

October 2000

INFLUENZA PANDEMIC

Plan Needed for Federal and State Response



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Abbreviations

CDC	Centers for Disease Control and Prevention
DNA	deoxyribonucleic acid
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
mg	milligram
NIH	National Institutes of Health
WHO	World Health Organization



United States General Accounting Office
Washington, D.C. 20548

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The Honorable Tom Bliley
Chairman, Committee on Commerce
House of Representatives

The Honorable Fred Upton
Chairman, Subcommittee on Oversight and Investigations
Committee on Commerce
House of Representatives

Each year influenza viruses cause epidemics somewhere in the world and an annual average of more than 20,000 deaths in the United States. New strains of the virus continually evolve, causing remarkable variability in the intensity and severity of illness. Periodically, but unpredictably, a major genetic change in the virus results in a strain that can cause widespread disease and death. Three such global epidemics—called pandemics—occurred in the 20th century. The worst occurred in 1918 and killed more than 20 million people worldwide. Recent books and media attention have recounted the devastation of this pandemic and noted the prospect of a similar influenza outbreak.

In recent years, public health experts have raised concerns about the ability of the nation's public health system to detect and respond to emerging infectious disease threats, such as pandemic influenza. The response effort would need to include the ability to quickly produce and distribute a vaccine and antiviral drugs effective against the pandemic strain, as well as the ability to vaccinate or treat the population against pneumonia and its complications, which are most often the actual cause of death. You asked us to examine (1) the capability to develop and produce a vaccine to protect the nation from a pandemic influenza virus, (2) the capability to use other measures, such as antiviral drugs and pneumococcal vaccine, to help protect or treat people exposed to a pandemic virus, and (3) the status of federal and state plans to address the purchase, distribution, and administration of vaccines and antiviral drugs in a pandemic.

To address issues related to the production and use of vaccines and antiviral drugs, we interviewed officials and reviewed influenza-related documents from three Department of Health and Human Services (HHS) agencies—the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the National Institutes of Health

(NIH), as well as the Department of Veterans Affairs. We also interviewed private sector representatives from the 4 manufacturers producing influenza vaccine for the United States, 4 of 12 manufacturers of antiviral drugs, and various professional associations representing distributors and administrators of vaccines and drugs. To gather information on federal and state influenza pandemic planning efforts, we also interviewed HHS officials from the Office of the Assistant Secretary for Planning and Evaluation, Office of Emergency Planning, and National Vaccine Program Office, and officials in a judgmental sample of 11 of 29 states that either have drafted a plan or have begun to draft one. Although states have a lead role for public health response in the United States, state programs vary widely. The results from our analysis of state efforts are illustrative and cannot be generalized to other states. We conducted our work in accordance with generally accepted government auditing standards from April to September 2000.

Results in Brief

The results of our review show that vaccines, which are considered the first line of defense to prevent or reduce influenza-related illness and death, may be unavailable, in short supply, or ineffective for certain portions of the population during the first wave of a pandemic. Experience has shown that the vaccine production cycle takes at least 6 to 8 months after a virus strain has been identified. However, new strains of influenza virus sometimes appear too late to be included in the yearly influenza vaccine production for the United States. Also, vaccines for some influenza strains have been difficult to mass-produce, causing further delay. Even if sufficient quantities of the vaccine are produced in time, studies show that it is uncertain how well this can help prevent or control the spread of a pandemic influenza virus. Vaccines against various strains differ in their ability to produce antibodies to neutralize the virus, and each person's immune system may respond somewhat differently. Limited studies have shown that when the vaccine provides a good antibody response to the virus, approximately 70 to 90 percent of healthy young adults may be protected from influenza. This protection drops to about 30 to 40 percent for the elderly and those suffering from chronic illness or disease.

Antiviral drugs and vaccines against pneumonia are expected to be in short supply if a pandemic occurs and influenza vaccine is unavailable. Antiviral drugs, which can be used against all strains of influenza, have been as effective as vaccines in preventing illness from influenza and have the advantage of being available now. HHS assumes shortages will occur in a pandemic because demand is expected to exceed current rates of

production and increasing production capacity of antiviral drugs can take at least 6 to 9 months, according to manufacturers. HHS is studying the feasibility of stockpiling these drugs to preclude shortages. Among people who become ill with influenza, prior immunization against pneumococcal pneumonia, an infection that frequently follows influenza, may help reduce the number of deaths or the severity of illness. Shortages of this vaccine are also expected during a pandemic because only about an estimated 7 million doses of vaccine are produced each year as most of the population is not targeted to receive the vaccine. Increasing immunization rates now, particularly among high-risk groups, has been suggested by HHS as the primary strategy to mitigate shortages in a pandemic because the vaccine provides immunity for at least 5 to 10 years.

Federal and state influenza pandemic plans are in various stages of completion and do not completely or consistently address key issues surrounding the purchase, distribution, and administration of vaccines and antiviral drugs. HHS is working on a national plan, 10 states either have developed or are developing plans using general guidance from CDC, and 19 more states have plans under development. Outstanding issues remain, however, because certain key federal decisions have not been made. For example, HHS has not determined the proportion of vaccines and antiviral drugs to be purchased, distributed, and administered by the public and private sectors or established priorities for which population groups should receive vaccines and antiviral drugs first when supplies are limited. As a result, policies may differ among states and between states and the federal government, and in the event of a pandemic these inconsistencies could contribute to public confusion and weaken the effectiveness of the public health response. To improve the nation's ability to respond to an influenza pandemic, we are recommending that HHS determine the capability of the private and public sectors to produce, distribute, and administer vaccines and drugs and complete the national response plan. In commenting on a draft of this report, HHS generally concurred with our recommendations.

Background

In almost every year an influenza virus causes acute respiratory disease in epidemic proportions somewhere in the world. Influenza—also called “the flu”—is more severe than some of the other viral respiratory infections, such as the common cold. Most people who get the flu recover completely in 1 to 2 weeks, but some develop serious and potentially life-threatening medical complications, such as pneumonia. People who are age 65 or over or who have severe chronic conditions are much more likely to develop serious complications than are younger, healthier people. In an average flu

season (winter months), influenza contributes to as many as 20,000 deaths and 114,000 hospitalizations in the United States.

Occasionally, worldwide influenza epidemics—called pandemics—occur that can have successive “waves” of disease and last for up to 3 years. Documented accounts of such pandemics cover the past 300 years, with three occurring in the 20th century. Notable among these was the pandemic of 1918—called the “Spanish flu”—which killed at least 20 million people worldwide, including 500,000 in the United States. For reasons still not completely understood, many of the fatalities during the 1918 pandemic were young adults, and many people reportedly died within hours after the first symptoms appeared. The pandemics of 1957 (“Asian flu”) and 1968 (“Hong Kong flu”) caused dramatically fewer fatalities—70,000 and 34,000, respectively, in the United States—primarily because of antibiotic treatment of secondary infections and more aggressive supportive care.¹ Nevertheless, both were associated with high fatality rates and social disruption resulting from high absenteeism among providers of health care and other essential community services such as police and firefighters.

The characteristics of influenza viruses make the disease difficult to control, and its eradication is not a realistic expectation. Influenza viruses undergo minor but continuous genetic changes from year to year.² Periodically, but unpredictably, an influenza virus changes so significantly that any immunity conferred by previous vaccinations or infections is not effective, creating the potential for a pandemic. The dramatic genetic changes that produce variants responsible for widespread illness and death, such as those that caused the 1957 and 1968 pandemics, probably involve the mixing of two strains in a single host. For example, strains of the influenza virus that are found in birds can mix with strains found in other host animals, such as pigs, to produce a new, and possibly virulent, strain that infects people. In 1997 a second—never before seen—method for dramatic change was revealed when an avian influenza virus not previously known to infect people directly infected humans without an intermediate host. The virus killed 6 of the 18 people in Hong Kong who became ill. Although the disease did not readily spread among humans, had it acquired the ability to do so, it might have become very difficult to

¹The names reflect popular impressions of where the pandemics began, although many experts believe all three originated in China.

²Variants of the influenza B virus and all subtypes of A evolve separately, have distinct characteristics, and may respond differently to vaccine.

control. Because new influenza viruses will continue to emerge, many experts believe another pandemic is inevitable.

Public health experts and state and federal officials view influenza vaccine as the cornerstone of efforts to prevent and control annual epidemic influenza as well as pandemic influenza. Deciding which viral strains to include in the annual influenza vaccine depends on data collected from domestic and international surveillance systems that identify prevalent strains and characterize their effect on human health. In the United States, CDC monitors data on the disease and the virus from surveillance that occurs in all 50 states and the District of Columbia year-round but with intensified efforts during the October through May flu season. Domestic surveillance consists of test data from 138 laboratories that receive specimens year-round, mortality data from 122 cities that account for about one-third of all deaths, and weekly reports from about 400 physicians and state epidemiologists regarding the extent and intensity of influenza illness. In addition, CDC participates in international disease and laboratory surveillance sponsored by the World Health Organization (WHO), which operates in 83 countries.

Officials at HHS, WHO, and state public health agencies have begun to develop strategies to reduce influenza-related illness, death, economic loss, and social disruption, such as the closure of schools and hospitals and decreased access to utilities and other essential services. In many cases, state and federal officials are integrating these strategies with response plans for such public health emergencies as natural disasters and bioterrorist events. However, unlike many natural disasters, which often have fairly localized effects, an influenza pandemic is likely to affect many locations simultaneously. This widespread nature may preclude the ability to shift human and material resources from unaffected areas to locations in great need, a possibility that heightens the importance of planning during the prepandemic period.

Vaccine Availability May Be Limited in a Pandemic

Vaccines are considered the first line of defense against influenza to prevent infection and control the spread of the disease. The ability to successfully use vaccines to prevent influenza-related illness and death during the first wave of a pandemic, however, relies on certain conditions that have not been realized in the past, and may not occur in the future. Problems experienced in past influenza pandemics include the inability to produce a sufficient quantity of vaccine before outbreaks occur in the United States and variations in the extent to which the manufactured

vaccine is effective in preventing illness among various sectors of the vaccinated population.

Problems Related to Vaccine Production

Annual influenza vaccine production is a complex process involving vaccine manufacturers, health care experts, and federal agencies, primarily the FDA. The process, which involves growing the virus for vaccine in fertilized chicken eggs, requires several steps, generally taking at least 6 to 8 months between about January and August each year, as shown in table 1. Administering the vaccine to the population is estimated to take an additional 1 to 2 months, or even longer if a second dose of vaccine is required. After inoculation, it takes about 2 weeks for adults and up to 6 weeks for children to achieve optimal protection under a one-dose regimen, with an additional 4 weeks if a booster shot is needed a month later.

Table 1: Annual Vaccine Production Process

Production step	Responsible entity	Time
Develop reference virus strain for production	FDA	4–10 weeks
Manufacture test strains	Vaccine manufacturers	2–4 weeks
Develop potency test reagents ^a	FDA	10–12 weeks
Manufacture and test vaccine	Vaccine manufacturers/FDA	10–12 weeks
Total production time		6–8 months^b

^aReagents are substances that laboratories use to help identify or measure other substances.

^bNumbers higher than total because some steps overlap.

Annual production capacity for vaccine is about 80 million doses per year, which FDA officials and vaccine manufacturers agree can be expanded to produce vaccine for the entire U.S. population under certain conditions.³ However, these conditions were not realized during the pandemics of 1957 and 1968, when immunization efforts failed to have any perceptible effect because too little vaccine was administered too late. HHS officials and vaccine manufacturers agree that because of the complexity of the vaccine production cycle, problems are also likely to occur in a future pandemic. Several factors can hinder timely vaccine production, including (1) the speed of production compared to the speed at which the virus infects a population, and (2) how well the virus can be replicated for mass production.

Problems Related to Speed of Vaccine Production Compared to Speed of Infection of Population

While the global influenza surveillance system provides valuable information for deciding which viral strains to include in the annual influenza vaccine, limits on the speed with which vaccines can be produced may hinder pandemic response capability. Because people lack immunity to a pandemic strain and such a virus may be more virulent, pandemic strains may spread more quickly. Experts involved in monitoring the identification and spread of influenza viruses estimate that a pandemic strain originating in a foreign country could arrive in the United States sooner than vaccine could be produced. FDA officials and vaccine manufacturers told us that production of influenza vaccine cannot be shortened to less than the current 6 to 8 months given the existing technology and safety standards. However, as table 2 shows, past pandemics and new strains that might have heralded a pandemic have generally spread to the United States in less time.

³The time required to produce vaccines depends, in part, on the number of viral strains in the vaccine, satisfactory growth and yield of the virus in chicken eggs, the number of doses required to build immunity, and access to raw materials. All other things being equal, vaccines that include a single strain can be produced in less time and in greater quantities than vaccines containing multiple strains because no additional time is needed to produce and combine additional strains. For example, current production capacity is about 80 million doses of a vaccine containing three viral strains; the same capacity could produce about 240 million doses of a vaccine containing a single virus in less time. Other factors that affect timing include testing by FDA and manufacturers to determine vaccine potency and the development of a standardized serum used for such testing.

Table 2: Months for Newly Detected Influenza Viruses to Reach the United States

Influenza virus and year	Country where first detected	Months to reach United States
Pandemic year		
Spanish flu, 1918	United States ^a	0 ^a
Asian flu, 1957	Republic of China	4–5
Hong Kong flu, 1968	Hong Kong	2–3
Year new strains detected		
Swine flu, 1976	United States	0
Russian flu, 1977	Russia	3–4
Chicken flu, 1997	Hong Kong	Did not reach United States

^aIt is unknown whether the virus originated in the United States, China, or Europe. Some researchers suggest that the virus began circulating in midwestern U.S. military camps.

NIH is developing a library of reagents of all strains known to circulate among animals that has the potential to shorten the time required to identify a new virus.⁴ More rapid identification could help reduce the time needed to produce an effective vaccine should these strains appear in humans. However, more rapid production would not ensure that sufficient vaccine would be available before the first wave of influenza outbreak occurs, especially if the pandemic originates in the United States. Even assuming that the next pandemic originates outside of the United States, experts estimate the warning time prior to reaching U.S. soil may range from about 1 to 6 months. NIH⁵ and others are sponsoring research to develop new types of vaccines, but an all-purpose vaccine effective against a broad spectrum of influenza strains that could be produced in advance of a pandemic has not materialized.

⁴Reagents in this context are materials such as antibodies and purified proteins that are used by laboratories to measure vaccine potency and identify new influenza viruses.

⁵NIH support for influenza research related to basic biology, immunology, epidemiology, vaccine and drug development, and evaluation totaled over \$10 million in fiscal year 1999.

The inflexibility of the vaccine production cycle also could contribute to delays in the availability of an influenza vaccine. To help ensure that vaccines are ready to be distributed in time for the flu season each fall, annual influenza vaccine production in the United States routinely occurs earlier in the year, from January through August.⁶ Because no market exists for vaccine after this period, manufacturers switch their capacity to other uses between about mid-August and December. This annual vaccine production cycle may not coincide with the timing needed to respond to an outbreak of a new influenza strain. For example, in July 1997, public health officials at CDC determined on the basis of surveillance data from Australia that a new influenza strain was circulating and would be likely to cause widespread illness in the United States during the upcoming flu season. But by July, vaccine production was almost complete, and the new strain could not be added. As a result, the vaccine for the 1997-98 flu season in the United States was, according to CDC reports, less effective in preventing influenza illness than in previous years. As table 3 shows, other pandemic and newly detected virus strains have also been identified after the annual vaccine production cycle had begun.

Table 3: Time of Year Influenza Illness Appeared

Strain and year	Month appeared
Pandemic strain	
Spanish flu, 1918	March ^a
Asian flu, 1957	April
Hong Kong flu, 1968	July
New strains with limited effect	
Swine flu, 1976	February
Russian flu, 1977	November
Chicken flu, 1997	August

^aEstimates range from spring to early summer.

Manufacturers say they are willing to maintain year-round production capacity should the government wish to fund the necessary costs of maintaining unused capacity during nonpandemic periods. To date, HHS

⁶In addition, approximately 6 months before vaccine production begins manufacturers must place their orders for new chicken flocks to support egg production.

has not developed contingency plans for expanded capacity or analyzed whether government funding to maintain ongoing manufacturer capacity is feasible or desirable. Such an analysis would need to consider other potential production problems that may further preclude vaccine availability.

Problems Related to Mass Production of Vaccine

One potential production problem is that influenza strains differ in how well they can be mass-produced for vaccine, which may negatively affect the quantity of vaccine that can be produced in a given year. To create a vaccine, manufacturers first receive the reference strain of virus from FDA. This reference, or “seed,” virus is generally made up of bits of the selected influenza virus that have been combined with another influenza virus that grows more quickly. Manufacturers then mass-produce this “high-growth-reassorted” virus in fertilized chicken eggs and harvest it to make the vaccine. Problems have occurred when a particular virus strain either cannot be grown in eggs or grows too slowly. For example, the strain identified in Hong Kong in 1997 was an avian strain that killed chick embryos, a factor that complicated U.S. production of a vaccine. More recently, difficulties replicating and processing one strain included in the vaccine for the 2000-01 influenza season have contributed to lower-than-anticipated production yields and delays in distributing vaccine supplies.

To address this problem, manufacturers and others are studying the feasibility of switching from an egg-based to a tissue-based production method, but the latter method has not been licensed by FDA and the overall benefits are not clear. For example, while some avian strains of influenza may grow more readily in tissue than in chicken eggs, others may not. Alternative attempts to grow the 1997 Hong Kong virus in cell substrates other than eggs were, in some cases, more successful than egg-based methods, but difficulties still hindered mass vaccine production. Some manufacturers told us that the cost of switching production methods may not be worth the investment because tissue-based production may result in lower yields of vaccine. For example, one manufacturer said that growing the virus in tissue takes approximately 5 days, while growing the virus in eggs takes 11 days, saving less than 1 week in the total production cycle. New technology based on a DNA vaccine may resolve these production problems, while reducing production time. However, researchers estimate it will be at least 5 to 10 years before this technology is available for vaccine production.

Problems Related to Vaccine Effectiveness

Vaccinating the entire U.S. population does not guarantee everyone will be protected from influenza-related illness and death. Information regarding the extent to which vaccines have been effective in preventing influenza is limited, but available studies indicate vaccine effectiveness may vary significantly from year to year based on both vaccine-related factors and the demographics of the population receiving the vaccine. For example, vaccine preparation, dosage, and the degree to which the vaccine matches the virus circulating in the community all affect vaccine effectiveness. Demographic factors that influence how well each person's immune system responds to the vaccine generally include the person's age and extent of underlying chronic illness or disease.

Although up to about 80 million doses of vaccine are administered each year, no regular program exists to determine how effectively the vaccine performs. While HHS officials told us they see some effect from vaccination coverage, other experts point to national data trends that have not shown a clear correlation between changes in influenza-related illness and death relative to changes in the proportion of the population vaccinated.⁷ Using data sets from managed care organizations, CDC intends to continue retrospective studies of vaccine effectiveness to better determine how well vaccine prevents influenza or mitigates its severity in various populations.

In the meantime, information on vaccine effectiveness is generally limited to small studies of primarily vaccinated populations. These studies have shown that when the vaccine generates a good antibody response to the circulating virus, influenza vaccine may prevent illness in approximately 70 to 90 percent of healthy persons under 65 years of age. However, vaccine effectiveness drops sharply for the elderly and people with chronic illness, who are considered most vulnerable to influenza-related illness and death.⁸ For example, studies have shown influenza vaccine may be about 30 to 70 percent effective in reducing hospitalization among the noninstitutionalized elderly population. Overall effectiveness in preventing influenza among the elderly has been even lower, often ranging from 30 to

⁷One difficulty in comparing effectiveness across years is the growing number of persons who are at high risk for serious complications. As more people age and more survive with immune-compromising diseases, this high-risk group will continue to grow.

⁸According to CDC, about 90 percent of influenza-related deaths occur among people aged 65 and older, with most other deaths occurring in people suffering from underlying disease.

40 percent. Approaches to improve the effectiveness of the influenza vaccines include conducting research to develop alternative methods of administering existing vaccines and new vaccines such as weakened live virus vaccine or DNA vaccines that, in theory, may produce broader and longer-lasting protective immune responses.

Antiviral Drugs and Pneumococcal Vaccine May Be in Limited Supply During a Pandemic

Antiviral drugs and vaccine against pneumonia are two additional measures that can help prevent or mitigate influenza-related illness and death until an influenza vaccine becomes available. However, both are expected to be in short supply during a pandemic, and increasing production capacity for antiviral drugs and vaccine in response to increased demand could take at least 6 to 9 months. Creating a stockpile of antiviral drugs is an option to mitigate shortages during a pandemic. However, HHS officials told us that additional analysis is needed to determine the feasibility and desirability of such an effort. One option to minimize shortages of pneumococcal vaccine during a pandemic is to immunize the population now against possible future infection. However, immunization rates for elderly and high-risk groups remain below established targets, and immunization recommendations have not been expanded to include healthy children and young adults because they are at low risk for pneumococcal pneumonia during nonpandemic periods.

Problems Related to Availability of Antiviral Drugs

Antiviral drugs can be used against all strains of pandemic influenza and have immediate availability both as a prophylactic to prevent illness and as a treatment if administered within 48 hours of the onset of symptoms. Studies of these drugs have shown them to be as effective as vaccines in preventing influenza infection in healthy young adults if taken under the prescribed regimen,⁹ and, when used for treatment, to shorten the duration and severity of infection.¹⁰

Twelve manufacturers produce antiviral drugs approved by FDA for use against influenza in the United States. These drugs vary in both their costs and their benefits, as shown in table 4. For example, the older and less expensive drugs amantadine and rimantadine have been approved for prophylaxis of all age groups against the influenza virus strains most likely to cause a pandemic. However, their side effects, particularly those of amantadine, include central nervous system disturbances, such as delirium or behavioral changes, that may preclude their use in certain populations.¹¹ The newer and more expensive drugs, zanamivir and oseltamivir, have a lower incidence of side effects and are effective against a broader range of virus strains. However, as of August 2000 they had FDA approval only for treatment, not prevention. In addition, they have not been approved for use in younger age groups, and zanamivir is not recommended for certain other segments of the population.¹² None of the antiviral drugs have been studied extensively for long-term use or in large populations.

⁹As with vaccine, in studies of healthy young adults antiviral drugs were generally 70 to 90 percent effective in preventing influenza. For the two antiviral drugs approved for preventing influenza, the standard adult dosage is 200 milligrams (mg) per day, taken as two 100-mg tablets or 4 teaspoonfuls of syrup until approximately 1 week after the end of the outbreak.

¹⁰CDC evaluations have shown antiviral drugs shorten the duration of influenza by about 1 day, with some reduction of severity and prevention of secondary infections.

¹¹These more severe side effects have been associated with high plasma drug concentrations and observed most often among persons who have renal insufficiency, seizure disorders, or certain psychiatric disorders and among elderly persons taking amantadine as prophylaxis at a dose of 200 mg/day.

¹²Special caution is advised in using zanamivir in patients with underlying asthma or chronic obstructive pulmonary disease because FDA has received several reports of deterioration of respiratory function following its use.

Table 4: Antiviral Drugs Approved for Influenza by FDA

Antiviral drug	Year approved	Approved use	Influenza virus strains affected by drug	Approved population	Number of manufacturers	Cost per daily dose ^a
Amantadine	1976	Prophylaxis and treatment	All A strains	Adults and children	9	\$0.10 ^b
Rimantadine	1993	Prophylaxis and treatment	All A strains	Adults and children ^c	1	\$1.07 ^d
Zanamivir	1999	Treatment only	All A and B strains	7 years and older	1	\$5.38
Oseltamivir	1999	Treatment only	All A and B strains	18 years and older	1	\$6.49

^aCost to federal government based on lowest prices in the federal supply schedule.

^bCost varies from \$0.10 to \$0.27 for generic tablets and \$1.06 to \$1.10 for brand name tablets. Cost varies from \$0.52 to \$1.46 for generic syrups and is \$2.26 for brand name syrup.

^cRimantadine is approved only for prophylaxis in children; however, CDC reports that many experts also consider rimantadine appropriate for treatment in children.

^dCost is for rimantadine tablets. Cost for rimantadine syrup is \$1.37.

CDC historically has supported use of antiviral drugs during nonpandemic periods as an adjunct to vaccine to prevent influenza among high-risk populations in certain circumstances. Antiviral drugs may be used (1) when influenza vaccine is unavailable, (2) during the 2 to 6 weeks after inoculation until the vaccine becomes effective, and (3) for people who cannot tolerate the vaccine because of allergies or other factors. However, CDC cautions against the use of antiviral drugs in the face of the vaccine shortages expected for the 2000-01 influenza season. CDC states that even if a vaccine shortage develops, it does not support routine and widespread use of antiviral drugs to prevent influenza, because it is an untested and expensive strategy that could result in large numbers of persons experiencing adverse effects.

While shortages of antiviral drugs have not been a problem in the past, HHS officials expect the amount produced will be well below demand during a pandemic. This assumption, supported by drug manufacturers, is based on the fact that current production levels of antiviral drugs are set in response to current demand, whereas demand in a pandemic is expected to increase significantly if vaccines are unavailable as a means to prevent the disease. Manufacturers told us that expanding supply to meet increased demand is possible to some extent but that the lead time required to produce at least one type of antiviral drug can be at least 6 to 9 months. Manufacturers say that knowing how much drug CDC expects them to produce for a pandemic would assist them in determining whether their existing surge capacity is sufficient, and the extent to which they would need to develop contingency

plans to expand capacity even further. Both FDA and CDC started collecting data on the production capacity of antiviral drug manufacturers in May and June 2000, but data collection efforts remain incomplete. HHS has not developed contingency plans with manufacturers to expand production capacity or analyzed whether government funding to maintain ongoing manufacturer capacity is feasible or desirable. In the absence of federal decisions about drug availability and use, state officials are uncertain whether or to what extent they should include strategies that rely on antiviral drugs to prevent or treat infection until vaccine becomes available.¹³ HHS officials plan to convene an expert panel to determine how antiviral drugs should be used in the event of a pandemic or in the face of vaccine shortages.

Creating a stockpile is another option to ensure availability of antiviral drugs for a pandemic. HHS has not formally evaluated whether creating a stockpile to preclude shortages is warranted and feasible.¹⁴ CDC officials have noted several factors that must be addressed in deciding to create a stockpile. For example, officials need to determine whether to build or rent storage facilities and where to locate them, develop a distribution system, assess the feasibility of rotating stock given the shelf-life of the drug and current market capacity, and determine how to finance the stockpile. The recent creation of the National Pharmaceutical Stockpile to help prepare for a bioterrorist attack has provided experience in these areas. This program, administered by CDC and financed by a federal appropriation of \$51 million in fiscal year 1999 and \$52 million in fiscal year 2000,¹⁵ maintains a medical stockpile considered to be adequate to respond to a bioterrorist attack but lacks all the pharmaceuticals, supplies, and equipment that may be necessary to respond to an influenza pandemic. Under this program, the Department of Veterans Affairs, as CDC's agent, purchases drugs, supplies, and equipment, which are stored as active

¹³The six state pandemic plans we reviewed do not rely on using antiviral drugs, in part because supplies are expected to be very limited.

¹⁴In deciding whether stockpiling antiviral drugs is feasible, officials managing the National Pharmaceutical Stockpile state that someone must look at the outcome or value-benefit of the costs involved, which would include the projected lives saved as well as overall decrease in illness and economic damage. For example, the overall costs of a prevention program for influenza may be matched against CDC estimates that, if no action is taken in a moderately severe pandemic, up to 207,000 people could die, 90 million could become ill, and economic damages could total \$167 billion.

¹⁵The HHS budget proposal for fiscal year 2001 includes \$54 million to continue development of the National Pharmaceutical Stockpile.

inventory in vendor warehouses. In developing the National Pharmaceutical Stockpile, CDC relied in part on our recent review of two other federally maintained stockpiles to assess management oversight of items in the stockpile.¹⁶

Use and Availability of Pneumococcal Vaccine

Inoculation with pneumococcal vaccine, which helps protect against pneumococcal pneumonia, a type of pneumonia that frequently follows influenza infection, may help reduce a substantial number of influenza-related deaths.¹⁷ Depending on the severity with which the disease attacks different population groups, available vaccine supplies might be needed to help protect groups other than those typically considered at risk, such as young adults. Although national mortality statistics have directly attributed about 1,000 deaths per year to influenza during the last decade, CDC attributes at least 20,000 more deaths per year to secondary infections of influenza, such as pneumonia.¹⁸ As shown in table 5, the numbers of deaths over and above these annual estimates of influenza-related deaths—called excess deaths¹⁹—have generally been even higher during pandemics, especially during the pandemic of 1918, when antibiotics and advanced medical care to treat secondary infections were unavailable.

¹⁶*Combating Terrorism: Chemical and Biological Medical Supplies Are Poorly Managed* (HEHS/AIMD-00-36, Oct. 29, 1999).

¹⁷Pneumococcal vaccine provides protection against pneumococcal pneumonia, especially when other pneumococcal infections such as bacterial meningitis and infection of the bloodstream are present.

¹⁸Influenza by itself is not generally regarded as a fatal disease, but as a debilitating infection that prepares the way for a secondary invader. Historically, the most frequent complication has been pneumonia. Over the years an increasing proportion of excess deaths have been attributed to other causes, primarily chronic obstructive pulmonary disease.

¹⁹The hallmark of pandemic influenza has been excess mortality, defined in 1847 by William Farr in London, England, as the number of deaths observed during an epidemic of influenza-like illness in excess of the number expected.

Table 5: Excess Influenza-Related Deaths Estimated for Pandemic and Nonpandemic Periods in the United States, 1918-91

Period	Years	Annual average of excess deaths	Crude death rate per 100,000 persons
Pandemic	1918-20	225,000	218.4
Nonpandemic	1920-33	28,338	23.0
Nonpandemic	1933-57	10,108	7.5
Pandemic	1957-60	38,567	22.0
Nonpandemic	1960-68	14,363	7.5
Pandemic	1968-72	27,982	13.9
Nonpandemic	1972-81	22,089	10.3
Nonpandemic ^a	1981-91	20,000	10.0

^aEstimated.

Source: W. Paul Glezen, "Emerging Infections: Pandemic Influenza," *Epidemiologic Reviews*, Vol. 18, No. 1 (1996), pp. 64-76.

CDC officials generally attribute about one-third of the excess deaths each year to influenza-related pneumonia, and most of these deaths are attributed to a type of bacterial pneumonia that may be prevented with the pneumococcal vaccine. The exact number of deaths caused by pneumococcal pneumonia is unknown,²⁰ but HHS reports that at least in some epidemics, the disease has been responsible for up to half of influenza-related deaths. Because pneumococcal vaccine provides immunity for at least 5 to 10 years, it can provide benefit during nonpandemic as well as pandemic years. CDC reports that during nonpandemic periods, the populations most at risk for hospitalization and death due to pneumococcal disease include approximately 35 million persons aged 65 or older and approximately 33 to 39 million persons of all ages with chronic illness. Therefore, CDC recommends that pneumococcal vaccine be administered to persons in these groups.

²⁰The precise incidence of pneumococcal pneumonia is difficult to determine because routine diagnostic tests are insufficiently specific and sensitive. Nonetheless, CDC estimates that up to 175,000 hospitalizations for pneumococcal pneumonia occur in the United States each year and up to 12,500 deaths, accounting for more deaths than any other vaccine-preventable bacterial disease. Approximately half of these deaths potentially could be prevented through use of vaccine, according to CDC.

CDC officials expect shortages of pneumococcal vaccine during a pandemic because only about 7 to 9 million doses are currently produced each year,²¹ the vaccine production process takes about 8 to 9 months, and current overall immunization rates remain below target. CDC officials say that manufacturers produce vaccine according to the current demand for the product. Therefore, increasing the extent that the population is currently immunized would help preclude shortages of vaccine during a pandemic, not only by increasing production capacity, but also by reducing the number of people that remain to be immunized.

In 1995 we reviewed the efforts of HHS to improve pneumococcal vaccination rates for adults aged 65 and older.²² As part of its response, CDC and other HHS agencies developed the Adult Immunization Action Plan, which focused efforts on raising awareness of the importance of the vaccine among clinicians, public health professionals, and the public. Specific steps include encouraging (1) health care provider organizations to revise current immunization policies and include directives clinicians can use in their practices to increase immunization, particularly among high-risk groups, and (2) accrediting organizations to urge requiring hospitals and other care facilities to adopt directives aimed at immunizing high-risk individuals. In addition, CDC has developed and disseminated brochures and other educational material for the public and health care providers that stress the health benefits of vaccination.

Since CDC initiated these actions, immunization rates have increased, particularly for adults aged 65 and older. As of 1997, 43 percent of people aged 65 and older and 11 percent of younger at-risk populations have been immunized with pneumococcal vaccine. Preliminary data from 1999 indicate that the rate for those aged 65 and older has increased further to 54 percent. Despite this progress, rates remain below the HHS year 2000 goal of 60 percent for each of these noninstitutionalized populations. Moreover, the year 2010 goal for people aged 65 and older increases to 90 percent, well above the current goal. CDC officials cite the continued lack of awareness about the availability and importance of pneumococcal vaccine

²¹There are two manufacturers of the pneumococcal vaccine for the United States, and CDC officials state that the vaccine has a shelf-life of 2 years.

²²*Immunization: HHS Could Do More to Increase Vaccination Among Older Adults* (GAO/PEMD-95-14, June 8, 1995).

as the primary barrier to increasing immunization rates.²³ Officials from all but one of the 11 states we contacted planned to expand existing programs to increase nonpandemic use of pneumococcal vaccines by such means as raising awareness among physicians and public health officials and educating the public.

Shortages of pneumococcal vaccine could also be exacerbated by the fact that there may be a high need for it among people under age 65 as well as for the older population. For example, in the 1918 pandemic the influenza-related death rate for young adults was more than 3 times that for people over age 65, just the opposite of the situation in nonpandemic years, when the influenza-related death rates for those over age 65 were 8 to 15 times greater than those for younger people. Of the estimated 550,000 excess deaths for all age groups in the years 1918 and 1919, over 280,000 pneumonia deaths were reported in young adults, aged 20 to 39 years. Since 1980, those under 65 have generally accounted for less than 10 percent of the influenza-related excess deaths. However, CDC officials have estimated that in a future pandemic up to 50 percent of deaths may fall within the age group of 0 to 64 years. CDC has not estimated the number of deaths that may be prevented with pneumococcal vaccine. According to CDC officials, current recommendations for pneumococcal vaccine are unlikely to be expanded to include healthy young adults because pandemic scenarios are not considered when setting immunization policy.

Plans Incomplete to Purchase, Distribute, and Administer Vaccines and Drugs

Federal and state pandemic response plans are in various stages of completion and do not completely or consistently address the problems related to the purchase, distribution, and administration of supplies of vaccines and antiviral drugs during a pandemic. HHS has provided interim draft guidance to facilitate state plans, but final federal decisions necessary to mitigate the effects of potential shortages have not been made.²⁴ Until such decisions are made, the timeliness and adequacy of response efforts may be compromised.

²³A recent report by the Institute of Medicine notes that without a renewal and strengthening of the state and federal immunization financial and policy partnership, gains in immunization rates can be expected to decline (Institute of Medicine, *Calling the Shots: Immunization Finance, Policy, and Practices* (Washington, D.C.: National Academy Press, June 2000)).

²⁴CDC's draft interim guidance notes that it has not been officially approved or endorsed but is intended to guide state planning efforts until national planning efforts are completed.

Status of Federal and State Pandemic Response Plans

The federal government developed the first national pandemic plan in 1978, after the threat of a pandemic swine flu in 1976 clearly demonstrated the need for advance planning to support a mass immunization and response effort within the United States. Lessons learned from that experience, which was the government's first attempt at immunization of the entire U.S. population, included the need for the federal government to reach agreements with private and public sector entities responsible for the timely purchase, distribution, and administration of vaccines and drugs.²⁵ More recent experience with vaccine shortages also demonstrated the need for federal guidance in distributing limited quantities of vaccines and drugs to priority groups within the population. In 1993 the federal government convened a panel of experts from the public and private sectors to review and revise the pandemic response plan. As of October 2000, HHS officials directing the planning effort had not set a date to complete and distribute a revised national plan.

To foster state and local pandemic planning and preparedness, CDC first issued interim planning guidance in draft form to all states in 1997, outlining general federal and state planning responsibilities. As of September 2000, 28 states were actively preparing a pandemic plan, 10 states characterized their planning efforts as in the conceptual stage, and 1 state did not comment on the stage of planning efforts, according to a recent survey by the Council of State and Territorial Epidemiologists.²⁶ The remaining 11 responding officials said their states were not engaged in pandemic planning. Beginning in 1999, HHS funded 9 states with up to \$13,000 each to develop plans.²⁷ An additional 19 states were developing plans using other federal and state resources.²⁸

²⁵A summary of the response effort to address the 1976 swine flu and associated problems is discussed in *The Swine Flu Program: An Unprecedented Venture in Preventive Medicine* (GAO/HRD-77-115, June 27, 1977).

²⁶In May 2000, the Council of State and Territorial Epidemiologists surveyed all 50 states and the District of Columbia about their planning efforts. By September 2000, they had received 50 responses. For purposes of this report, the District of Columbia is referred to as a state.

²⁷Four states—California, Maryland, Minnesota, and South Carolina—produced draft plans in April 2000, with the remaining five—Florida, Indiana, Massachusetts, New Hampshire, and New Jersey—to complete plans in April 2001.

²⁸CDC has also provided more general assistance in terms of funding and technical assistance to enhance public health epidemiologic, laboratory, and communications capacity more generally.

Officials from 32 states said that influenza plans will be integrated with existing state plans to respond to natural or man-made disasters, such as flood or bioterrorist attack. Although to a certain extent planning efforts for other emergencies can be used for pandemic response, additional planning is important to deal with the specific aspects of pandemic response. This includes developing plans to address the wide-scale emergency needs of an entire population, including mass distribution and administration of limited vaccines and drugs with an uncertain amount of available resources. State officials say that CDC's financial and technical assistance has greatly helped in these planning efforts.

Federal Government Planning Responsibilities

In the most recent version of its planning guidance for states, CDC lists several key federal decisions related to vaccines and antiviral drugs that have not been made. These decisions include determining the amount of vaccines and drugs that will be purchased at the federal level; the division of responsibility between the public and private sectors for the purchase, distribution, and administration of vaccines and drugs; and how population groups will be prioritized and targeted to receive limited supplies of vaccines and drugs. In each of these areas, until federal decisions are made, states will not be able to develop strategies consistent with federal action.

Incomplete Plans for Purchase, Distribution, and Administration of Vaccines and Antiviral Drugs

HHS has indicated in its interim planning guidance that how vaccines and drugs will be purchased, distributed, and administered by the private and public sectors will change during a pandemic, but some decisions necessary to prepare for these expected changes have not been made. During a typical annual influenza response, influenza and pneumococcal vaccines are purchased through a combination of public and private sector funds. Vaccine and antiviral drug distribution is primarily handled directly by manufacturers through private vendors and pharmacies. About 90 percent of vaccines and antiviral drugs are administered or prescribed to the population on a first-come, first-served basis by private physicians, nurses, and other health care providers, with most states and counties participating to a relatively small extent through publicly funded programs.

During a pandemic, however, HHS draft interim guidance indicates that many of these private sector responsibilities may be transferred to the public sector at the federal, state, or local level, and priority groups within the population should be established for receiving limited supplies of vaccines and drugs. For example, the draft interim guidance for state pandemic plans says that resources can be expected to be available from the national level for federal contracts to purchase influenza vaccine and at

least some antiviral agents, but some state funding may be required. In addition, federal grants or reimbursement for public sector vaccine distribution and administration may be provided to states, but the draft interim guidance contains no recommendations on how the level and nature of such resources might differ in response to the severity of the pandemic.

Professional organizations representing vaccine manufacturers and pharmacists have questioned the necessity of moving responsibility for distribution and administration to the public sector during a pandemic. According to these organizations, existing private systems are in place and can operate more smoothly in response to federal direction than an as-yet-to-be-defined public sector system. At least one professional organization has contacted CDC requesting to assist the federal government in expanding capacity for private sector vaccine administration. HHS has not determined the extent to which federal funding will be made available or developed more guidance for states to use in planning how to use public and private sector resources to distribute and administer vaccines and antiviral drugs. In the absence of decisions regarding the extent of federal responsibility and investment in pandemic response, however, state officials are uncertain of how much state funding will be required and what level of state response can be supported. Two say that without more detail and commitment on federal assistance they plan to respond to the pandemic using state resources alone.

Incomplete Plans for Prioritizing Population Groups for Limited Distribution of Vaccines and Drugs

State officials are particularly concerned that a national plan has not finalized recommendations for how population groups should be prioritized to receive vaccines and antiviral drugs. In its most recent (1999) interim draft guidance sent to states, HHS lists eight different population groups that should be considered in establishing priorities among groups for receiving vaccines and drugs during a pandemic. The list includes such groups as health care workers and public health personnel involved in the pandemic response, persons traditionally considered to be at increased risk of severe influenza illness and mortality, and preschool and school-aged children.

The interim guidance states that recommendations on the relative priority of each group are still under study and will be based on a number of factors, including the need to maintain community pandemic response capability. Other factors include limiting mortality among high-risk groups, reducing mortality in the general population, and minimizing social disruption and economic losses. HHS officials say they are still committed

to publishing recommendations on the relative priority for each population group. However, the recommendations need to be flexible to recognize the different situations that could emerge. For example, officials point out that the severity with which the pandemic attacks specific population groups would have to be taken into consideration in setting priorities.

State officials acknowledge the need for flexibility in planning because many aspects of a pandemic cannot be known in advance. However, these officials say that the absence of more detail regarding how and when federal recommendations will be made leaves them uncertain about how to plan for the use of limited supplies of vaccine and drugs. For example, knowing federal government recommendations under different conditions allows states to better estimate the extent to which priority groups can be vaccinated, to develop strategies to target those groups, and to determine the number of additional personnel and locations that will be needed for vaccine and drug administration.

Another concern, particularly for state officials, is that without federal decisions to establish priorities for which population groups should receive the limited quantities of vaccines and drugs, inconsistencies could arise both among states and between states and the federal government. Several state officials say such policy differences among states and between states and the federal government in the use and distribution of vaccines and antiviral drugs may contribute to public confusion and social disruption, as shown by recent experience. Specifically, in 1998, after 3 of 11 children who developed meningitis died, one state initiated a mass vaccination program for people between the ages of 2 and 22 using a strategy of shared public and private sector responsibility for administering the vaccine.²⁹ Surrounding states that did not have an increase in reported cases did not initiate similar programs or recommend vaccination for everyone in this age group. The differences in state recommendations caused some residents of bordering states to seek immunization for their children by crossing state lines. The intense media attention and demand for vaccinations, coupled with a perceived shortage of meningococcal vaccine, created substantial confusion in some communities as fearful parents

²⁹The federal Advisory Committee on Immunization Practices recommends routine use of meningococcal vaccine only for certain high-risk individuals in this age group, not the general population.

overwhelmed private providers with phone calls and office visits, according to officials responsible for the vaccination program.³⁰

Conclusions

While experts consider an influenza pandemic to be inevitable, no one knows when it will occur or how severe it will be. What is known is that traditional response strategies for obtaining, using, and distributing vaccines and drugs during annual influenza epidemics may be insufficient or inappropriate to control or minimize the effect of pandemic disease, particularly in its early stages, on the population and the economy. Although not much can be known about a pandemic viral strain until it appears, planning a response that relies on vaccines and drugs depends, at least in part, on knowing the amounts that can be produced and developing strategies for reaching various populations that might be at risk. Because influenza vaccine must be tailored specifically to the pandemic strain that appears, an effective response plan also depends, in part, on the ability to rapidly identify the strains that are newly infecting people and to produce influenza vaccine using alternative methods in the event existing ones cannot be used. Moreover, acting now to increase the extent to which vulnerable populations, particularly those aged 65 and older, receive pneumococcal vaccine can help protect them from the complications of influenza in the event of a pandemic. Despite recent gains in the use of vaccines, the rate of pneumococcal immunization among high-risk groups remains below established goals, indicating the need for HHS to maintain its efforts to raise awareness about the importance of this vaccine.

Stronger federal leadership is needed to analyze alternative strategies to increase the availability and relative effect of vaccines and drugs among various populations. Because new strategies may replace familiar response patterns to address the unique aspects of a pandemic, advance planning is particularly important to obtain agreement on how the traditional roles and responsibilities of the public and private sector response effort are likely to change. Federal leadership, including development of a national plan that integrates strategies for the use of vaccines and antiviral drugs, is needed to address national issues as well as help harmonize the various public and private sector plans.

³⁰To relieve the pressure on private providers, allow them to care for ill patients, and restore order, this state health department assumed full responsibility for vaccinations and began an aggressive public communications effort to alleviate public concern. Within 4 weeks, communities had vaccinated over 90 percent of the targeted population.

Recommendations for Executive Action

To improve the nation's ability to respond to the emergence of a pandemic influenza virus and help ensure an adequate and appropriate level of public protection, we recommend that the Secretary of Health and Human Services take the following actions. First, we recommend that the Secretary take steps to fill the knowledge gaps in the capability of the private and public sectors to produce, distribute, and administer vaccines and antiviral drugs to various population groups to control the spread and effect of a pandemic. Specifically, we recommend that HHS

- explore and evaluate alternative methods to produce and distribute influenza vaccine and strategies to help quickly identify newly detected strains of the influenza virus,
- identify the capability of all manufacturers to produce antiviral drugs and pneumococcal vaccines and their existing "surge capacity" to expand production as needed during a pandemic, and
- if existing surge capacity is insufficient, work with manufacturers to determine the investment and time required to expand production capacity, or the feasibility of creating a stockpile against projected shortages.

Second, we recommend that the Secretary establish a deadline for completing and publishing a federal response plan that will address

- how priorities for receiving limited influenza and pneumococcal vaccines and antiviral drugs during a pandemic will be established among population groups, and
- how private and public sector responsibilities might change during a pandemic for the purchase, use, and distribution of influenza and pneumococcal vaccines and antiviral drugs.

Agency Comments

In commenting on our draft report, HHS agreed that the issues surrounding the production, purchase, and distribution of vaccines and antiviral drugs merit continued high priority. It discussed several initiatives under way or planned. HHS generally concurred with our recommendations. It also discussed several concerns.

HHS concurred with our recommendation to improve estimates of manufacturers' vaccine and antiviral production capacity and to develop strategies to ensure adequate production levels in the event of a pandemic. However, HHS commented that it believed the draft report inappropriately

emphasized the development and use of antiviral drugs and pneumococcal vaccine over the use of pandemic influenza vaccine. HHS also stated that the wording of our recommendation in the draft report to fill knowledge gaps about vaccines and drugs placed undue and potentially misleading emphasis on the role of antiviral drugs and pneumococcal vaccines in pandemic influenza preparedness. We agree with HHS that influenza vaccine is the first line of defense against an influenza virus, but to the extent that it is in short supply, antiviral drugs and, to a lesser extent, pneumococcal vaccine become important interventions. Our recommendation was intended to include steps to enhance all three interventions, including the availability of influenza vaccine. We have expanded the recommendation to include resolving knowledge gaps surrounding influenza vaccine production and distribution.

In a related comment, HHS stated that the draft did not convey the appropriate use of pneumococcal vaccine. HHS said that the availability of the vaccine will not be a major factor of the federal response plan for pandemic influenza. Rather, it stated that efforts should be directed toward increasing pneumococcal vaccination rates among high-risk groups before the health care delivery system is overwhelmed by a pandemic crisis. We agree that HHS' strategy has merit and gave it greater prominence in the final report.

In its general comments HHS stated that the draft report did not address the full range of activities it considers essential to ensure pre-pandemic preparedness and an adequate pandemic response capability. HHS cited as examples three important aspects of pandemic preparedness that were not addressed in the report: (1) a robust disease surveillance system, (2) the presence of community emergency preparedness protocols, and (3) good public health practices to minimize and control the spread of disease. We recognize that these factors are important aspects of pandemic preparedness and response capability. However, our work focused on the production and distribution of vaccines and drugs, which are also widely regarded as direct and critical interventions needed to help protect the population from an influenza pandemic.

HHS concurred with our recommendation to establish a deadline to complete and publish a federal response plan for pandemic influenza and stated that it will keep the Congress informed of the proposed timetable and progress toward the milestones established. HHS also agreed that the plan needs to include key decisions such as those related to the private and public sector responsibilities for vaccine purchase and delivery. HHS said

that it is working to create a flexible plan that will accommodate a wide variety of contingencies.

HHS' comments are reprinted in appendix I. It also provided technical comments, which we incorporated in the report as appropriate.

As agreed with your offices, unless you publicly release its contents earlier, we will make no further distribution of this report until 30 days after its issue date. At that time, we will send copies of this report to the Honorable Donna E. Shalala, Secretary of Health and Human Services; the Honorable Jeffrey Koplan, Director, Centers for Disease Control and Prevention; and other interested parties. We also will make copies available to others on request.

This report was prepared by Frank Pasquier, Lacinda Baumgartner, Evan Stoll, and Cheryl Williams. If you or your staffs have any questions, please contact me at (202) 512-7119.

A handwritten signature in black ink that reads "Janet Heinrich". The signature is written in a cursive, flowing style.

Janet Heinrich
Director, Health Care—Public Health Issues

Comments From the Department of Health and Human Services



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of Inspector General

OCT 25 2000

Washington, D.C. 20201

Ms. Janet Heinrich
Director, Health Care-Public Health Issues
United States General
Accounting Office
Washington, D.C. 20548

Dear Ms. Heinrich:

Enclosed are the Department's comments on your draft report entitled, "Influenza Pandemic: Plan Needed for Federal and State Response." The comments represent the tentative position of the Department and are subject to reevaluation when the final version of this report is received.

The Department also provided extensive technical comments directly to your staff.

The Department appreciates the opportunity to comment on this draft report before its publication.

Sincerely,

A handwritten signature in cursive script, appearing to read "June Gibbs Brown".

June Gibbs Brown
Inspector General

Enclosure

The Office of Inspector General (OIG) is transmitting the Department's response to this draft report in our capacity as the Department's designated focal point and coordinator for General Accounting Office reports. The OIG has not conducted an independent assessment of these comments and therefore expresses no opinion on them.

**Comments of the Department of Health and Human Services
on the General Accounting Office's Draft Report
"Influenza Pandemic: Plan Needed for Federal and State Response"**

The Department of Health and Human Services (Department) thanks the General Accounting Office (GAO) for undertaking this important study and providing the Department with the opportunity to comment on the draft report. In general, the report calls needed attention to the challenges and resource needs of mounting an effective response to an influenza pandemic. The Department welcomes GAO's decision to focus attention on 1) the capability to develop and produce a vaccine to protect the Nation from a pandemic influenza virus, 2) the capability to use other measures, such as antiviral drugs and pneumococcal vaccines to help protect or treat people exposed to a pandemic influenza virus, and 3) the status of Federal and State plans to address the purchase, distribution, and administration of vaccines and antiviral drugs in a pandemic. The Department agrees that the issues that surround the production, purchase, distribution, and administration of vaccines and antiviral drugs merit continued high priority. Addressing these issues is critical to the Nation's ability to quickly and effectively respond to, and provide public protection against, pandemic influenza.

In recognition of the challenging and multifaceted nature of a pandemic influenza threat the Department has undertaken several coordinated planning efforts. Through these efforts, we have identified and addressed a broad range of issues involving science, law and policy related to pandemic influenza. Although this response does not provide an opportunity for a full discussion of the Department's planning efforts, we offer highlights of this multi-faceted work.

Since 1993, the Department's National Vaccine Program Office (NVPO) has been working on pandemic influenza planning. Efforts were intensified in 1998, when HHS established a departmental steering committee, which has been working on many of the policy issues outlined in GAO's draft report. The steering committee established draft national goals and objectives and developed a decision-making matrix. That matrix was tested utilizing a table top exercise including HHS, the Federal Emergency Management Agency, the Department of Defense, and the American Red Cross.

In addition, in order to strengthen the federal government's ability to help states respond to a pandemic, the Department directed the NVPO to take the lead role in coordinating Federal agencies involved in developing the technical aspects of a Federal Response Plan for pandemic influenza. A Pandemic Influenza Annex to the Federal Response Plan has been drafted and is being reviewed at the departmental level. Finally, as an adjunct to work being done by NVPO and its Inter-Agency Vaccine Group (IAG), the National Vaccine Advisory Committee (NVAC) has convened a work group on pandemic influenza. The work group consists of leaders in influenza virology, immunology, epidemiology, public policy, and biomedical ethics.

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Comments From the Department of Health
and Human Services**

General Comments

While we welcome GAO's attention to these issues, the Department has some significant concerns. First, we believe the report inappropriately emphasizes the development and use of antivirals and pneumococcal vaccine over the use of a pandemic influenza vaccine. Second, we are concerned that the current draft of the report does not address the full range of activities, many of which are being pursued by HHS, that are essential to ensure pre-pandemic preparedness and pandemic response capabilities. The conclusions offered in the report focus only on a few of the many critical issues involved in influenza pandemic response planning. The following highlight some key aspects of pandemic preparedness that are not addressed in the current draft of GAO's report:

- **Robust disease surveillance efforts** are essential to maximizing the lead time available for vaccine development, identifying risk factors associated with the disease, and other appropriate responses.
- **Emergency preparedness** is key to preparing for pandemic influenza. Emergency preparedness encompasses readiness to cope with the potentially large numbers of illnesses, hospitalizations, deaths, and the disruption to our societal infrastructure. Community preparation to mount basic emergency protocols, absent external support mechanisms, is critical to pandemic preparedness planning.
- **Good public health practices** to minimize and control the spread of disease must be employed by State and local health departments. While the best defense against influenza is vaccine, it is possible that adequate vaccine supply will not be available or may not be available until well into a pandemic. Good public health practices include the use of appropriate control measures and prevention education for the public and health care professionals.

Comments on Recommendations for Executive Action

GAO Recommendation

To improve the nation's ability to respond to the emergence of a pandemic influenza virus and help ensure an adequate and appropriate level of public protection, we recommend that the Secretary of HHS first take steps to fill the knowledge gaps on the capability of the private and public sectors to produce, distribute, and administer vaccines and antiviral drugs to various population groups to control the spread and effect of a pandemic. Specifically, we recommend that HHS:

- identify the capability of all manufacturers to produce antiviral drugs and pneumococcal vaccines and their existing "surge capacity" to expand production as needed during a

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pandemic, and if existing surge capacity is insufficient, work with manufacturers to determine the investment and time required to expand production capacity, or the feasibility of creating a stockpile against projected shortages.

Department Comment

The Department agrees with GAO's recommendation to improve estimates of manufacturers' vaccine and antiviral production capacity and to develop strategies to ensure adequate production levels in the event of a pandemic. We are concerned, however, that the proposed recommendation places undue, and potentially misleading, emphasis on the role of antiviral drugs and pneumococcal vaccines in pandemic influenza preparedness. As currently drafted, the recommendation suggests that the availability of pharmaceutical agents is the only capacity required to respond to the emergence of pandemic influenza. As our General Comments indicate, we believe the report may shift attention away from other critical components of preparedness, such as robust surveillance, adequate emergency response capacity, and good public health practices.

In addition to minimizing the range of activities required to ensure prepandemic preparedness and pandemic response capabilities, the recommendation suggests that antiviral drugs and pneumococcal vaccines represent the centerpiece of a clinical response strategy. We believe that for pandemic flu, the cornerstone of clinical disease control and treatment interventions should be the rapid development of an effective influenza vaccine. Although GAO's report accurately reflects that the clinical response to pandemic influenza will likely include a combination of influenza vaccination, antiviral drugs and pneumococcal vaccination, the emphasis on pneumococcal vaccines and antiviral drugs obscures the resource and development needs related to influenza vaccine development.

Each of the pharmaceutical agents discussed by GAO carries with it a distinct set of production capacity, distribution strategy, and effectiveness issues:

Influenza Vaccine.

Evaluating the capacity and capability to produce a pandemic flu vaccine has been a major emphasis of departmental efforts. HHS has evaluated the pandemic flu vaccine capacities and capabilities of manufacturers; and as described in the GAO Report, inherent in the essential vaccine production process are significant barriers to developing and producing a pandemic influenza vaccine. At a minimum these efforts will take 6-8 months. The Department believes, however, that establishing conditions that maximize capacity and minimize the time needed to produce vaccine are essential to planning efforts. We continue to work with manufacturers to support increased capacity and capability for influenza vaccine production and the development of breakthrough technologies. For example, in 2000, the Department's National Institutes of Health (NIH) awarded approximately \$5 million to three private sector companies which also committed their own matching dollars for the development of non-egg based vaccines and the production of experimental lots of vaccines using avian influenza viruses.

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In addition, NIH has supported the development of a live influenza virus vaccine that is administered as a nasal spray. The ease of administration of this vaccine has the potential of increasing the public's acceptance of influenza vaccines. This is potentially important because strategies that increase annual demand for influenza vaccine allow manufacturers to build their production capacity, thereby helping to ensure increased capacity in the event of a pandemic. Because influenza vaccine must be tailor made for each emerging strain, stockpiling is not possible, and increased production capacity takes on added significance.

An additional strategy aimed at addressing a vaccine shortage in the event of a pandemic flu focuses on dose response research. Because of concerns about a delay of influenza vaccine for the 2000 to 2001 influenza season, NIH conducted a clinical trial to compare a full-dose versus a half dose of the current inactivated vaccine in healthy adults. The Department's Food and Drug Administration and CDC participated in this study by conducting all of the laboratory assays. Preliminary results of this study were presented to the Advisory Committee on Immunization Practices on October 18, 2000. Final results are anticipated next year.

Antiviral Drugs.

Antiviral drugs, such as amantadine and rimantadine, have been demonstrated to be effective in preventing illnesses caused by naturally occurring strains of type A influenza viruses in adults and children and can also reduce the severity and duration of illness. However, issues related to potential adverse drug reactions and the emergence of drug-resistant viruses resulting from the widespread use of these antiviral agents argue for limiting the potential role for these drugs in the event of a pandemic. These concerns lead to the proposal that the use of antivirals in response to a pandemic should be targeted, rather than broad-based. The NVPO, IAG, and the NVAC work group are convening a technical panel to consider the use of antiviral drugs, manufacturer production capabilities, and other related issues. The role of the newly licensed neuraminidase inhibitor class of antiviral drugs will also be assessed by this panel. While creating stockpiles of raw materials, bulk drugs, or finished drugs are being considered, the importance of antiviral drugs in a pandemic influenza response should not be overstated.

Pneumococcal Vaccines.

We do not believe that GAO's report accurately conveys the appropriate use of pneumococcal polysaccharide vaccine. In advance of a pandemic, it will be important to fully immunize high-risk populations, as recommended by the Advisory Committee on Immunization Practices, to reduce their risks of acquiring pneumococcal infection, a potential complication of influenza infection, as outlined in Healthy People 2010. Immunity resulting from pneumococcal vaccine is sustained over the course of many years. Thus efforts should be directed toward increasing vaccination rates before the

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health care delivery system is overwhelmed by a pandemic crisis. In the event of a pandemic, however, it is unlikely that the availability of pneumococcal polysaccharide vaccine will be as critical as implied by GAO's report. We do not believe that availability of this vaccine will be a major factor of the Federal response plan for pandemic influenza.

GAO Recommendation

Second, we recommend that the Secretary establish a deadline to complete and publish a federal response plan that will address:

- how population groups will be prioritized during a pandemic for receiving limited influenza and pneumococcal vaccines and antiviral drugs and
- how private and public sector responsibilities might change during a pandemic for the purchase, use, and distribution of influenza and pneumococcal vaccines and antiviral drugs.

Department Comment

The Department concurs with the recommendation to establish a deadline to complete and publish a Federal response plan for pandemic influenza. The Department is committed to developing a comprehensive plan in a timely fashion and will keep GAO and Congress informed of our proposed timetable and progress toward the milestones established.

The Department acknowledges that key decisions related to private and public sector responsibilities for vaccine purchase, distribution, and delivery are not yet finalized. Work on the prioritization of groups for vaccination is proceeding as we develop models that will allow a flexible response dependent on the course of the disease. We appreciate the importance of resolving these issues in the near future. In addition, we recognize that resolution will help states proceed with their planning activities. Typically, public health and disaster relief efforts are implemented by the States with federal coordination and assistance. Mindful of that model, the Department has worked extensively with the states to promote and assist with their planning activities. We have published draft guidelines and provided funding for a number of states to develop model plans. At the federal level, we are working to create a flexible plan that will accommodate a wide variety of contingencies. Because the response plan represents a complex set of decisions, we are pursuing a careful, thoughtful approach involving multiple constituencies, including State and local governments, Congress, and drug manufacturers and distributors.

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Penalty for Private Use \$300**

Address Correction Requested

<p>Bulk Rate Postage & Fees Paid GAO Permit No. GI00</p>

