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Tick-Tock: Preparing for the Next Influenza Pandemic

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OVERVIEW — *This paper describes the nature of pandemic influenza and highlights key challenges for responding to this disease threat. It explains how an influenza pandemic would differ from annual influenza outbreaks and examines how a pandemic virus could emerge. It also explores important issues involved in pandemic preparedness capabilities, including disease surveillance, vaccine production and distribution, antiviral stockpiling, health care system readiness, and public health containment measures. The national pandemic preparedness plan is briefly reviewed, and unresolved policy issues related to the plan's implementation are identified.*

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Tick-Tock: Preparing for the Next Influenza Pandemic

Over one-fourth of the nation's population has been stricken by a mysterious, fast-moving, and virulent communicable disease. Among the huge number of people who have contracted the disease, a small but significant proportion die. In mere months, the killer disease has left over half a million people dead nationwide and over 21 million dead globally. Death rates among young adults are particularly high.

Severe shortages of nurses and doctors leave many to suffer alone without medical attention. Schools, churches, and other community organizations close. Essential services such as police protection, transportation, and telecommunications nearly grind to a halt due to the staggering number of people incapacitated by the disease. The economic impact is enormous and millions of dollars are lost. In many urban areas, the bodies of the dead begin to pile up because morticians are unable to keep pace with the number of fatalities, adding to the public's sense of panic and despair.

To prevent further disease spread, Congress dedicates unprecedented resources for identifying the cause of the disease and developing an effective treatment. The U.S. Public Health Service also investigates a widely held theory that Bayer aspirin¹ has been intentionally contaminated to spread the disease.

This grim scenario may appear to be a modern day bioterrorism nightmare. It is, in fact, a description of the influenza pandemic that swept the globe in 1918, commonly (though mistakenly) called the Spanish flu. Since then, the world has witnessed two, less lethal pandemics, and most experts believe it is simply a question of when—not if—another influenza pandemic will confront us.

A MATTER OF TIME

In many ways, we are much better prepared to confront the challenges of another pandemic than at the turn of the century. Advances in virology have enabled the development of influenza vaccines that provide disease immunity. Effective antibiotics exist to control the secondary bacterial infections that contributed to the high mortality rates in 1918. Diagnostic technology and surveillance capacity are much more sophisticated than they were in the early 20th century.

Despite improvements to medical technologies and public health practice, pandemic influenza still brings challenges, perhaps even greater than those of 1918. There is still no *cure* for influenza. Antivirals add therapeutic

pan·dem·ic [from the Greek *pan* (all) + *demos* (people)]: used to describe a world-wide epidemic.

value and lessen the disease's impact, but these agents are in short supply and have other significant limitations. Also, while antibiotics are now available, antibiotic resistance has become extremely common; therefore, the reliability of existing antibiotics cannot be assured. Further complicating these risks, a much larger number of people are immunocompromised, such as the elderly and persons with HIV/AIDS, placing new demands on contemporary medical and public health systems.

Most disturbingly, the vaccine development process will be measured in months, whereas disease spread may be measured in hours. The globalization of human society along with the ease of air travel mean that influenza will spread across the planet much more quickly than it did nearly a century ago. Demographic shifts further compound the rapidity with which a pandemic is likely to spread. Since 1918, the world's population has grown threefold and is increasingly concentrated in large, densely populated metropolitan areas.

The recent outbreak of SARS initially caused many public health officials to worry that the next pandemic had indeed arrived. Heroic work by virologists around the world quickly revealed that the disease agent responsible for SARS was not influenza. Although SARS itself represented a significant health challenge, the public health community breathed a collective sigh of relief that the sands of time had not yet run completely through the pandemic hourglass. The SARS scare did serve as a compelling reminder that the next infectious disease threat could be just a plane ride away and that the international spread of a communicable organism is rapid. Had SARS been as difficult to contain as a pandemic influenza, international penetration would have been not only rapid, but complete.

Developing an adequate response to pandemic influenza represents an immediate challenge to policymakers. The difficult decisions involved in this challenge are grounded in a host of complex scientific and technical issues that characterize the unique nature of pandemic influenza. Policymakers will rely, to a large extent, on the recommendations of scientific experts who are well versed in these complexities. However, it is critical for the elected officials who will make pandemic-related decisions to gain a clear understanding of the pandemic influenza threat. Although they will not have to confront many of these decisions until a pandemic occurs, many more choices must be grappled with now to ensure an effective response when needed.

NATURE OF THE BEAST

Influenza is generally an acute, self-limiting upper respiratory infection that is easily transferred from person to person through respiratory droplets (via coughing, sneezing, etc.). It is highly communicable for a variety of reasons, including its ease of transmission, short incubation period, infectivity before the onset and in the early stages of symptoms, and ability to remain viable outside the body for hours, especially in cold weather.

The next infectious disease threat could be just a plane ride away.

During the annual influenza season, complications and death occur in a limited proportion of cases, particularly among high-risk groups like older persons and young children whose bodies are immunologically weaker. Common complications include secondary bacterial infections and exacerbation of existing chronic conditions, like cardiopulmonary disease. A “normal” influenza season in the United States typically results in 36,000 deaths and 114,000 hospitalizations nationally, with mortality and severe morbidity largely concentrated in persons over the age of 65.²

Differences Between Pandemic Influenza and the Annual “Flu”

The influenza virus is a particularly vexing public health threat due to its ability to change over time and elude the body’s natural defense mechanisms. When infected by a microorganism, the human body produces antibodies that react with and incapacitate the invader. These antibodies are highly specific to substances (antigens) on the outer surface of the infective agent, and generally form about 10 to 14 days after initial contact with the antigen. (The time frame varies depending on the type and dose of the antigen.)

A second exposure to the same or a closely related antigen will result in a much quicker and stronger production of antibodies, preventing or greatly reducing the impact of illness. In this way people acquire immunity or resistance to specific disease agents, and this “immunological memory” generally lasts a lifetime. The influenza virus, however, is able to essentially outsmart the body’s immunological memory by changing its outer surface through genetic mutation. Thus, people are susceptible to infection even if they’ve already contracted influenza or have been previously immunized.

The degree to which the influenza virus will change is highly unpredictable, as is the impact these changes will have on individuals’ ability to mount an immune response. Human influenza viruses are classified into three main types: A, B, and C. During nonpandemic periods, influenza A and B viruses evolve by accumulating mutations, a process called “antigenic drift.” These new strains created by antigenic drift necessitate annual changes in the composition of the influenza vaccine. However, because the changes are relatively minor, most people will be able to mount an immune response that offers some protection to a new strain (due to prior exposure to similar strains) even if they have not been vaccinated.

Occasionally, the influenza virus will undergo a sudden, dramatic change, in one or both of two surface proteins called haemagglutinin (H) and neuraminidase (N). This type of change is known as “antigenic shift,” and may result in a pandemic. When the antigenic profile of the virus changes rapidly and significantly, it is likely that the surface of the virus will look completely different than what the body has seen before, superseding the immunological memory capacity of most people and leaving

them highly vulnerable to this particular strain. Such “novel” subtypes have not previously infected humans or have not infected humans for a long time.

Pandemic strains spread rapidly throughout the global population precisely because few (if any) people are immune. During normal influenza epidemics, portions of the population have complete or partial immunity to the circulating strain. Fully immune persons act as brakes on the spread of the disease. Because they don’t become infected, they are unlikely to spread the disease to others. When a population includes a large number of immune persons, the population is said to have “herd immunity.” Under these conditions, the virus cannot find enough susceptible people to infect and transmission is slowed dramatically. In a pandemic, no herd immunity exists, almost everyone is susceptible, and the disease spreads unchecked throughout the population.

Causes of Antigenic Shift

Antigenic shift is typically caused by genetic reassortment, which occurs when human influenza viruses exchange genes with animal influenza viruses, allowing the virus to acquire new H or N antigens. The resulting strains are identified by their H or N subtype. In other words, a pandemic strain represents a new “breed” of influenza virus, whereas the changes observed annually reflect variations within a breed.

The number of animal hosts that can contract influenza compounds the potential for antigenic shift. Type A influenza³ infections are common in free-living aquatic birds and also occur in many types of domesticated animals, including chickens, ducks, turkeys, swine, and horses. These animals are often referred to as disease reservoirs. Although the viral strains that infect these animals generally do not transmit to humans, such transmission is possible. Fortunately, if animal-to-human transmission does occur, these viral strains do not usually transmit well between humans.

The potential for genetic reassortment, and thus a possible pandemic, is perhaps greatest when a person or animal is simultaneously infected with both a human influenza virus and an animal influenza virus. This type of co-infection might allow a human influenza virus (already well adapted for person-to-person spread) to acquire an unfamiliar antigenic profile through reassortment. Co-infection is not, however, a necessary prerequisite for a pandemic. An animal influenza virus could gain the ability to infect people and transmit between people through spontaneous genetic mutation, rather than reassortment, but such events are thought to be very rare.

Novel Virus: Cause for Concern, but Not Alarm

Although all pandemics begin with the emergence of a novel virus, not all novel viruses spread or cause pandemics. For example, in 1976 a novel

Not all viruses spread or cause pandemics.

subtype of influenza caused a localized outbreak at Fort Dix and the first person known to have contracted the virus died. Laboratory testing showed that the strain (H1N1) was related to the strain that created the 1918 pandemic. Many at the fort were found to have contracted the virus, suggesting the likelihood of person-to-person spread within the barracks.

A major campaign was initiated to develop a vaccine and vaccinate the population against this “swine flu.” However, the virus did not spread widely beyond the camp. Some believe that the decision to initiate and promote a vaccine program was premature, damaged the credibility of public health, and contributed to the public’s complacency about infectious disease threats. As it is often said, however, hindsight is 20/20. In the case of swine flu, the specter of another influenza pandemic prompted aggressive, albeit flawed, decision making.

The Next Pandemic

Though “near misses” do not necessarily generate pandemics, they are cause for serious concern. As the number of human cases infected by animal viruses increases, the probability of co-infection increases, and the chances of reassortment improve. The genetic reassortment that can take place during co-infections is as uncertain as a roll of the dice: A pandemic strain may or may not emerge. If one does, that strain’s characteristics, such as virulence, communicability, and pathological properties, cannot be determined in advance.

Although the characteristics of the next pandemic virus are impossible to predict, the scale of any influenza pandemic ensures significant levels of social disruption and increased mortality relative to a “normal” flu season. Preliminary estimates indicate that an influenza pandemic would cause between 88,000 and 227,000 deaths and economic losses in the range of \$71 to \$166 billion in the United States alone.⁴

These severe health and social consequences have galvanized global planning efforts to prepare for the next pandemic. Recent cases of humans becoming infected with a highly pathogenic avian influenza (H5N1) in Thailand and Vietnam have heightened the concerns of public health authorities. The World Health Organization (WHO) has confirmed 34 human cases of H5N1 infection as of March 24, 2004, and 23 of these cases resulted in death.⁵ Although the number of human cases has been relatively small thus far, the human fatality rate associated with these cases is high and the prevalence of the H5N1 strain in poultry throughout China and Southeast Asia is widespread and persistent. The H5N1 strain has also been identified in pigs in China, a worrisome finding as pigs can also serve as hosts to human influenza viruses.⁶ The prevalence of the pathogenic strain increases the likelihood that it might adapt to people through either co-infection resulting in reassortment or a spontaneous mutation, making H5N1 a candidate for the next pandemic.

It may not be possible to prevent the next pandemic from occurring, but careful planning may delay the emergence and slow the spread of a pandemic strain, as well as mitigate the risks associated with an influenza pandemic. Public health officials in the United States and around the world have been working collaboratively for several years to improve pandemic preparedness. These planning efforts have revealed a number of challenges that must not be overlooked. As the following narrative illustrates, some of these challenges relate to improving interpandemic capacities and others to making important decisions in advance to increase the speed and efficiency of a pandemic response.

IMPROVED SURVEILLANCE AND OTHER PUBLIC HEALTH MEASURES

Time is of the essence in pandemic preparedness, and robust surveillance is the key to a timely response. The sooner a human infection by a novel virus is identified, the sooner an investigation into the efficiency of person-to-person transmission can commence. If the novel virus is found to be communicable, steps can then be taken to initiate vaccine production and begin containment strategies. Failure to identify the novel virus early could ensure widespread disease and contribute to its health and economic toll.

Ongoing influenza surveillance is conducted by a worldwide network of 110 National Influenza Centers and many other WHO laboratories in 83 countries.⁷ Each year, a sample of influenza virus isolates drawn from these labs are intensively analyzed by WHO Reference Centers in London, Atlanta, Melbourne, and Tokyo. These reference centers examine the viruses to identify emerging strains, and this information is used to formulate a vaccine for the next flu season. Although this process is very effective for monitoring antigenic drift, it is unlikely that these routine surveillance methods will detect an antigenic shift or novel virus. Routine laboratory analysis is conducted on a relatively small sample of influenza cases worldwide, therefore the probability that a novel virus will be detected from this sample is very low.

Recognizing an antigenic shift will likely depend on alert clinicians, good relationships between health professionals and public health authorities, and a robust public health infrastructure. Influenza is not a “reportable” disease, but health professionals are advised to alert public health authorities of any unusual occurrence of infectious disease. The expectation in most developed countries is that careful attention should be paid to influenza outbreaks that are associated with unusual health outcomes, such as those that cause death in healthy adults not considered at high risk for influenza mortality. It is hoped that such cases would be intensively investigated and that WHO Reference Center laboratories would analyze clinical specimens quickly to determine if a novel virus has emerged.

Robust surveillance is the key to a timely response.

Unfortunately, the parts of the world most hospitable to the emergence of pandemic influenza are the least likely to have robust surveillance capabilities. Novel viruses are more likely to emerge in places where humans and animals known to be influenza reservoirs, such as pigs and chickens, live in close proximity. Conditions in China and Southeast Asia may be particularly conducive to influenza reassortment due to the number of households that contain domesticated livestock and the prevalence of avian influenza in those regions. The influenza surveillance capabilities in many of those countries affected by the recent avian flu outbreak are poor to nonexistent. Although several human cases of infection by a novel virus have been documented, experts worry that many more cases are occurring without being detected or investigated.

Though international public health authorities have particular concerns about specific parts of the world, it is worth noting that novel viruses and pandemics can emerge anywhere. In fact, one theory suggests that the 1918 flu originated in Kansas. Furthermore, the strength of surveillance capacity within the United States is not above reproach; numerous studies have demonstrated the delays associated with infectious disease reporting in this country. Even at the height of the anthrax scare, health professionals waited days before contacting public health officials, in some cases.

Public health measures may be effective in preventing the emergence of a pandemic strain if initiated early. Actions to minimize the potential for animal-to-human transmission, such as destroying poultry flocks infected with pathogenic avian influenza virus, reduce the likelihood of human infection by a novel virus. Should human infection occur, isolation and aggressive treatment of affected patients may decrease the likelihood of a reassortment event.

Opportunities for delaying the spread of a possible pandemic virus are greatest when only a few clusters of cases have occurred, that is before a pandemic has been declared. At this stage, a variety of public health measures, such as isolation of ill persons, contact tracing, quarantine of contacts, and aggressive treatment with antiviral agents, may prevent or slow further transmission. However, this window of opportunity is likely to close quickly if strong public health actions are not implemented rapidly. The time sensitivity of these interventions underscores the need for effective surveillance to identify early cases.

Phases of a Pandemic

Phase 0, Preparedness Level 0

Inter-Pandemic Period: Three or four strains of influenza virus circulating which are similar to strains that have circulated in the recent past.

Phase 0, Preparedness Level 1

Initial Report of a New Strain in Humans

Phase 0, Preparedness Level 2

Novel Virus Alert: Human infection is confirmed.

Phase 0, Preparedness Level 3

Human Transmission Confirmed

Phase 1

Confirmation of Onset of Pandemic: Efficient person to person transmission is confirmed.

Phase 2

Regional and Multiregional Epidemics

Phase 3

End of First Pandemic Wave

Phase 4

Second or Later Waves of Pandemic (typically 3 to 9 months following initial epidemic)

Phase 5

End of Pandemic: Reversion to Phase 0.

Source: World Health Organization

Experts caution that surveillance capabilities both domestically and internationally require additional investment. These needs include:⁸⁹

- Better integration of clinical disease surveillance and laboratory-based testing on influenza isolates.
- Additional resources to support existing human surveillance activities, particularly in the developing world, including the development of multidisciplinary teams to investigate unusual case clusters.
- Expanded disease and virologic surveillance of animal reservoirs and increased collaboration with veterinary disciplines to improve coordination of animal and human surveillance activities.
- Development of additional diagnostic tools (such as reagents and standardized laboratory protocols) for quickly identifying influenza viruses of all subtypes circulating in both human and animal populations and prioritizing those known to have caused human infection.
- Improved international efforts to coordinate data collection and management.
- Better education of health care professionals to enable recognition of suspect cases and reporting to appropriate authorities.

Even with enhanced surveillance capacities, many experts believe that a pandemic threat may not be evident until the disease has already become widespread within a geographic area. This may happen either because early surveillance failed to detect initial clusters or the virus emerged with a full-fledged capacity for efficient human transmission.

Once a pandemic is officially declared, it is unclear whether additional opportunities for slowing international spread and minimizing disease penetration within affected populations are still available. Travel warnings, exit screening of travelers from affected areas, and measures to increase social distance (such as cancellation of mass gatherings and school closings) may help to slow the spread of the disease. At this point, contact tracing and quarantine of health contacts is not likely a wise use of resources, because the virus will have become too widespread to contain through such targeted measures. Surveillance emphasis should also shift at this point to monitor total disease burden and track epidemiological trends to identify high-risk populations.¹⁰

Public anxiety will be running high if a pandemic is beginning to sweep the globe, and public health officials must be prepared to respond to these concerns. Skillful risk communication will be necessary to reduce panic and help individuals make informed decisions. People will want information on what they can do to reduce the possibility of exposure, even simple directives such as hand washing and when they should seek medical care if they become ill.

One of the biggest communication challenges will be helping the public understand why vaccine will not be available early in the pandemic and why it will be in short supply once it is produced. Some public health

agencies are already using the annual influenza season to educate the public on influenza vaccine production and to reinforce the importance of good hygiene. These types of pre-pandemic efforts may help communications with the public during a pandemic, although the level of public unrest likely during a pandemic will call for a more aggressive communications strategy.

VACCINE PRODUCTION AND DISTRIBUTION

Vaccination is the best defense against influenza. Available treatments have serious limitations, and traditional public health containment efforts can only hope to slow—not stop—a fast-moving, highly communicable disease like influenza. The vaccine serves to “jump start” the body’s immune response by providing the body with antigenic material similar to the circulating viral strains, thus prompting the body to begin antibody production. Should the vaccinated person come into contact with the influenza virus, their immune response will be poised to combat the disease agent.

The annual flu vaccine is safe and effective. Inactivated influenza vaccine has been used widely for 60 years, and manufacturers have made significant improvements since its introduction.¹¹ Although whole, inactivated viruses were first used, partially disrupted viruses (split vaccines) and purified envelope antigens (subunit vaccines) have since been introduced to improve safety while maintaining effectiveness. Although a single inoculation of inactivated vaccine is generally sufficient for persons who have had prior exposure to a similar strain, two inoculations are generally needed for persons with no prior exposure (a circumstance likely during a pandemic).

Given current technology, it will likely take a minimum of six months to begin manufacturing vaccine. Development and production of pandemic influenza vaccine cannot be initiated until a novel virus is identified and isolated. In light of the long lead time for development and the critical importance of vaccine, pandemic preparedness efforts have focused substantially on shortening the time frame between the emergence of a pandemic virus and the availability of vaccine for distribution. While some of these efforts center on improved surveillance, most target the vaccine production process.

The Vaccine Production Process

Influenza vaccines are produced by inoculating embryonated hens’ eggs (that is, eggs with embryos in them) with influenza virus. In the event of a pandemic, the first step in this process will be the development of virus “seeds” that match the antigenic profile of the circulating pandemic virus. In some cases, new strains do not grow well in the eggs, and a “high growth reassortant virus” is developed to increase the yield of vaccine virus per egg. In the recent past, such growth problems have delayed the shipment of annual flu vaccine.

It will likely take a minimum of six months to produce a pandemic influenza vaccine.

It is also very possible that the emergent strain will be highly pathogenic both for the embryonated chicken eggs and for the people involved in vaccine production. These issues will likely require both the use of specialized biocontainment facilities and the introduction of genetic manipulation techniques, known as reverse genetics, to allow for the timely creation of a safe, high-growth vaccine seed virus. Scientists estimate that the development of such a vaccine seed takes two to three months to complete once a target strain is identified.¹²

After the eggs are inoculated, vaccine lots first become available within four to five months.¹³ During this period, the vaccine virus replicates within the eggs. Once sufficient growth has occurred, harvested egg fluids are processed to concentrate, purify, and inactivate the virus from which the vaccine will be produced. Further steps for purification and standardization of vaccine potency are then completed.

Similar to most vaccine products, the capital-intensive, specialized nature of the influenza vaccine production process tends to limit the number of manufacturers willing to compete in the market. Only three firms currently produce influenza vaccine for the U.S. market. Both Aventis Pasteur, Inc. and Chiron produce inactivated vaccine, and MedImmune, Inc., produces a live, attenuated (or weakened) vaccine product. Because production is highly concentrated among so few manufacturers, problems encountered by any one manufacturer can have a substantial impact on the availability of vaccine supply.

Proposals to Improve Production Capabilities

Ongoing efforts and proposals to speed the availability of influenza vaccine in the event of a pandemic have focused on two major issues: (a) improving the production capacity of existing technologies and (b) developing new production technologies that allow more vaccine to be produced in a more timely manner. These efforts and proposed strategies include:

■ **Increasing Annual Influenza Vaccine Rates.** In 2003, approximately 87 million doses of influenza vaccine were produced for the U.S. market.¹⁴ Assuming one dose per person, this production level would support annual vaccination of roughly 30 percent of the U.S. population.¹⁵ In fact, the true vaccine coverage rate is probably lower, given that some individuals, such as children receiving the vaccine for the first time, require two doses. Manufacturers strive to peg production volume, and thus production capacity, to the anticipated demand in order to minimize financial losses due to unused supply. The long lead time in vaccine production and the short “shelf life” of flu vaccine make it difficult to respond quickly to changes in demand. When demand is unexpectedly high, like it was in the 2003–2004 flu season, vaccine shortages occur. Prompting and sustaining greater demand for the annual vaccine would encourage manufacturers to invest in expanded production capacity and might entice more manufacturers to enter the

market. Some observers have advocated for guaranteed government purchase of surplus vaccine and for public education to increase vaccination rates and help make yearly demand levels more predictable and robust. However, opinions regarding the merit of this strategy are mixed, as some observers have expressed concern about the long-term effects of government purchase guarantees and how they might affect market dynamics.

■ **Ensuring Year-round Egg Supply to Increase Surge Capacity.** The influenza vaccine is currently dependent on embryonated hens' eggs, a production process which in turn is dependent on the reproductive biology of chickens. Vaccine manufacturers generally place orders for eggs approximately 6 months before inoculation with the vaccine seed. Depending on the time of year when the pandemic strikes, a supply of eggs may not be available to support vaccine production. Ensuring year-round availability of embryonated eggs could reduce the time to vaccine production, and the Department of Health and Human Services (DHHS) has made investments in this regard.

■ **Developing Non-Egg-based Production Procedures.** Cell culture-based growth media for vaccine production is available and currently licensed in some countries. Cell lines are necessary for reverse genetic technologies and promise to eliminate some of the limitations inherent to egg-based vaccine production. Expanding this capacity will involve increasing the availability of suitable cell lines and encouraging manufacturers to diversify their production processes to include this technology through regulatory and perhaps payment incentives. Efforts to achieve these objectives have already been initiated. A move to cell-based vaccines would also require surveillance laboratories worldwide to begin using cell lines approved for human vaccine use, a requirement that would have significant resource and operational implications.

■ **Initiating Advance Preparation of Vaccine Production Seeds.** Preparation of vaccine seeds and production reagents for all known virus subtypes currently present in animal reservoirs could significantly expedite vaccine production when a pandemic strain emerges. If a library of virus subtypes suitable for vaccine seeds were developed, the first phase of vaccine production could be completed in advance of the pandemic, reducing the production time line by several months. Although the preselected vaccine would not likely be an exact antigenic match to the pandemic strain, it would provide at least partial protection until a tailored vaccine could be produced. Priority could be given to subtypes known to cause human infection, including the H2, H5, H7, and H9 subtypes.¹⁶ The use of reserve genetic techniques to engineer safe, high-growth variants of these subtypes could facilitate the ease and speed of production. Clinical trials on experimental vaccines produced from the seed library would also need to be conducted to determine dosage requirements and to identify possible adverse reactions. The National Institute of Allergy and Infectious Diseases has already awarded two contracts to support the production and testing of

Guaranteed government purchase of surplus vaccine may help to expand vaccine production capacity.

an investigational vaccine based on the avian strain of influenza (H5N1) implicated in the recent, highly pathogenic outbreaks in Asia.

■ **Reducing Legal Disincentives to Vaccine Production.** A variety of legal and regulatory concerns may hinder efforts to implement the improvements described above. Vaccine manufacturers' concerns related to liability and compensation, variations in international licensing standards, and intellectual property rights regarding organisms developed through reverse genetics are several factors that may discourage investments in needed improvements or might delay response activities in the event of a pandemic. Some manufacturers have advocated for federal liability protections and a harmonization of international laws and regulations related to vaccine development and production to address these concerns.

■ **Engaging in Additional Research.** In addition to the development activities described above, a wide range of other promising approaches merit further research. For example, the use of live influenza vaccines (currently licensed, but not in widespread use) needs to be evaluated in light of the stronger immune response they elicit. This attribute could be important in reducing the amount of vaccine required to produce an immune response, thus stretching the available supply to cover more people. Similarly, alternative vaccination techniques, such as new dosage approaches and the use of adjuvants, may increase immune response and conserve vaccine. Furthermore, some researchers believe it may be possible to develop a "universal" influenza vaccine that would be effective against all subtypes and would not be vulnerable to antigenic shift or drift. Although such a breakthrough is not likely in the foreseeable future, its long-term potential is intriguing.

Distribution Concerns

If the vaccine production challenges were not daunting enough, additional challenges will be faced once the first supplies of a pandemic vaccine are available for distribution. The first production lots will not be adequate to vaccinate the entire population, and hard decisions will have to be made in selecting priority populations. Essential personnel, such as health care workers, police, and other first responders, are likely to be prioritized for vaccination, as are high-risk populations. Older persons and others with compromised health status will be at high risk for severe illness. The degree to which other groups will also be at elevated risk for severe outcomes is not certain, however, because the pathological characteristics of the pandemic virus cannot be ascertained until it emerges and begins to spread.

It is unclear whether the market-based approach currently used for the purchase and distribution of the annual flu vaccine will be suitable under pandemic conditions. The urgent need to rush production, focus limited vaccine supplies on priority populations, and ensure that vaccinations are

administered immediately suggest that a more coordinated, government-sponsored purchase and distribution arrangement could be needed. It is unlikely that existing private sector contracts for vaccine supply would be valid for a pandemic strain, as these contracts are specifically negotiated each year for that year's annual vaccine. Furthermore, existing distribution mechanisms would probably not be sufficiently timely or targeted. When shortages were experienced in recent flu seasons, public health officials encountered a number of difficulties in attempting to redistribute supplies to target those at highest risk, illustrating the shortcoming of a market-based approach. However, a clear consensus regarding the most appropriate approach to vaccine procurement and distribution has not yet been reached.

Even if a coordinated distribution process is put into place, there will be additional hurdles associated with implementing a mass immunization program under conditions of social unrest and fear. Security measures will be necessary to ensure that supply is not inappropriately diverted in transit. Supplies will be limited, and tens of millions of vaccinations will need to occur in a very short time frame. Such mass vaccinations will require strong collaboration among public health authorities at the federal, state, and local levels and with private sector health care professionals. State and local public health planning and exercises for mass vaccination and drug distribution in preparation for bioterrorism attacks should be helpful in this regard.

Clinical considerations will include ensuring the availability of trained personnel to administer the vaccine. Logistical considerations will include identifying and preparing vaccination sites, securing necessary supplies (such as syringes), designing patient flow processes, and ensuring security. Legal concerns related to informed consent must be addressed, and administrative processes must be established to document persons vaccinated, verify their priority status, and document any adverse effects of the vaccine.

ANTIVIRALS AND OTHER MEDICAL INTERVENTIONS

Because vaccine is not likely to be available in the early months of the pandemic and initial supplies will be extremely limited, antiviral medications have the potential to play a very important role in pandemic response. Four antiviral agents—amantadine, rimantadine, oseltamivir, and zanamivir—have been documented as effective for both prevention (chemoprophylaxis) and early treatment of influenza. At this time, however, the Food and Drug Administration (FDA) has approved zanamivir for treatment purposes only and limits prophylactic use of oseltamivir to persons over the age of 13. Generic versions of amantadine and rimantadine are available. Zanamivir (trade name Relenza) and oseltamivir (trade name Tamiflu) are produced under patent by GlaxoSmithKline and Roche Laboratories, Inc., respectively.

Government-sponsored purchase and distribution of a pandemic vaccine may be needed.

For prophylactic purposes, antivirals have the advantage, relative to vaccine, of providing rapid onset of protection; unlike vaccine, however, this protection is short lived. For prophylaxis, antivirals must be taken daily for the entire time influenza is active in a community. For treatment purposes, antivirals must be taken within two days of illness onset to be effective.

Stockpiling Decisions

The biggest limitation regarding antiviral treatments is inadequate availability and limited production surge capacity. Unlike vaccine, however, antiviral agents can be stockpiled and planning efforts are examining this strategy. Important considerations include the mix and volume of drugs to include in the stockpile, the need to “forward deploy” these stockpiles regionally ahead of the spread of disease, and the costs associated with these fairly expensive products.

Even with enhanced stockpiles, strategic decisions will need to be made regarding antiviral use. Essential personnel (such as police, public health workers, and medical professionals) and high risk populations (such as the aged, those in institutional settings, and others, depending on the epidemiology of the disease) are likely candidates for priority populations to receive prophylactic antivirals. Targeting treatment supplies to those at highest risk may be more difficult, as the delivery of care will be highly decentralized.

In light of limited supplies, trade-offs between using the antivirals for prophylaxis or treatment are inevitable. Mathematical modeling can help to elucidate health impacts and cost effectiveness of alternative use and distribution strategies. Available modeling evidence suggests that mass prophylactic use of antivirals would not be efficient and that reserving available stocks for treatment and targeted prophylaxis (such as for essential personnel or for initial contacts in the very earliest stages of the pandemic) would be more prudent. Furthermore, the huge supply of antivirals that would need to be stockpiled for mass prophylaxis make this approach prohibitively expensive.

Some of the antiviral agents are known to stimulate the emergence of resistant influenza viruses, a fact that will also influence both stockpile composition and distribution strategies. Because these antiviral agents are sometimes used to treat annual influenza outbreaks, there are concerns that the pandemic strain may emerge resistant to these agents as well. Of particular concern is that the influenza viruses isolated from human cases of avian flu in Asia show resistance to amantadine and rimantadine. Other factors to consider are the side effects caused by available antiviral agents and the safety concerns these create.

Efforts to begin stockpiling antiviral agents will be influenced by the activities of other nations as well. Japan has already begun stockpiling Tamiflu. It is unclear what impact the small number of

manufacturers, limited production capacity, and potential for competing orders internationally will have on the cost and the timetable for U.S. stock-pile efforts.

Readiness of the Health Care Delivery System

Although antiviral agents will be important to managing an influenza pandemic, other types of medical care, such as proper hydration and nutrition, antibiotic therapy to treat secondary bacterial infections, and respiratory support interventions, are also important for reducing morbidity and mortality. Efforts to increase pneumococcal immunization rates now could reduce the threat of one of the more common secondary bacterial infections that often accompanies influenza. Pneumococcal immunization would also bring immediate health benefits for the elderly and children by decreasing the current incidence of pneumonia and ear infections.

Even if the next pandemic turns out to be relatively benign, the sheer volume of people requiring medical care will likely place heavy demands on the health care delivery system. In the event of a pandemic, emergency departments will be flooded and hospitalization rates will soar. Respiratory support equipment, such as ventilators, will also be in short supply. Hospital emergency departments are already severely stressed and are increasingly going on diversion status. This overcrowding is due, in part, to capacity constraints related to inpatient beds, particularly in intensive care units. In light of existing limitations for surge capacity, an influenza pandemic threatens to unravel an already frayed emergency care system. The Centers for Disease Control and Prevention (CDC) has developed two modeling tools, FluAid and FluSurge, to assist public health agencies and health care organizations in recognizing needs and planning resource requirements under different scenarios.

The combination of surge capacity needs and infection control requirements will place extraordinary demands on the health care delivery system. Although the very nature of a pandemic would make patient isolation infeasible, stringent infection control techniques (such as use of personnel protective equipment, hand washing, and environmental disinfection) will be needed, and some efforts must be made to limit contact between the sick and healthy in health care settings (such as the use of restricted waiting areas).

As with the pandemic of 1918, the constraints on availability of medical personnel, particularly nurses, will be problematic. Given existing workforce constraints and the likely event that many health professionals will themselves be severely ill, there are concerns that there will not be enough people to care for the sick. Hospitals and communities must anticipate these shortages and consider strategies to respond to these extraordinary surge pressures.

Current activity related to bioterrorism preparedness will undoubtedly help hospitals and health professionals prepare for large-scale infectious

In light of existing limitations for surge capacity, an influenza pandemic threatens to unravel an already frayed emergency care system.

disease events. However, unlike a bioterrorist event, which could be concentrated in only a few communities, the pandemic is certain to affect the entire nation—and the world—at the same time. Therefore, “borrowing” personnel from neighboring jurisdictions will probably not be an option. These workforce challenges, combined with bed and other physical constraints and infection control considerations, pose daunting planning challenges for health care delivery systems.

THE U.S. PANDEMIC INFLUENZA PREPAREDNESS AND RESPONSE PLAN

DHHS, in collaboration with multiple federal partners, recently released a national plan to prepare for and respond to the next influenza pandemic.¹⁷ The department has articulated three major goals for pandemic preparedness and response: (a) decrease the burden of disease, (b) minimize social disruption, and (c) reduce economic impacts.¹⁸

The plan consists of a “core” that describes national coordination roles and decision-making authority, provides an overview of key issues, and outlines response actions at national, state, and local levels.¹⁹ It also includes annexes that offer guidance for state and local health departments and for health care organizations. Additional annexes provide detailed technical information on issues related to surveillance, vaccine development and production, vaccine and antiviral use strategies, interventions to decrease influenza transmission, communications, future research priorities, lessons learned from the 1976 swine flu program, and comparisons between influenza and other infectious diseases.

Preparedness and response require collaboration internationally, across federal agencies, with state and local health officials, with private sector health care organizations and professionals, and with the public at large. Therefore, DHHS released this plan as a “draft” document, to elicit comments. The department anticipates that this process will help to refine the plan, which in fact must be continually modified over time to accommodate scientific advances and other changes in the world landscape.

The national plan provides a clear framework for advancing pandemic planning, but does not conclusively resolve a number of important decisions, due in part to the unpredictable nature of the pandemic threat. Although there is fairly strong scientific consensus regarding the steps that should be taken to enhance pandemic preparedness, many unresolved policy questions remain:

■ **Resource Allocation.** In many respects, pandemic influenza planning involves resource allocation decisions. What level of resources would be needed to implement all of the preparedness steps that have been proposed? Given that resources are likely to be limited in some fashion due to competing policy goals, how should priorities in funding be set? Which pandemic preparedness investments promise

What level of resources could be needed to implement all of the preparedness steps proposed?

to be most cost-effective? Which are most critical for ensuring adequate response? How should funding obligations be shared internationally and domestically? Are targeted appropriations required, or should important pandemic initiatives be absorbed within agencies' existing budgets? The national plan does not include specific budgetary recommendations, therefore pending decisions related to the funding and financing of pandemic preparedness investments will likely guide the extent of and time frame for readiness capabilities.

■ **Federal Role in Vaccine Purchase and Distribution.** The plan does not establish a definitive federal role in purchasing and distributing a pandemic vaccine in advance of a pandemic crisis. The plan allows for alternative scenarios, including complete federal purchase and distribution to states, partial federal purchase, and minimal federal purchase, depending on the nature of the pandemic. The plan also suggests that the federal role in vaccine purchase is likely to shift as the pandemic unfolds and vaccine becomes increasingly more available. Who should control the limited supply of vaccine? What criteria will be used to determine if complete federal purchase is warranted or when partial or minimal purchase should commence? Who will make decisions regarding how vaccine will be allocated across populations and across jurisdictions? Current ambiguity related to these questions requires states to develop multiple approaches to vaccine distribution and raises concerns about whether state-level public purchasing should be pursued. Industry representatives are equally apprehensive about these questions because the decisions will have important implications for their own marketing and investment strategies. The uncertain federal government role in vaccine procurement and distribution extends to multiple "second order" policies related to legislative authority, financing mechanisms, contractual agreements, and price negotiations. Absent a resolution of the federal role, multiple contingency plans must be established for these second order policies.

■ **Antiviral Stockpile Strategy.** The composition of, size of, and deployment strategy for the antiviral stockpile are presently open issues. Which antiviral agents should be stockpiled? How much of each should be secured? Where and how should the stockpile be deployed? Again, these decisions will have ripple effects throughout the pharmaceutical industry and public health infrastructure. One proposal being considered is whether to procure some of the antiviral agents in "jumbo" containers, rather than in traditional single or multiple dose units. Such an approach would save on packaging costs and could help to minimize acquisition costs, but would also raise logistical challenges and dispensing costs for those responsible for distributing antivirals. Further analyses of the costs and benefits of alternative strategies will help to clarify the best approach to antiviral stockpiling.

■ **Determination of Priority Populations.** The national plan charges states with establishing priority populations and offers broad guidance in this regard. Identifying which populations will get priority in receiving

vaccine and antiviral agents is likely to be a fairly controversial topic. Prioritizing essential personnel relative to high-risk individuals will probably generate a fair amount of debate, as will identifying specific groups of essential personnel, such as health care workers, police, fire and rescue personnel, and public health personnel. Potential differences in strategy across states may give rise to perceived inequities. How can these differences be harmonized? At the local level, classes of prioritized populations must be translated into actual, current lists of individuals to determine the quantity of vaccine and antiviral agents that will be required. This exercise suggests that the prioritization will be an iterative process and is tied to expectations regarding available vaccine supply as the pandemic evolves.

■ **International Distribution of Vaccine.** Planning related to vaccine purchase and distribution in the United States will need to be considered in the context of international demand. Some observers have noted that any given nation will only have access to the vaccine supplies produced within their borders in the event of a pandemic. If this is the case, U.S. planning efforts will need to make clear distinctions between domestic and imported vaccine production capacity. At the same time, U.S. policy will ultimately need to consider whether domestically produced vaccine will be made available to other nations and under what circumstances.

■ **Vaccine Production Improvements.** Expanding vaccine production capabilities may involve a balance between increasing the capacity of prevailing technologies and accelerating the development and adoption of new technologies. Though there is likely to be an attempt to pursue both strategies simultaneously, resource constraints may force a decision to favor one approach over the other. Which approaches appear to be the most cost effective? The most expedient?

■ **Liability Protections and Other Legal Considerations.** Observers have noted that a variety of legal concerns create significant disincentives to manufacturers considering the adoption of new vaccine production technology. These concerns relate to the potential liability exposure created by new approaches, intellectual property rights that limit the application of new techniques, and regulatory provisions that discourage investment in new production methods. Would addressing these issues increase the vaccine industry's motivation to pursue change? What are the costs and consequences of decreasing these legal burdens?

■ **Research Agenda.** A broad variety of new and future insights and scientific advances in influenza virology have the potential to reshape the parameters of influenza preparedness. Investments in these pursuits provide long-term promise but do not translate into immediate improvements in readiness. Balancing short-term versus long-term objectives represents a complex policy trade-off.

■ **Surveillance Enhancements.** Improvements in both domestic and international influenza surveillance involve a variety of investments, ranging from information systems development and laboratory

Under what circumstances might U.S. vaccine supply be made available to other countries?

enhancements to the training of personnel. Debate is likely to focus on who should be responsible for making these investments. Should the U.S. contribute to surveillance capacity in other nations? Should states bear some or all of the costs of surveillance improvements within their borders?

■ **Public Health Capacity and Health System Readiness.** Although the federal government is likely to assume responsibility for a number of key functions in pandemic preparedness and response, public health and health care delivery systems at the local level will very likely be asked to deliver vaccine, antivirals, health care services, and public health protections. These parties will look to the national plan to determine the depth and quality of the guidance it offers for carrying out these responsibilities. How much standardization in response protocols and capabilities is warranted? Should the federal government fund the planning and capacity building required to meet such standards? The national plan encourages states to program funding from the Bioterrorism Cooperative Agreement and the 2004 Immunization Continuation Grant for pandemic preparedness planning. State health departments and health care providers will likely seek greater clarity regarding the degree to which federal resources will be available to support pandemic influenza planning.

Many of these issues will require legislative action of some type and will rely on Congress for final resolution. While some of these policy questions may be considered and resolved in advance of the pandemic crisis, as additional analyses and negotiations are completed, others may be entirely dependent on the unique epidemiological and clinical characteristics of the pandemic virus. This degree of uncertainty is reflected in the national influenza plan as different contingencies are explored.

Although it cannot answer all open questions, the release of the national plan will encourage dialogue among public health officials at all levels of government and will facilitate the development of well integrated state- and local-level plans. As countries across the world develop national plans, international coordination can also be carried out under the auspices of the WHO. Such coordination will help minimize inconsistencies across states or nations that might impede a pandemic response. This interactive and interdependent response is critical in light of the global nature of the pandemic threat.

CONCLUSION

“The pandemic clock is ticking. We just don’t know what time it is.”²⁰ These words accurately capture the challenge of pandemic influenza. Although there is a sense of urgency among public health officials, mustering political will and public attention may be difficult given the unpredictable (though inevitable) nature of the pandemic influenza. When confronted by immediate health threats and other social priorities, it may be tempting to forgo or delay investment in pandemic

“The pandemic clock is ticking. We just don’t know what time it is.”

preparedness and response capabilities. The difficult compromises and horrible consequences conjured by thoughts of a pandemic create discomfort, threaten to alienate responsible parties, and dampen open discourse. Lessons from the past, along with promising developments in the present, argue for confronting the challenges of this certain future threat sooner rather than later.

ENDNOTES

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14. Centers for Disease Control and Prevention, "Questions & Answers: Flu Vaccine," December 10, 2003; accessed August 26, 2004 at www.cdc.gov/flu/about/qa/flu vaccine.htm#2.
15. Vaccine coverage rates for a pandemic virus could be significantly higher. All people would probably need two doses for an effective immune response to a pandemic strain;

however, existing production capacity supports the development of a trivalent vaccine that includes three strains of virus. If current production capacity were directed at a monovalent vaccine that only targeted the pandemic strain, the total number of doses produced has the potential to increase threefold, depending on dosage requirements.

16. R. J. Webby and R. G. Webster, "Are We Ready for the Pandemic Influenza?" *Science*, 302 (November 28, 2003): 1519.

17. Department of Health and Human Services, Pandemic Influenza Preparedness and Response Plan, August 2004; accessed at www.hhs.gov/nvpo/pandemicplan/ on August 26, 2004.

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19. B. Gellin, "Pandemic Influenza: Threat, Preparedness, and Response," presentation given at Secretary's Council for Public Health Preparedness, May 3, 2004.

20. Unattributed quote from presentation by Gellin, May 3, 2004.