination [15]. Vaccination coverage with pneumococcal polysaccharide vaccine among elderly persons has also increased but only to 54% [15]. However, recent surveys have also revealed inequities in coverage for certain groups; coverage rates are substantially lower among African Americans and the poor [15, 16]. In addition, vaccination coverage with both influenza and pneumococcal vaccines among high-risk groups aged <65 years remains below the 60% target set in the Healthy People 2010 objectives [17].

2. Work with industry to ensure adequate capacity for production of influenza vaccine and antiviral drugs.

Introduction of new techniques, such as the use of high-yield reassortants, more-advanced automation in manufacturing procedures, and improved testing and lot-release methods, has improved both the quantity and quality of influenza vaccine available. Indeed, domestic influenza vaccine production has increased dramatically during the past decade (>70 million doses of trivalent vaccine were produced annually during 1997–2000) and is now at a level at which vaccination of virtually the entire US population against a pandemic strain (with monovalent vaccine) can be considered feasible, if no other influenza vaccine would be required during the same season. Nevertheless, current production techniques require large numbers of embryonated chicken eggs, a requirement that could severely limit vaccine production outside the normal production cycle (which is January–August, in most years). Even under optimum conditions, with current technology, 6–9 months would be needed from the time that a new virus variant is identified until the time that tens of millions of doses of vaccine would be available for administration. Diminished yields of a vaccine strain and manufacturing problems, both of which occurred in 2000, can lead to significant delays in the delivery of influenza vaccine to the public [18]. As discussed in the previous report in 1997 [6], development of alternative vaccines, use of cell substrates other than chicken eggs, and further improvements in high-growth reassortants used in vaccine production continue to be high priorities for vaccine research [19].

The development and use of the antiviral agents amantadine and rimantadine have expanded options for both prevention and treatment of type A influenza; however, the emergence of influenza strains resistant to these antivirals continues to raise concerns and could limit their use in a pandemic. The recent approval in the United States of 2 neuraminidase inhibitors for treatment of influenza (and 1 for chemoprophylaxis against infection) increases the options for influenza control, but all of the available drugs have potential risks and limitations [3].

New information on the optimal role for these drugs in control of a pandemic needs to be integrated as it becomes available. In addition, the potential supply of antiviral drugs in a pandemic is uncertain; this should be clarified to permit effective recommendations to be made. An adequate supply of these drugs would permit them to be used more widely than at present. Advances in the diagnosis and treatment of secondary complications of influenza, such as bacterial pneumonia, have led to decreases in morbidity and associated mortality. However, much of this success has already begun to be undermined by the insidious emergence of antibiotic-resistant strains of Streptococcus pneumoniae and other pathogens, which can cause secondary bacterial infections.

3. Develop communication networks and protocols for prompt dissemination of information to public health officials, health care providers, legislators, the news media, and the general public.

4. Foster a strong, sustained basic and applied research program targeted at pandemic influenza.

Research on influenza provides insights into how new influenza viruses emerge and cause disease and improves our understanding of the determinants of susceptibility or immunity to infection in human and animal populations. Novel breakthrough technologies, such as the recently developed ability to genetically engineer influenza viruses entirely from cloned DNA, not only may improve our ability to produce vaccines against epidemic and pandemic viruses but also, more intriguingly, may allow the influenza virus to serve as a vector for producing vaccines against other diseases. Through applied research, investigators are engaged in a multifaceted effort to improve the current inactivated influenza vaccine [20]. These efforts include the development and clinical evaluation of vaccines that contain live attenuated viruses or that no longer have to be produced in chicken eggs [21–23].

Despite these advances, there remain many understudied areas that must be addressed if we wish to respond effectively to an influenza pandemic. Because, in a pandemic, the amount of vaccine initially available will be limited, additional studies are needed to test vaccine adjuvants or use of reduced dosages of the current inactivated vaccine as a means to extend the vaccine supply. Other high-priority research activities include the following: assessment of the mechanisms and clinical relevance of antiviral drug resistance, extension of the shelf life of antiviral drugs, more-thorough assessment of antiviral drug effectiveness in children, prevention of the complications of influenza, increasing influenza surveillance in animals, preparation and testing of vaccines with novel influenza proteins or common epitopes, and updating and expansion of the influenza reagent library as a resource to the world’s research community [6, 24, 25].
SUMMARY

The ability to respond to pandemic influenza depends on substantially strengthening the infrastructure devoted to the control of influenza in the United States during the present interpandemic period. Ongoing activities related to the detection and control of new variants of influenza virus are critical and require strengthening of the current infrastructure for surveillance, vaccination, and other essential activities at the state and local levels. Steps should be taken now to identify important gaps in existing activities so that the United States will be adequately equipped to respond to the next pandemic. Key elements of the plan must also be integrated with ongoing related initiatives, such as the adult and childhood immunization initiatives [26–28] and emergency preparedness planning for acts of biological and chemical terrorism [13]. An effective influenza pandemic preparedness plan must be national in scope and should not be restricted to consideration of federal or government responsibilities. Broad and active participation by a wide variety of organizations in the public and private sectors at the national, state, and local levels will be needed.

Influenza control has improved markedly since the last pandemic in 1968, with great progress in many areas, such as surveillance, vaccine production and coverage, and chemoprophylaxis. However, inherent limitations in some areas, such as the ability to rapidly produce the current inactivated vaccine, its lower effectiveness in older and immunocompromised populations, and diminished medical inpatient care capacity, pose significant challenges for annual influenza control, particularly so for an influenza pandemic. Planning for a pandemic has been underway for a number of years at the national and state levels and should help maximize efficient use of available resources. The current planning efforts for bioterrorism preparedness complement and enhance those for pandemic influenza.

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