

December 2007

INFLUENZA PANDEMIC

Efforts Under Way to Address Constraints on Using Antivirals and Vaccines to Forestall a Pandemic





Highlights of [GAO-08-92](#), a report to congressional requesters

Why GAO Did This Study

Pandemic influenza poses a threat to public health at a time when the United Nations' World Health Organization (WHO) has said that infectious diseases are spreading faster than at any time in history. The last major influenza pandemic occurred from 1918 to 1919. Estimates of deaths worldwide if a similar pandemic were to occur have ranged between 30 million and 384 million people. Individual countries and international organizations have developed and begun to implement a strategy for forestalling (that is, containing, delaying, or minimizing the impact of) the onset of a pandemic. Antivirals and vaccines may help forestall a pandemic.

GAO was asked to examine (1) constraints upon the use of antivirals and vaccines to forestall a pandemic and (2) efforts under way to overcome these constraints. GAO reviewed documents and consulted with officials of the Departments of State and Health and Human Services (HHS), international organizations, and pharmaceutical manufacturers.

WHO commented that the report was comprehensive and useful. HHS stressed that vaccines and antivirals must be viewed in a larger context. State and HHS commented that the term "forestall" is ambiguous and misleading. However, GAO has used the word in a way that is consistent with WHO's use of the term.

To view the full product, including the scope and methodology, click on [GAO-08-92](#). For more information, contact Marcia Crosse at (202) 512-7114 or crossm@gao.gov, or David Gootnick at (202) 512-3149 or gootnickd@gao.gov.

INFLUENZA PANDEMIC

Efforts Under Way to Address Constraints on Using Antivirals and Vaccines to Forestall a Pandemic

What GAO Found

The use of antivirals and vaccines, two elements of the international strategy to forestall a pandemic, could be constrained by their uncertain effectiveness and limited availability. To use antivirals effectively, health authorities must be able to detect a pandemic influenza strain quickly through surveillance and diagnostic efforts and use this information to administer antivirals. The effectiveness of antivirals could be limited if they are used more than 48 hours after the onset of symptoms or by the emergence of strains resistant to antivirals. Unlike antivirals, vaccines are formulated to target a specific influenza strain in advance of infection. The effectiveness of vaccines in forestalling a pandemic could be limited because such a targeted pandemic vaccine cannot be developed until that strain has been identified. Due to the time required to identify the virus and develop and manufacture a pandemic vaccine—20 to 23 weeks according to HHS—such vaccines are likely to play little or no role in efforts to forestall a pandemic in its initial phases. The availability of antivirals and vaccines in a pandemic could be inadequate due to limited production, distribution, and administration capacity. WHO has stated that it is unlikely that sufficient quantities of antivirals will be available in any country at the onset of a pandemic. The distribution and administration capacity for antivirals and vaccines is limited in some countries by poor or nonexistent delivery plans and networks, a lack of facilities for administering the drugs, and small numbers of personnel trained to administer them.

The United States, its international partners, and the pharmaceutical industry are investing substantial resources to address constraints on the availability and effectiveness of antivirals and vaccines. Efforts are under way to improve influenza surveillance, including diagnostic capabilities, so that outbreaks can be quickly detected. Increased demand and government support has led manufacturers to increase research into more effective antivirals and vaccines. Manufacturers are developing new antivirals to combat influenza. New methods for developing vaccines are being studied in order to reduce the amount of vaccine that is needed and to increase the number of strains against which it is effective. Pre-pandemic vaccines, which are formulated to target influenza strains that have the potential to cause a pandemic, are being developed. However, these vaccines may or may not be effective against the pandemic strain that ultimately emerges. To overcome limitations on the availability of antivirals and vaccines, manufacturers are working to increase production at existing facilities and build new facilities. To address constraints on the distribution and administration of antivirals, stockpiles are being established to allow faster delivery of antivirals to countries experiencing outbreaks. WHO is also working to establish stockpiles of pre-pandemic vaccines. Additionally, other efforts also face limitations. For example, increasing production capacity of vaccines and antivirals will take several years as new facilities are built and necessary materials acquired.

Contents

Letter		1
	Results in Brief	4
	Background	6
	Uncertain Effectiveness and Limited Availability Would Likely Constrain the Use of Antivirals and Vaccines to Forestall the Onset of a Pandemic	19
	U.S. Government and International Partners' Efforts Are Under Way to Address Constraints on Use of Antivirals and Vaccines, but Certain Efforts Face Limitations	30
	Agency Comments and Our Evaluation	54
Appendix I	Comments from the Department of Health and Human Services	60
Appendix II	Comments from the Department of State	66
Appendix III	GAO Contacts and Staff Acknowledgments	69
Related GAO Products		70
Tables		
	Table 1: Influenza Vaccine Types	11
	Table 2: Antiviral Drugs Available for the Prevention and Treatment of Influenza	13
	Table 3: HHS Contracts Awarded to Companies in December 2006 to Develop Rapid Diagnostic Tests for Influenza	36
	Table 4: HHS Contracts Awarded in May 2006 to Develop Cell-Based Vaccines	45
	Table 5: HHS Contracts Awarded in January 2007 to Develop Influenza Vaccines Containing an Adjuvant	46
Figure		
	Figure 1: Pandemic Vaccine Production Timeline	24

Abbreviations

CDC	Centers for Disease Control and Prevention
FAO	Food and Agriculture Organization of the United Nations
FDA	Food and Drug Administration
GLEWS	Global Early Warning and Response System for Major Animal Diseases, including Zoonoses
HHS	Department of Health and Human Services
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
NIH	National Institutes of Health
OFFLU	OIE/FAO Network of Expertise on Avian Influenza
OIE	World Organisation for Animal Health (Office International des Epizooties)
WHO	United Nations' World Health Organization

This is a work of the U.S. government and is not subject to copyright protection in the United States. It may be reproduced and distributed in its entirety without further permission from GAO. However, because this work may contain copyrighted images or other material, permission from the copyright holder may be necessary if you wish to reproduce this material separately.



United States Government Accountability Office
Washington, DC 20548

December 21, 2007

The Honorable Edward M. Kennedy
Chairman
Committee on Health, Education,
Labor and Pensions
United States Senate

The Honorable Daniel K. Akaka
Chairman
Subcommittee on Oversight of
Government Management, the Federal
Workforce, and the District of Columbia
Committee on Homeland Security and
Governmental Affairs
United States Senate

The Honorable Bennie G. Thompson
Chairman
Committee on Homeland Security
House of Representatives

The Honorable Judd Gregg
United States Senate

An influenza pandemic—caused by a novel strain of influenza virus that is virulent and highly transmissible among humans—would be of global significance. While some scientists and public health experts believe that the next influenza pandemic could be caused by a strain of the H5N1 avian influenza virus (also known as “bird flu”) that is currently circulating in parts of Asia, Europe, and Africa, it is unknown when an influenza pandemic will occur, where it will begin, or whether an H5N1 strain or another strain would be the cause. Pandemic influenza poses a grave threat to global public health at a time when the United Nations’ World Health Organization (WHO) has said that infectious diseases are spreading faster than at any time in history. Of the three pandemics of the twentieth century, the most deadly was the pandemic of 1918-1919 in which scientists estimate that there were 50-100 million deaths worldwide, including at least 675,000 in the United States, making it among the most deadly events in human history. The U.S. government has estimated that as many as 2 million U.S. citizens could die in the next pandemic. If an

influenza pandemic were to occur on the same scale as the 1918-1919 pandemic, estimates of deaths worldwide have ranged between 30 million and 384 million people.

The concern regarding an influenza pandemic has prompted the United States, other governments, and international organizations such as WHO to develop and begin to implement an international strategy to respond to the threat of an influenza pandemic.¹ The international strategy comprises local, national, regional, and global strategies, which include a variety of countermeasures designed to contain or delay a pandemic or to minimize its impact once it emerges. Included among the elements of these strategies aimed at forestalling a pandemic (that is, containing, delaying, or minimizing the impact of) are antivirals and vaccines. Both could potentially be used to prevent infection and, in the case of antivirals, to also treat infected individuals.²

The important role that antivirals and vaccines could play in containing or limiting the spread of a pandemic has led to questions regarding their use. For example, antivirals and vaccines could be needed in greater quantities than ever before. As agreed with your offices, we are reporting on (1) the constraints upon the use of antivirals and vaccines to forestall the onset of a pandemic and (2) the efforts under way to overcome these constraints.

To report on these issues, we reviewed documents and consulted officials from the Departments of Health and Human Services (HHS) and State, WHO, the Asian Development Bank, and pharmaceutical manufacturers.³ Within HHS, we examined documents and consulted officials from the Office of the Secretary, the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the National

¹WHO is the United Nations agency for health. It is responsible for coordinating the global response to human cases of H5N1, monitoring the spread of the disease, and determining when a virus has caused a global pandemic. It also provides the international community with guidelines, procedures, and recommendations on addressing infectious disease outbreaks, including H5N1.

²Antivirals can prevent or reduce the severity of a viral infection, such as influenza. Vaccines are used to stimulate the production of an immune system response to protect the body from disease.

³The Asian Development Bank provides funding and technical assistance aimed at improving the welfare of people in the Asia-Pacific region. WHO has stated the Asian Development Bank has become a major partner in providing financial assistance to support WHO's pandemic response activities.

Institutes of Health (NIH). We obtained information from the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), including information about influenza vaccine development projects initiated by members of its Influenza Vaccine Supply International Task Force.⁴ We reviewed reports published by the Institute of Medicine focusing on pandemic influenza. In addition, we interviewed experts and attended academic symposia on pandemic influenza and the challenges to addressing its threat. We determined the data on the funding of antiviral and vaccine research as well as the data on the manufacturing, use, and availability of antivirals and vaccines were sufficiently reliable for the purposes of this report. Our goal in collecting the information in this report was to provide a picture of ongoing efforts by the U.S. government, other national governments, international organizations like WHO, and industry to prepare for a pandemic. This often involved reporting technical information on the research and development on antivirals and vaccines. In some cases, rapid scientific advances may have outpaced the timing of this report such as, for example, the initiation of a new area of research not specifically identified in the report. In other cases, there is no consensus on the appropriate use and likely results of various medical countermeasures, including different types of antivirals and vaccines. This report was not intended to provide the most complete, current, or definitive discussion of scientific developments and knowledge concerning the use of antivirals and vaccines. We have, instead, sought to report information that is necessary to understand the challenges faced by the U.S. government and others in their efforts to develop measures involving antivirals and vaccines in efforts to forestall a pandemic. We conducted our work from January 2006 through December 2007 in accordance with generally accepted government auditing standards.

In recent related work, we examined the extent to which U.S. agencies and their international partners have assessed pandemic risk by country and prioritized countries for international assistance. In addition, we examined the steps that U.S. agencies and their international partners have taken to improve global preparedness to forestall a pandemic.⁵ This work was also

⁴Members of the IFPMA Influenza Vaccine Supply International Task Force represent more than 95 percent of worldwide influenza vaccine production.

⁵GAO, *Influenza Pandemic: Efforts to Forestall Onset Are Under Way; Identifying Countries at Greatest Risk Entails Challenges*, [GAO-07-604](#) (Washington, D.C.: June 20, 2007).

conducted in accordance with generally accepted government auditing standards.

Results in Brief

The use of antivirals and vaccines to forestall the onset of a pandemic would likely be constrained by their uncertain effectiveness and limited availability. Health authorities must be able to detect the virus strain quickly through surveillance and diagnostic efforts and use this information to test and administer effective antivirals. The effectiveness of antivirals could be limited if they are used more than 48 hours after the onset of symptoms and by the emergence of influenza strains that are resistant to antivirals. Due to the time required to detect the virus and develop and manufacture a targeted vaccine for a pandemic—about 20 to 23 weeks according to HHS—pandemic vaccines are likely to play little or no role in efforts to stop or contain a pandemic, at least in its initial phases. Furthermore, weaknesses in the global influenza surveillance system, including weaknesses in diagnostic capability, could limit the effectiveness of antivirals and vaccines in treating and preventing cases of infection because of limitations in many countries that impede the detection of influenza strains. In addition, the supply of antivirals and vaccines available in the event of a pandemic would probably be inadequate due to limited production, distribution, and administration capacity. WHO has stated that it is unlikely that sufficient quantities of antivirals will be available in any country at the onset of a pandemic. The supply of pandemic vaccine would likely not be able to meet demand without additional production capacity, achieved either by current manufacturers scaling up production or by increasing the number of manufacturers. The distribution and administration capacity for antivirals and vaccines is limited in some countries by poor or nonexistent delivery plans and networks, a lack of facilities suitable for administering the drugs, and small numbers of personnel trained to administer them.

The United States, its international partners, and the pharmaceutical industry are investing substantial resources to address constraints on the availability and effectiveness of antivirals and vaccines, but some of these efforts face limitations and are not expected to produce results for several years. To better ensure the effectiveness of antivirals and vaccines by being able to quickly identify a pandemic strain, the United States and its international partners are involved in efforts to improve influenza surveillance, including diagnostic capability. WHO's revised International Health Regulations seek to minimize the international spread of disease, in part by improving disease surveillance in humans. International surveillance networks for influenza in animals have been established and

efforts are under way to improve data sharing among scientists. However, WHO and HHS officials have raised concerns regarding Indonesia's refusal to share influenza samples and how this could harm global public health. Indonesia has refused to consistently share influenza samples because of concerns that the resulting vaccines would not be available to developing countries and from a desire for royalties from any invention derived from an influenza sample isolated within its borders. Increased demand and government support have encouraged manufacturers to increase their research and development into more effective antivirals and vaccines. For example, the U.S. government awarded a \$103 million contract to one company to develop a new antiviral. The United States also has awarded approximately \$1.1 billion to companies to develop a new influenza vaccine production technology that would expand vaccine manufacturing capacity in the United States. Alternative methods for developing vaccines are also being studied in order to reduce the amount of vaccine that is needed to provide protection and to increase the number of strains against which a vaccine is effective. Pre-pandemic vaccines, which are formulated to target influenza strains that have the potential to cause a pandemic, are being developed. However, these vaccines may or may not be effective against the pandemic strain that ultimately emerges. To overcome limitations on the availability of effective antivirals and vaccines, national governments and international organizations are working with pharmaceutical manufacturers to expand global production capacity to increase production at facilities and build new production facilities. To address constraints on the distribution and administration of antivirals, international organizations and pharmaceutical manufacturers have established global and regional antiviral stockpiles to deliver these drugs more quickly to countries experiencing outbreaks. WHO has recently begun to establish a pre-pandemic vaccine stockpile for use in countries without influenza production capacity or the ability to purchase vaccines. Several industrialized countries, including the United States, have established pre-pandemic influenza vaccine stockpiles to vaccinate critical workforce and primary health care workers at the onset of a pandemic. However, some of these efforts face limitations. For example, increasing global production capacity of vaccines and antivirals will take several years as new production facilities are built, materials necessary for production are acquired, and the necessary approval is received to market these medical products in various countries.

In commenting on a draft of this report, WHO provided comments via e-mail and stated that the report was comprehensive and useful. HHS stressed that vaccines and antivirals should be viewed in the context of a broader pandemic strategy. The Departments of State and HHS

commented that the term “forestall” is ambiguous and misleading. However, we have defined the term in a way that is consistent with how WHO has used the word in describing its efforts to respond to a pandemic. We defined the term to mean contain, delay, or minimize the impact of a pandemic.

Background

WHO, in conjunction with the United States and other governments, has developed an international strategy for forestalling the onset of an influenza pandemic. Elements of this strategy include restricting the movement of people in and out of the affected area, isolation of ill persons, and school closures. Antivirals are also an important element of this strategy. Studies suggest that using antiviral drugs, along with other interventions, to treat infections and prevent illness might contain a pandemic at the site of the outbreak or at least slow its international spread, thus gaining time to put emergency measures in place and begin producing matched vaccines that would be effective in preventing individuals from being infected with the strain of influenza causing the pandemic.

Influenza

Influenza, also called “the flu,” is caused by a virus that primarily attacks the upper respiratory tract—the nose and throat—and sometimes the lungs. Influenza is characterized by cough, fever, headache, and other symptoms and is more severe than some viral respiratory infections, such as the common cold. In almost every year a seasonal influenza virus causes acute respiratory disease in epidemic proportions somewhere in the world.⁶ Most people who contract seasonal influenza recover completely in 1 to 2 weeks, but some develop serious and potentially life-threatening medical complications, such as pneumonia.⁷ Most healthy adults may infect others 1 day before getting symptoms and up to 5 days after they first develop symptoms. Some young children and people with

⁶Seasonal influenza is an outbreak of influenza that occurs every year. There are two influenza seasons, one in the northern hemisphere and one in the southern hemisphere. The influenza season in the northern hemisphere is from November to April while the influenza season in the southern hemisphere is from May to October. An epidemic is the occurrence in a community or region of cases of an illness in excess of what is normally expected.

⁷People aged 65 years and older, people of any age with chronic medical conditions, children younger than 2 years, and pregnant women are generally more likely than others to develop severe complications from seasonal influenza.

weakened immune systems may be contagious for more than a week. WHO estimates that seasonal influenza affects about 5 to 15 percent of the world's population each year, causing 3 to 5 million cases of severe illness worldwide including 250,000 to 500,000 deaths.

There are three types of influenza viruses: A, B, and C. However, only influenza A viruses cause pandemics.⁸ Influenza A viruses are further categorized into subtypes according to differences in the “HA” and “NA” proteins that are on the outer surface of the virus.⁹ These influenza A subtypes are further characterized into strains. Influenza strains mutate, or genetically change, over time. As strains mutate, new strains of influenza viruses appear and may replace older, circulating strains. When a new strain of human influenza virus emerges, immunity that may have developed after a previous infection or vaccination may not provide protection against the new strain. Small mutations in the influenza virus are the reason why someone who has previously been infected with influenza can still be susceptible to seasonal or common influenza. More substantial changes in the influenza virus can result in the emergence of a pandemic influenza subtype.¹⁰

Pandemic human influenza is a virulent influenza that causes a global outbreak, or pandemic, of serious illness. It occurs when an existing strain of the influenza virus is replaced by a new influenza A strain to which humans have no immunity, resulting in widespread morbidity and mortality.¹¹ According to WHO, pandemic influenza can spread to all parts of the world very quickly, usually in less than a year, and can sicken more

⁸In addition to humans, influenza A viruses can infect a variety of other animals including horses, pigs, sea mammals, and birds. In this report, we differentiate between human influenza and animal influenza. Evidence suggests that all human influenza A viruses originate from influenza A viruses in wild waterfowl.

⁹Sixteen types of HA or H (hemagglutinin) proteins and 9 types of NA or N (neuraminidase) proteins have been identified. Each combination of these proteins (for example, H5N1) is known as a subtype.

¹⁰Pandemic influenza can emerge through two principal mechanisms: reassortment and adaptive mutation. Reassortment is the mixing of human influenza and animal influenza viruses within an animal or human to create a new human influenza A subtype. Adaptive mutation involves changes in the virus whereby a virus gradually acquires the changes needed to improve its transmissibility among humans. If such changes result in a new influenza A virus subtype that can infect humans and spread easily from person to person, an influenza pandemic can occur.

¹¹Pandemics vary in severity. For example, the pandemic of 1918-1919 was more severe than the last two pandemics (in 1957 and 1968).

than a quarter of the global population.¹² Three conditions must be met before an influenza pandemic begins: (1) a new influenza virus subtype that has not previously, or at least recently, circulated in humans must emerge, (2) the virus must be capable of causing disease in humans, and (3) the virus must be capable of sustained human-to-human transmission. The H5N1 virus currently meets the first two of these three conditions but not the third.¹³

The current H5N1 pandemic influenza threat stems from an unprecedented outbreak of H5N1 influenza that first appeared in birds in southeastern China and Hong Kong in 1996 and 1997 and was first detected in humans in Hong Kong in 1997. The virus reappeared in late 2003 and early 2004 and has since spread in bird populations across parts of Asia, Europe, and Africa, with limited infections in humans.¹⁴ From December 1, 2003, to December 11, 2007, H5N1 was detected in animals in 60 countries. According to WHO, the geographical spread of H5N1 in animals in 2006 was the fastest and most extensive of any pathogenic avian influenza virus recorded to date. From January 1, 2003, through December 12, 2007, WHO reported 338 confirmed human cases, including 208 human deaths from the H5N1 virus in a total of 12 countries—a case fatality rate of 62 percent.¹⁵ Scientists and public health officials agree that the spread of the H5N1 virus in birds and the occurrence of infections in humans have increased the risk that this disease may change through adaptive mutation or reassortment into a form that is easily transmissible among humans, resulting in an influenza pandemic.¹⁶

¹²In the past, influenza pandemics have spread worldwide within 6 to 9 months. However, WHO has stated that given the current volume of international travel, it is likely that a pandemic would spread more quickly.

¹³H5N1 influenza is caused by influenza viruses that occur naturally among wild birds. All types of birds are susceptible to the virus, but outbreaks occur most often in chickens and turkeys. The H5N1 subtype is deadly to domestic fowl. Currently, humans are only rarely affected.

¹⁴While H5N1 is considered the most likely subtype to cause a pandemic at this time, experts have also cited the subtypes H2N2, H7N7, and H9N2 as having pandemic potential.

¹⁵The case fatality rate is defined as the number of people who die of a disease divided by the number of people who have the disease.

¹⁶According to HHS and WHO, there have been a limited number of human cases in which human-to-human transmission cannot be ruled out. However, H5N1 has not yet demonstrated an ability to spread efficiently among humans.

HHS stated that little is known about how to control a pandemic and that it is important to distinguish between seasonal influenza and pandemic influenza. Current knowledge about how antiviral drugs and influenza vaccines perform is largely drawn from experience with seasonal influenza. HHS stated that how antivirals and vaccines will perform against a pandemic influenza virus cannot be predicted, but as there are currently no better options, the agency has made plans for their use in response to a pandemic.

Vaccines

Vaccines are considered the first line of defense against influenza to prevent infection and control the spread of the disease. Vaccines stimulate immune responses which include causing the body to produce neutralizing antibodies to provide protective immunity to a particular virus strain.¹⁷ After vaccination, the body takes about 2 weeks to produce protective antibodies for that strain. For the one FDA-licensed H5N1 vaccine, two doses administered about 4 weeks apart would be required to provide what is believed to be an adequate immune response based on past experience with seasonal influenza vaccines. When a vaccinated person is exposed to the specific virus proteins in the vaccine, antibodies develop in response that will help either to prevent infection or reduce the severity of the illness caused by infection.¹⁸ To be most effective, an influenza vaccine needs to closely match the circulating influenza strain. However, because influenza viruses undergo minor but continuous genetic changes from year to year, a matched vaccine cannot be developed until the circulating strain has been identified. Generally, the purpose of vaccination is to prevent infection; however, in the event of a pandemic, the purpose could be broadened to include decreasing mortality or morbidity. The impact of such a change could be to increase vaccine availability since a vaccine that is not fully matched to the virus might be available more quickly and still help reduce mortality and morbidity.

¹⁷An antibody is a molecule produced by the immune system that helps fight infections.

¹⁸The ability of influenza vaccine to protect a person depends on the age and health status of the person getting the vaccine, and the similarity or “match” between the virus strains in the vaccine and those in circulation. When the vaccine and circulating virus are well-matched, influenza vaccines will prevent illness in approximately 70 to 90 percent of healthy adults under the age of 65. The protection drops to about 30 to 40 percent for the elderly. Vaccine effectiveness can also be lower for individuals with underlying medical conditions such as compromised immune systems.

In the case of vaccines for seasonal influenza, WHO, CDC, FDA, health officials around the world, and vaccine manufacturers participate in a system that develops and produces vaccines targeted to the influenza strains most likely to be in circulation during the next influenza season. This system collects and analyzes circulating influenza viruses, uses the information to determine the three human strains most likely to circulate in the upcoming year, and formulates and distributes virus reference strains to vaccine manufacturers, who produce seed viruses to manufacture influenza vaccines.¹⁹ Influenza vaccine is produced in a complex process that involves growing viruses in millions of fertilized chicken eggs. Seasonal vaccine production generally takes 6 or more months after virus strains have been selected.²⁰ The same general system would be used in the event of a pandemic to manufacture a vaccine targeted to the influenza strain causing it.

Influenza vaccines can be categorized into three types: seasonal, pre-pandemic, and pandemic. As discussed in table 1, seasonal vaccines protect against annual (i.e., seasonal) influenza strains. Pre-pandemic vaccines are formulated to match strains of influenza viruses that have had limited circulation in humans but have pandemic potential. However, they are not matched or targeted to the specific pandemic strain that may eventually emerge.²¹ Pandemic vaccines are formulated to match a pandemic strain that has already emerged. Influenza vaccines are made either from inactivated (i.e., killed) viruses or from live viruses that have

¹⁹We use the term seed virus to indicate the modified virus from which subsequent vaccine production for that strain is derived.

²⁰The 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. Other factors that affect timing include testing by FDA and manufacturers to determine vaccine strength and the development of a reagent for such testing. A reagent is a substance used in a chemical reaction to detect, measure, examine, or produce other substances. Reagents are used to determine the purity and strength of influenza vaccine, and must be developed each year for the specific new vaccine.

²¹A pre-pandemic vaccine may have both pre-pandemic and pandemic use. For example, a pre-pandemic vaccine might be given to those at high risk of exposure prior to a pandemic. The same vaccine might also be used to vaccinate critical workforce and primary health care workers in the early stages of a declared pandemic when a matched pandemic vaccine is not available.

been attenuated (i.e., weakened).²² Generally, inactivated influenza vaccines are made from parts of the influenza virus rather than the whole virus.

Table 1: Influenza Vaccine Types

Type	Definition
Seasonal	A vaccine produced annually that protects against that year's strains of seasonal influenza. Current seasonal vaccines are trivalent, meaning they contain three different strains of influenza viruses.
Pre-Pandemic	A vaccine against strains of influenza virus in animals that have caused isolated infections in humans and have pandemic potential. This vaccine is prepared prior to the emergence of a pandemic strain and may be a good or poor match (and hence of greater or lesser protection) for the pandemic strain that ultimately emerges.
Pandemic	A vaccine targeted to a specific novel influenza virus strain that has the capacity for sustained and efficient human-to-human transmission. This vaccine can only be developed once the pandemic strain emerges.

Sources: European Commission and U.S. Homeland Security Council.

Globally, influenza vaccine production is largely a private-sector activity and vaccine manufacturing is concentrated in Europe and North America, with approximately 90 percent of worldwide production capacity located in these areas. However, there are manufacturers throughout the world, including in Australia, China, and Japan. Some manufacturers have production facilities in more than one country. In some cases, more than one manufacturer may be producing vaccine for distribution in a particular country. For example, there were four manufacturers producing five vaccines for the 2006-2007 influenza season in the United States.²³ In the event of a pandemic, manufacturers would switch production from seasonal to pandemic vaccine, and would use the same facilities to produce the pandemic vaccine as they had used to produce seasonal

²²Research is also currently underway to develop what is called a universal vaccine, which would protect against multiple influenza strains. However, such a vaccine does not currently exist.

²³The five vaccines and their manufacturers were Fluarix (GlaxoSmithKline Biologicals), FluLaval (ID Biomedical Corporation, a subsidiary of GlaxoSmithKline Biologicals), FluMist (MedImmune Vaccines, Inc.), Fluvirin (Novartis Vaccines and Diagnostics, Inc.), and Fluzone (sanofi pasteur, Inc.). The policy of sanofi pasteur is to spell its name without capital letters.

vaccine.²⁴ Pre-pandemic vaccines are currently produced only during the 3- to 4-month period when manufacturers are not producing seasonal vaccine.

Antivirals

Antiviral drugs are also used against seasonal influenza in humans to reduce symptoms and complications and could be used in the event of a pandemic. Antivirals can be used to both prevent illness and treat those who are already infected by killing or suppressing the replication of the influenza virus. Antivirals are not reformulated to match a specific influenza strain and could be used from the early phase of an influenza pandemic.

As shown in table 2, two classes of antiviral drugs are currently available for the prevention and treatment of influenza, and two types of drugs within each class have been approved. Amantadine and rimantadine belong to the older class, adamantanes.²⁵ Tamiflu and Relenza belong to the newer class, neuraminidase inhibitors.²⁶ Amantadine is given as a capsule, syrup, or tablet, while rimantadine is administered as a syrup or tablet. Tamiflu can be administered as either a capsule or liquid. Relenza is a powder that must be inhaled using a special device. According to CDC, antivirals are about 70 to 90 percent effective for preventing illness in healthy adults; that is, they are about as effective as vaccines, when the vaccine and circulating virus strains are well matched, in preventing illness among healthy adults. For maximal effectiveness in preventing infection, the antiviral must be taken throughout the entire period of a community outbreak. According to current research involving seasonal influenza, if taken within 2 days of the onset of symptoms, these drugs can

²⁴The switch to pandemic vaccine production is a decision that manufacturers will make together with public health officials. This switch will impact the availability of the following year's seasonal vaccine since production facilities will be used to produce pandemic vaccine instead of seasonal vaccine. If such a decision is made and the pandemic does not occur, the pandemic vaccine will not likely protect against the following year's seasonal influenza. However, if a pandemic does occur and the decision is late, then that will add to the delay in the availability of a pandemic vaccine.

²⁵Adamantanes, also known as M2-ion channel inhibitors, are less expensive than neuraminidase inhibitors. Amantadine and rimantadine are no longer under patent protection and are referred to by their scientific (that is, generic) names.

²⁶Tamiflu and Relenza are both under patent protection in some countries, including the United States, and therefore are referred to by their brand names instead of their scientific names, oseltamivir and zanamivir, respectively.

shorten the duration of the illness by 1 or 2 days, alleviate symptoms, reduce complications and serious illness, and may make someone with influenza less contagious to others. However, it is unknown if antivirals will perform the same for pandemic influenza as they do for seasonal influenza. In addition, influenza virus strains can become resistant to one or more of these drugs, and so they may not always be effective for prevention or treatment.²⁷

Table 2: Antiviral Drugs Available for the Prevention and Treatment of Influenza

Class	Scientific name^a	Drug name(s)^b	Route of administration
Adamantanes (M2-ion channel inhibitors)	Amantadine	Symmetrel, Amantadine Hydrochloride	Oral (capsule, syrup, tablet)
	Rimantadine	Flumadine, Rimantadine Hydrochloride	Oral (syrup, tablet)
Neuraminidase inhibitors	Oseltamivir	Tamiflu	Oral (capsule, suspension) ^c
	Zanamivir	Relenza	Inhalation (powder)

Sources: HHS and WHO.

^aThe scientific name of a drug is also referred to as the generic name.

^bThese are the names under which the drug is currently marketed in the United States.

^cSuspension is a liquid dosage form that contains solid particles dispersed in a liquid.

WHO has stated that the neuraminidase inhibitors are preferred for prevention and treatment of influenza because there is lower risk for adverse events (compared historically to adamantanes), less evidence of drug resistance, and greater therapeutic value associated with these

²⁷ Antiviral resistance is the result of viruses changing in ways that reduce or eliminate the effectiveness of antiviral agents to treat or prevent infections. Antiviral resistance can emerge due to genetic changes in the virus from either natural mutation or as a result of the use of antivirals, including antiviral misuse such as not completing the full treatment course. According to HHS, antiviral resistance is one of several factors that could limit the effectiveness of antivirals. In addition, not all viral changes leading to reduced effectiveness of antivirals would generally be termed resistance. In this report, we use resistance to refer to changes in the virus that result in reductions in the effectiveness of antivirals in responding to influenza outbreaks.

particular antivirals.²⁸ Of the two currently available neuraminidase inhibitors, WHO strongly recommends the use of Tamiflu. Tamiflu is generally less expensive and easier to ship than Relenza and, because it is given as a capsule or liquid, it is easier to administer.

Pharmaceutical manufacturers are currently producing both brand name and generic versions of antivirals approved for preventing and treating influenza. Tamiflu is produced by Roche, a health care company that sells products throughout the world. Relenza is manufactured by GlaxoSmithKline, another health care company that sells products worldwide.²⁹ Neither drug is patent protected in all countries, so generic drug manufacturers may produce these drugs where they are not under patent protection.³⁰ Both amantadine and rimantadine are no longer under patent protection and, consequently, the number of manufacturers that can produce the drug worldwide is not limited by patent restrictions.

U.S. Government Entities Engaged in International Pandemic Influenza Preparedness

HHS, along with the Departments of Agriculture, Defense, and State and the U.S. Agency for International Development, carries out U.S. international animal and pandemic influenza assistance programs. The Department of State leads the federal government's international engagement on influenza and coordinates U.S. international assistance

²⁸However, concerns regarding Tamiflu and Relenza have recently increased. On November 13, 2006, FDA announced a change to the prescribing information for Tamiflu to include a precaution about neuropsychiatric events. The revision is based on postmarketing reports (mostly from Japan) of self-injury and delirium with the use of Tamiflu in patients with influenza. The reports were primarily among pediatric patients. On November 27, 2007, FDA's Pediatric Advisory Committee recommended stronger warning labels for both Tamiflu and Relenza because of reports of neuropsychiatric problems in children and teens.

²⁹The patent holders for Tamiflu and Relenza, Gilead Sciences and Biota Holdings Limited, respectively, have licensed these drugs to Roche and GlaxoSmithKline.

³⁰Tamiflu and Relenza are both patent protected in some countries, which limits the manufacture, use, sale, offering to sell, and importation of these drugs in those countries. Both Tamiflu and Relenza are patent protected in the United States. However, they are not patent protected everywhere. For example, generic drug makers in Bangladesh, India, and Taiwan manufacture a generic version of Tamiflu. These products can be sold in countries without patent protection for Tamiflu.

activities through an interagency working group.³¹ The Homeland Security Council is monitoring the U.S. efforts to improve domestic and international preparedness.

HHS provides technical assistance and financing to improve human disease detection and response capacity. HHS received total appropriations specifically available for pandemic-influenza-related purposes in fiscal year 2006 of \$5.683 billion.³² Of this amount, HHS allocated approximately \$3.2 billion to vaccines, \$1.1 billion to antivirals, and \$179 million to international collaboration with the remainder going to such areas as state and local preparedness and risk communications.

The U.S. Agency for International Development provides technical assistance, equipment, and financing for both animal and human health-related activities. In addition, the Department of Agriculture provides technical assistance and conducts training and research programs and the Department of Defense stockpiles protective equipment.

³¹In addition to the Departments of Agriculture, Defense, Health and Human Services, and State and the U.S. Agency for International Development, representatives from the Department of Homeland Security, the National Security Council, the Homeland Security Council, and U.S. intelligence agencies attend working group meetings. The Department of the Treasury has not been a regular participant. However, the Department of the Treasury has worked with U.S. executive directors at the World Bank, the Asian Development Bank, and other international financial institutions to encourage and support these entities' efforts to address influenza threats.

³²See Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 2006, Pub. L. No. 109-149, 119 Stat. 2833, 2857 (funds not limited to purposes related to pandemic or avian influenza); Department of Defense, Emergency Supplemental Appropriations to Address Hurricanes in the Gulf of Mexico, and Pandemic Influenza Act, 2006, Pub. L. No. 109-148, 119 Stat. 2680, 2783, 2786; Emergency Supplemental Appropriations Act for Defense, the Global War on Terror and Hurricane Recovery, 2006, Pub. L. No. 109-234, 120 Stat. 479 (includes \$30 million to be transferred to the U.S. Agency for International Development). HHS also received appropriations available for pandemic-influenza-related purposes, among other purposes, totaling \$50 million in fiscal year 2004, \$182 million in fiscal year 2005, and \$100 million in fiscal year 2007. 2004: Consolidated Appropriations Act, 2004, Pub. L. No. 108-199, 118 Stat. 3, 251; 2005: Consolidated Appropriations Act, 2005, Pub. L. No. 108-447, 118 Stat. 2809, 3138, Emergency Supplemental Appropriations Act for Defense, the Global War on Terror, and Tsunami Relief, 2005, Pub. L. No. 109-13, 119 Stat. 231, 276, 280; 2007: Revised Continuing Appropriations Resolution, 2007, Pub. L. No. 110-5, 121 Stat. 8, 33. Many of these appropriations remain available until expended, that is without fiscal year limitation.

International Strategy to Contain a Pandemic

WHO, in conjunction with the United States and other governments, has developed an international strategy on how to contain an emerging pandemic virus at the site of the outbreak, whether it is H5N1 or another influenza virus with pandemic potential.³³ Containment is a key element of the broad U.S. *National Strategy for Pandemic Influenza*.³⁴ The public health community has generally not attempted to contain an initial outbreak of a pandemic-potential strain or to eradicate it while it is still confined to a limited area.³⁵ WHO has noted that the success of the strategy in halting a pandemic or delaying its spread cannot be assured. However, WHO has stated that given the potential health, economic, and social damage a pandemic can produce, forestalling a pandemic must be tried. Further, WHO notes that should early containment fail, once a certain level of spread of the pandemic virus is reached, no interventions are expected to halt international spread, and the public health response will need to shift to the reduction of morbidity and mortality.

The international containment strategy is based on studies suggesting that efforts, centered on using antiviral drugs to prevent infection as well as treat cases, might contain a pandemic at the site of the outbreak or at least slow its international spread, thus gaining time to put emergency measures

³³WHO, *WHO Interim Protocol: Rapid operations to contain the initial emergence of pandemic influenza* (Geneva: WHO, Oct. 2007), http://www.who.int/entity/csr/disease/avian_influenza/guidelines/RapidContProtOct15.pdf (accessed Oct. 27, 2007). This rapid containment strategy is one of the five major strategic actions that form the basis of the *WHO strategic action plan for pandemic influenza*. (Geneva: WHO, May 2007), http://www.who.int/csr/resources/publications/influenza/WHO_CDS_EPR_GIP_2006_2/en/index.html (accessed July 19, 2007). In addition to these documents, we also have drawn on a number of other WHO documents dealing with forestalling a pandemic.

³⁴That strategy, released in November 2005, has three broad pillars: (1) preparedness and communications, (2) surveillance and detection, and (3) response and containment. In August 2007, the United States, Canada, and Mexico issued the *North American Plan for Avian & Pandemic Influenza*, which outlines how the three countries intend to work together to combat an outbreak of avian influenza or an influenza pandemic in North America.

³⁵An exception was the U.S. government decision to mass vaccinate the public against an outbreak of swine flu in New Jersey in 1976. That effort was halted when a small apparent risk emerged of contracting Guillain-Barre syndrome—an inflammatory disorder that can cause paralysis—from the swine flu vaccine, and there was no extensive spread of the influenza strain of concern.

in place and develop vaccines.³⁶ Such a strategy includes the creation of a geographically defined containment zone. According to WHO, the containment zone would be created around the cases where widespread antiviral and nonpharmaceutical countermeasures should be used. The containment zone should be large enough so that all known persons infected by the pandemic virus are located within the zone as well as many of the people in frequent contact with them. Rapid detection and reliable reporting of outbreaks, immediate availability of necessary antivirals for large numbers of people, and the restriction of the movement of people in and out of the affected area (or containment zone) are components of the strategy. Other elements of the strategy include isolation of ill persons, voluntary quarantine of people in contact with these persons, school closures, and cancellation of mass gatherings. These measures are meant to reduce the opportunities for additional human-to-human transmission to occur.

Disease surveillance in animals and humans has a critical role in the success of the international strategy to forestall the onset of a pandemic. The Director of CDC has stated that for optimal response, an emerging influenza pandemic outbreak anywhere in the world must be recognized within 1 to 2 weeks and then be investigated and confirmed within days. Infectious disease surveillance activities include detecting and reporting cases of disease, analyzing and confirming this information to identify possible outbreaks or longer-term trends, exchanging information related to cases of infectious disease, and applying the information to inform public health decision-making. HHS officials have noted that as outbreaks of animal influenza viruses spread and affect people, collaboration between animal and human influenza surveillance systems is needed. Additionally, WHO has stated early detection of animal diseases, which might be transmissible to humans, leads to quicker actions to reduce threats to humans. Alerts of animal outbreaks can provide early warning so that human surveillance can be enhanced and preventive action taken. When effective, surveillance can facilitate (1) timely action to control

³⁶WHO has stated that there are three opportunities for using antivirals. The first, and present situation, is when antivirals are used to treat infected patients and to prevent infection in close contacts, including family members and health care workers. The second is when surveillance indicates that the transmissibility of the virus among humans is beginning to become more efficient. In this circumstance, administration of antivirals to all members of a community in which clusters of cases are occurring might either stop the virus from further improving its transmissibility or delay international spread. The third opportunity is once a pandemic has been declared. Pending the availability of vaccines, antivirals will be the principal medical intervention for reducing morbidity and mortality.

disease outbreaks, (2) informed allocation of resources to meet changing disease conditions and other public health programs, and (3) adjustment of disease control programs to make them more effective.

Diagnostic tests are an important component of identifying pandemic influenza and putting measures in place to forestall its spread. Diagnostic tests for a range of viruses help assess patients for the presence of H5N1, other emerging influenza viruses, and seasonal influenza. Quick and accurate diagnosis of influenza is essential to early treatment. In addition, accurate, rapid diagnosis enables timely implementation of containment and treatment procedures, and will be critical in identifying the beginning of a pandemic and possibly slowing the spread of the disease. Rapid diagnosis allows more time for equipment and personnel to be mobilized to aid in pandemic response.

As part of the WHO Global Influenza Surveillance Network, individual countries, including the United States, collect and analyze influenza virus samples and submit selected samples to WHO Collaborating Centres for further analysis.³⁷ These samples allow WHO to perform a number of influenza-related public health activities, including:

- determining if the virus has acquired human genes or made other significant changes,
- tracking the evolution of the virus and its geographic spread,
- updating diagnostic tests and reagents,³⁸
- identifying potential vaccine strains, and
- testing to determine if the virus remains susceptible to antivirals.

The success of this network is dependent upon the participation of its members. According to HHS, the network has functioned efficiently in the past for the detection and characterization of newly emergent influenza viruses of epidemic potential.

³⁷The four WHO Collaborating Centres are located in the United States, Australia, Japan, and the United Kingdom. CDC is the Collaborating Centre in the United States.

³⁸Reagents are used to determine the purity and strength of influenza vaccine.

Uncertain Effectiveness and Limited Availability Would Likely Constrain the Use of Antivirals and Vaccines to Forestall the Onset of a Pandemic

The use of antivirals and vaccines to forestall the onset of a pandemic would likely be constrained by their uncertain effectiveness and limited availability. Weaknesses within the international influenza surveillance system impede the detection of strains, which could limit the ability to promptly administer or develop effective antivirals and vaccines to treat and prevent cases of infection to prevent its spread. The delayed use of antivirals and the emergence of antiviral resistance in influenza strains could limit their effectiveness. A targeted vaccine cannot be manufactured until the pandemic strain has emerged and been identified. The availability of antivirals and vaccines is constrained by existing limitations in their production, distribution, and administration. Current antiviral production capacity is inadequate to reach the number of antivirals WHO estimates will be needed to contain a pandemic. Vaccines targeted to match a pandemic strain are unlikely to be available for prevention of disease at the onset of a pandemic as, according to HHS officials, they would not become available until 20 to 23 weeks following detection of a pandemic. Moreover, most countries do not possess the capacity to distribute and administer these antivirals and vaccines quickly enough to forestall a pandemic.

The Effectiveness of Antivirals and Vaccines in Containing Initial Outbreaks Could Be Constrained by the Limited Capacity to Monitor the Virus and Successfully Treat and Prevent Cases

Antiviral and vaccine effectiveness depends upon their timely application. To achieve timely application, health authorities must be able to detect the virus strain quickly through surveillance efforts and use this information to administer or develop effective antivirals and vaccines. However, weaknesses within the global influenza surveillance system could limit the effectiveness of antivirals and vaccines in treating and preventing cases of infection. In addition, limited support for clinical trials could hinder their ability to improve understanding of the use of antivirals and vaccines against a pandemic strain.

The Effectiveness of Antivirals and Vaccines to Forestall a Pandemic Depends on Influenza Surveillance

An influenza surveillance system that can promptly detect outbreaks would facilitate the timely use of antivirals. The effectiveness of antivirals in containing an initial influenza outbreak of a new strain depends in part on the timely use of the appropriate drug. Experience with seasonal influenza indicates that antivirals are most effective for treatment if started within 48 hours of the onset of symptoms; therefore, rapid detection of human outbreaks of potential pandemic strains is necessary. If an individual is diagnosed too late, antivirals may not be effective. WHO has noted that a critical problem is the tendency of human H5N1 cases to be detected late in the course of the illness. Antivirals used for prevention should be started either before exposure or as soon as possible after initial exposure.

International surveillance is also required to monitor strain evolution for the development of vaccines targeted to a potential pandemic strain or the actual pandemic strain. A well-matched vaccine cannot be ensured until the pandemic virus strain has been identified. According to HHS officials, 20 to 23 weeks are currently required from the detection of a pandemic before a well-matched vaccine can be developed.³⁹ Consequently, well-matched vaccines are likely to play little or no role in efforts to stop or contain a pandemic, at least in its initial phases. However, an effective surveillance system is necessary to develop a safe and effective pandemic vaccine as soon as possible so that a vaccine is available for later stages of the pandemic.

Another concern is that influenza strains can be resistant to antivirals, rendering them ineffective in treating or preventing infection. Monitoring strain evolution to determine susceptibility or emergence of antiviral resistance is one element of assessing the likelihood that a particular antiviral will be effective. The effectiveness of an antiviral against one strain of seasonal influenza does not mean that it will be effective against an H5N1 strain or another potential pandemic strain. While both classes of antivirals, adamantanes and neuraminidase inhibitors, could potentially be used against a pandemic strain, experts caution against the use of adamantanes without prior indication that the emerging strain is susceptible to them. For example, CDC recommends against the use of adamantanes to treat or prevent currently circulating influenza because strains resistant to adamantanes have emerged. Similarly, WHO recommends only neuraminidase inhibitors be used to respond to H5N1 outbreaks unless neuraminidase inhibitors are not available or local surveillance data show that the H5N1 virus is known or likely to be susceptible to the adamantanes. A high proportion of H5N1 strains circulating in Indonesia, Thailand, and Vietnam have been resistant to adamantanes. Like adamantanes, the effectiveness of neuraminidase inhibitors against potential pandemic strains could also be constrained by the emergence of antiviral-resistant strains of the virus. In Vietnam, a study identified H5N1 strains resistant to Tamiflu, a neuraminidase inhibitor, and a few seasonal influenza viruses—less than .5 percent—have been resistant to Tamiflu. Another study examined the effectiveness of Tamiflu and Relenza, another neuraminidase inhibitor, against H5N1

³⁹There does not appear to be agreement on the time needed to produce a pandemic vaccine. In a document distributed for a November 2007 meeting on pandemic influenza preparedness, WHO stated that the total approximate time to produce an H5N1 vaccine is 28 to 52 weeks.

Weaknesses in International
Influenza Surveillance

viruses. The researchers found that there was little variation in the effectiveness of Relenza against all H5N1 viruses studied but that there was variation in the effectiveness of Tamiflu. For example, they reported that one group of H5N1 viruses was 15- to 30-fold less sensitive to Tamiflu than was another group of H5N1 viruses.

According to the U.S. *National Strategy for Pandemic Influenza Implementation Plan*, international capacity for influenza surveillance still has many weaknesses, including limited influenza sample collection and sharing. Surveillance requires the collection and sharing of virus samples and the genetic sequencing of these samples from both infected humans and animals to monitor if and how a strain is mutating.⁴⁰ According to WHO, global influenza surveillance in humans is weak in some parts of the world, particularly in developing countries. Surveillance systems in many of the countries where H5N1 influenza is of greatest concern are inadequate, particularly in rural areas where many cases have occurred. WHO has noted that to increase the likelihood of successfully forestalling the onset of a pandemic, surveillance in affected countries needs to improve, particularly concerning the capacity to detect clusters of cases closely related in time and place. Such clusters could provide the first signal that the virus has begun to spread more easily among humans. If early signals are not identified, the opportunity for preemptive action will be missed. In addition, some countries experiencing H5N1 influenza outbreaks (e.g., Indonesia) have at times not promptly shared human virus samples with the international community, thus further weakening international surveillance efforts.

Similarly, a surveillance network to monitor influenza in animals faces weaknesses. Global animal influenza surveillance can help provide early recognition of viruses with the potential for causing human influenza. Surveillance in animals may indicate how an influenza virus is spreading and evolving. WHO has recommended combining the detection of new outbreaks in animals with active searches for human cases. However, influenza surveillance in animals has weaknesses. For example, definitions of what constitutes an outbreak vary between countries and may be reported as a single infected farm, an affected village, or an affected province. In addition, only the number of outbreaks may be reported rather than more specific information. Moreover, animal disease

⁴⁰For an influenza virus, genetic sequencing reveals the complete genetic blueprint (sequence) of the virus.

surveillance is completely lacking in some countries. For example, Djibouti and Uganda have no capacity to collect, transport, and diagnose animal influenza samples. Just as with human influenza samples, there are concerns that animal samples have also not always been shared promptly, or for every outbreak.

According to WHO, few countries have the necessary expertise and facilities to diagnose H5N1. This leads to the need for countries lacking laboratories these facilities to wait until collected samples of a strain are tested by labs outside the country, possibly delaying both timely diagnosis and antiviral administration. Therefore, laboratories must have the necessary information, guidance, and materials to allow them to recognize, store, and safely transport H5N1 samples to more specialized laboratories in other countries. In a previous report, we reported, for example, that Indonesia and Nigeria both had limited capacity to collect, diagnose, or transport influenza in human samples.⁴¹

Currently, there is not a good way to quickly and easily determine whether a patient has H5N1 or a more common type of influenza. The accuracy of clinical diagnosis of influenza on the basis of symptoms alone is limited because symptoms from illness caused by other pathogens can overlap considerably with influenza. The amount of time required to attain results from diagnostic tests varies from minutes to several days, with accuracy often being the trade-off for rapid results. Existing point-of-care tests can provide results rapidly and determine if the patient is infected with seasonal influenza viruses A or B but cannot identify avian influenza H5N1.⁴² A viral culture test can provide specific information on circulating strains and subtypes of influenza viruses in 2 to 10 days but may require longer for more detailed analysis. In addition, the need to conduct viral culture tests in laboratories with enhanced safety levels can also restrict their usefulness. HHS recommends an H5 polymerase chain reaction test, which can be done without the specialized laboratory facilities required by viral culture tests, for the diagnosis of H5N1 influenza. This test is FDA-approved and is used by public health laboratories throughout the United States and in many parts of the world.

⁴¹GAO-07-604, 61.

⁴²Point-of-care testing refers to a laboratory test that can be performed outside of a laboratory facility, with results available to doctors and patients within minutes.

Limited Support for Clinical Trials

Limited support for clinical trials could hinder their ability to improve understanding of the use of antivirals and vaccines against a pandemic strain. Clinical trials improve the understanding of effectiveness, timing of administration, duration of treatment, optimal dosage, safety, and the balance of risks and benefits of antivirals and vaccines. Improved understanding gained through clinical trials would assist with updating international guidance on antiviral use. The current estimates on the effectiveness of antivirals in a pandemic are largely based on their use in treating and preventing influenza illness caused by seasonal influenza strains circulating at the times the studies were performed. However, the viral characteristics of a pandemic strain may be different. Similarly, clinical trials are an essential step in vaccine development and are used for testing the safety and effectiveness of vaccines. For instance, clinical trials could test for the optimal dosage of vaccines developed against a potential pandemic strain.⁴³ However, few governments are assisting vaccine manufacturers with funding and technical support for clinical trials.

Limited Production, Distribution, and Administration Capacity Could Constrain the Availability of Antivirals and Vaccines

The availability of antivirals and vaccines is constrained by limited production, distribution, and administration. Vaccine manufacturers' liability concerns might also limit their willingness to manufacture these drugs and make them available in certain countries.

Constraints on Antiviral and Vaccine Production

Current antiviral production is inadequate to reach WHO estimates for the number of antivirals needed to contain a pandemic. While WHO has not set a target for national antiviral stockpiles, it stated in 2007 that it is unlikely that sufficient quantities of antivirals will be available in any country at the onset of a pandemic. WHO estimates that the quantity of antivirals required to forestall a pandemic would be enough treatment courses for 25 percent of the population.⁴⁴ In addition, there would need to be enough preventative courses to last 20 days for the remaining

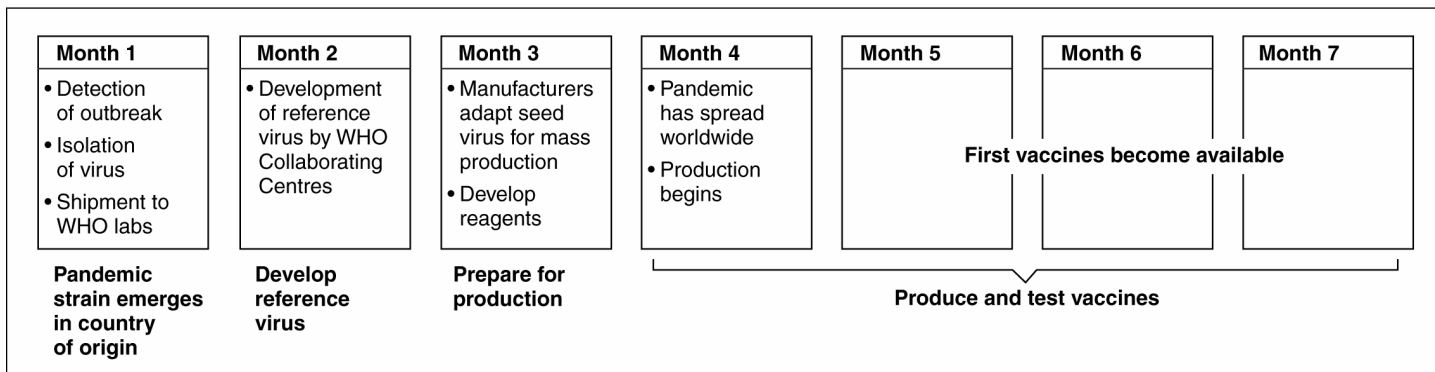
⁴³The dosage for current seasonal vaccines is 15 micrograms per strain in the trivalent vaccine, for a total dosage of 45 micrograms. However, it is unknown what dosage would be effective against a pandemic strain.

⁴⁴A treatment course is the number of doses needed to treat a person that has been infected with an influenza virus. A treatment course for Tamiflu contains 10 capsules taken over the course of 5 days.

75 percent of the population in the outbreak containment zone.⁴⁵ While Roche, the primary manufacturer of Tamiflu, has expanded production, it has stated that the demand for Tamiflu will need to further increase before there are any new increases in production.

While vaccination is considered to be the best defense against influenza, it is unlikely that a vaccine targeted to the pandemic strain will be available in time to forestall the onset of a pandemic. HHS has reported that 20 to 23 weeks are currently required from the start of a pandemic to the availability of a well-matched vaccine; WHO expects that once a pandemic strain emerges, it is likely that it will spread globally within approximately 3 months.⁴⁶ Figure 1 shows how WHO, its Collaborating Centres around the world, and pharmaceutical manufacturers would proceed to develop and produce vaccines designed to protect against a newly emerged pandemic strain, and how long it would take for the vaccines to become available.

Figure 1: Pandemic Vaccine Production Timeline



Source: GAO analysis of HHS, IFPMA, and WHO data.

Some health authorities have suggested that increased seasonal vaccination could play a limited role in forestalling the emergence of a pandemic by limiting the opportunities for human and animal influenza strains to combine and form a pandemic strain, but it is likely that the

⁴⁵A preventative course would be given to individuals within the containment zone that may have been exposed to the virus. In this case, a preventative course for Tamiflu would be 20 capsules taken over the course of 20 days.

⁴⁶HHS, *Pandemic Planning Update IV* (Washington, D.C.: 2007).

limited availability of seasonal vaccination would limit its role in forestalling an influenza pandemic. Seasonal vaccine would not prevent individuals from becoming infected with animal influenza. However, in the case of an H5N1 strain, promoting seasonal vaccination prior to the emergence of a pandemic strain, particularly among health care workers and others in contact with human cases of H5N1 infection and infected poultry, could reduce the likelihood of H5N1 and seasonal influenza coinfection in humans.⁴⁷ Experts fear that such co-infection could lead to the emergence of a reassorted influenza strain that has the transmissibility of the human seasonal strain and the virulence of the H5N1 strain, thus resulting in a pandemic. However, large-scale global seasonal influenza vaccination would be difficult to implement because of the lack of influenza vaccination programs in many countries. Additionally, seasonal vaccination of humans would not prevent influenza reassortment within animals.

According to WHO, current annual global production capacity for trivalent seasonal vaccines is approximately 565 million doses; these doses would only be enough to vaccinate about 9 percent of the world's population of 6.6 billion people.⁴⁸ WHO has also stated that the current demand for and supply of seasonal influenza vaccine is approximately equal. Thus, without additional production, either by current manufacturers scaling up their production or by increasing the number of manufacturers, the supply of seasonal vaccine would not be able to meet the increased demand that would stem from the promotion of seasonal vaccination. In fact, due to limitations in vaccine production capacity, even countries with existing seasonal vaccine programs have experienced shortages. For example, the United States experienced vaccine shortages as recently as the 2004-2005 influenza season due to production problems experienced by one manufacturer.⁴⁹

This limited vaccine production capacity would also limit the availability of a pandemic vaccine in the event of a pandemic since the processes used to manufacture seasonal and pandemic vaccines are similar and the

⁴⁷Another benefit resulting from seasonal vaccination is that it would decrease the chance of confusing the diagnosis of cases of seasonal influenza with H5N1.

⁴⁸This represents an increase in capacity of 215 million doses over the 350 million dose capacity in 2006.

⁴⁹GAO, *Influenza Vaccine: Shortages in 2004-05 Season Underscore Need for Better Preparation*, [GAO-05-984](#) (Washington, D.C.: Sept. 30, 2005), 3.

manufacturing would take place in the same facilities. If a monovalent vaccine (that is, a vaccine that contains only one influenza strain) were produced for a pandemic strain, experts estimate that approximately three times the number of trivalent doses could be produced. Consequently, if annual production capacity is sufficient to produce 565 million doses of trivalent vaccine, 1.695 billion doses of monovalent vaccine could be produced each year. However, the actual number of doses that could be produced would depend on a number of factors including how well the virus strain grows in eggs and the dosage required. For instance, if a dose larger than 15 micrograms—the dose required for current seasonal vaccine—was needed, fewer doses could be produced. Testing on a sanofi pasteur H5N1 vaccine approved by FDA in April 2007 indicates that a single 15 microgram dose would not be sufficient to confer immunity. Instead, the testing indicated that 45 percent of individuals who received two 90 microgram doses of this vaccine—or twelve times as much—developed an immune response expected to reduce the risk of getting influenza. If this dosage were required during a pandemic, instead of having the capability to vaccinate 1.695 billion people, only 141,250,000 (one-twelfth as many) could be vaccinated. This would likely be well below global demand, given a global population of 6.6 billion people.

The location of vaccine manufacturing facilities could also limit the role that vaccines would play in forestalling an influenza pandemic. Experts fear that the concentration in a few countries of vaccine production capacity could, in the event of a pandemic, lead to vaccine shortages in countries without domestic manufacturing capacity. According to WHO, 90 percent of vaccine production capacity is concentrated in Europe and North America.⁵⁰ Currently, only one manufacturer's entire seasonal influenza vaccine production facilities are located completely within the United States. There is concern among experts that countries without domestic manufacturing capacity would not have access to vaccines in the event of a pandemic if the countries with domestic manufacturing capacity prohibited the export of vaccine until their own needs were met. Many countries experiencing H5N1 influenza outbreaks, such as Cambodia and Indonesia, do not have domestic manufacturers that produce influenza

⁵⁰According to IFPMA, many noninfluenza vaccines are manufactured in large volumes and used around the world, including in developing countries. This is not the case with influenza vaccine due primarily to low demand for seasonal influenza vaccines in such countries and the unpredictability of the occurrence of pandemic influenza. For these reasons, manufacturing capacity for seasonal influenza vaccines in developing countries has been limited and expansion is considered to be economically difficult.

vaccines, and according to WHO, would require financial and technical support from the international community to create a domestic pharmaceutical infrastructure.⁵¹

Constraints on Distribution and Administration

Limited global, national, and local-level distribution and administration capacity could restrict the availability of antivirals at the site of outbreaks for use in forestalling the onset of a pandemic. Distribution and administration capacities require plans, delivery networks, facilities suitable for administering the drugs, trained personnel, and funding to get antivirals to where they are needed and administer them promptly. As discussed earlier, experience with seasonal influenza indicates that antivirals are most effective in treating influenza if they are taken within 48 hours of the onset of symptoms. This requires an efficient distribution network to get the drugs to where they are needed.

Antiviral distribution networks are poor or nonexistent in some countries. We previously reported that as of October/November 2005, 10 of 17 countries reviewed did not have distribution plans for the release of antiviral stockpiles and there was insufficient information available to reach conclusions for 4 others.⁵² Studies of national pandemic preparedness plans in Europe and the Asia-Pacific region found that most did not adequately address how antivirals would be transported to locations where they are needed and how they would be administered to individuals.⁵³ Thirteen of the 21 European plans had guidance on priority groups for treatment with antivirals, but none described the process by

⁵¹Countries creating production infrastructure may require starting materials, such as reagents, to develop and produce vaccines and may need assistance in establishing new facilities. A reagent is a substance used in a chemical reaction to detect, measure, examine, or produce other substances. Reagents are used to determine the purity and strength of influenza vaccine.

⁵²[GAO-07-604](#), 61.

⁵³Sandra Mounier-Jack and Richard J. Coker, "How Prepared is Europe for Pandemic Influenza? Analysis of National Plans," *The Lancet*, vol. 367, no. 9520 (2006) and Richard Coker and Sandra Mounier-Jack, "Pandemic Influenza Preparedness in the Asia-Pacific Region," *The Lancet*, vol. 368, no. 9538 (2006).

which individuals belonging to priority groups would be identified.⁵⁴ Most of the plans in Asian-Pacific countries did not identify such priority groups. The timely administration of antivirals would also likely be constrained if there is a scarcity of trained professionals as well as packaging and instructions that are printed in languages foreign to those administering the drugs. In addition, countries that depend upon outside sources to provide antivirals might not have these drugs available in time to contain an outbreak. Many countries do not have national stockpiles of antivirals and are dependent on outside sources to provide these drugs for distribution in the event of an outbreak. Antiviral stockpiling is expensive, and it may not be feasible for many countries to establish their own national stockpiles.

Similarly, the availability of vaccines could be affected by limitations in countries' capacity for distributing and administering vaccines. For example, a lack of supplementary medical supplies (such as syringes) could impede the administration of vaccines. Countries' experience with seasonal vaccination programs indicates potential problems in the event of a pandemic. IFPMA has noted that many developing countries have insufficient health care systems to deliver vaccines. Most countries have little seasonal influenza vaccine distribution infrastructure and lack financial and human resources to implement national seasonal influenza vaccination programs. In 2005, WHO reported that about 50 of the 193 countries in the world, mainly those that are industrialized and some countries in rapid economic development, offer influenza vaccination to nationally defined high-risk groups.⁵⁵ However, even in industrialized nations such as the United States, vaccine distribution and administration issues arise. For example, during the vaccine shortage in the 2004-2005

⁵⁴In a follow-up study, the authors found that Europe had become better prepared for a pandemic. However, they noted that countries' plans on antivirals and vaccines varied and that operational planning remained weak. For example, they found that determining how to deliver antivirals within 48 hours to individual patients remained largely unresolved. Many countries are delegating this responsibility to local officials but are providing little guidance. Similarly, although most study countries had prioritized groups for receiving antivirals and vaccines, the details on how these policies would be implemented had not been put in place. See Sandra Mounier-Jack, Ria Jas, and Richard Coker, "Progress and Shortcomings in European National Strategic Plans for Pandemic Influenza," *Bulletin of the World Health Organization*, vol. 85, (2007). Published online ahead of print at http://www.who.int/bulletin/published_ahead_of_print/en/index.html (accessed Oct. 15, 2007).

⁵⁵Economic development refers to the process of raising the level of prosperity and material living in a society through increasing the productivity and efficiency of its economy.

Manufacturers' Liability Concerns

influenza season, CDC developed a plan to allocate the available vaccine among states. However, the formula for allocating each state's allocation was imperfect, resulting in some states having more vaccine than needed to cover demand and other states having too little.⁵⁶

Manufacturers' concerns regarding product liability in individual countries could also hinder the global availability of vaccines. Experts and vaccine manufacturers have said that the lack of liability protection increases liability concerns for manufacturers, which may hinder their willingness to manufacture and distribute vaccines in countries where they might be held liable for any adverse effects that occurred from their administration. Concerns regarding potential liability for the vaccines could hinder efforts by WHO to get companies to donate vaccines to countries where they are not licensed.⁵⁷ Industry representatives have stated that manufacturers would need advance assurance that governments would provide liability protection.

⁵⁶See [GAO-05-984](#), 17. In the United States, influenza vaccine production and distribution are largely private-sector activities. HHS has limited authority to control vaccine distribution directly. Manufacturers sell influenza vaccine to resellers (such as medical supply distributors and pharmacies), federal agencies, state and local public health departments, or directly to providers. Individuals can obtain an influenza vaccination at a number of places, including physicians' offices, public health clinics, nursing homes, and nonmedical locations such as workplaces or retail outlets. During the 2004-2005 influenza season, CDC took actions in addition to the allocation plan discussed to deal with the vaccine shortage. For example, CDC developed a revised recommendation on who should be vaccinated, so that vaccine could be directed to those at high risk and to other priority groups, and worked with one manufacturer to increase production.

If the Secretary of HHS determines and declares a public health emergency, the Public Health Service Act authorizes the Secretary to "take such action as may be appropriate" to respond. According to the act, to declare a public health emergency, the Secretary must determine that (1) a disease or disorder presents a public health emergency, or (2) a public health emergency, including significant outbreaks of infectious disease or bioterrorist attacks, otherwise exists. The federal government and some states are currently building pharmaceutical stockpiles that they would control.

⁵⁷If granted liability protection, manufacturers generally would not have to pay compensation to individuals injured by a vaccine. IFPMA's Influenza Vaccine Supply International Task Force issued a position statement in May 2006, calling for a waiver of liability for the manufacturing and use of pandemic vaccines.

U.S. Government and International Partners' Efforts Are Under Way to Address Constraints on Use of Antivirals and Vaccines, but Certain Efforts Face Limitations

The United States, its international partners, and the pharmaceutical industry are investing substantial resources in efforts to address the uncertain effectiveness and limited availability of antivirals and vaccines. Efforts to make effective antivirals and vaccines more available include (1) improving disease surveillance on an international scale in order to monitor the evolution of influenza strains and the effectiveness of antivirals and vaccines against those strains, (2) increasing global demand for antivirals and vaccines to encourage production and spur research and development, and (3) increasing global distribution and administration capacity. However, some of these efforts face funding and logistical limitations and will take several years to complete.

Efforts Are Under Way to Improve Surveillance in Order to Increase the Effectiveness of Antivirals and Vaccines

The U.S. government and its international partners are supporting efforts to increase the effectiveness of antivirals and vaccines by improving influenza surveillance. International surveillance is required for monitoring strain evolution in humans and animals to detect the emergence of new influenza strains and evaluate the continued effectiveness of antivirals and vaccines as the virus evolves. Governments, international organizations, manufacturers, and scientists have initiatives under way to improve international surveillance by improving disease surveillance in humans, creating animal surveillance networks, improving animal and human sample sharing and analysis, increasing international collaboration in monitoring influenza strains, and improving diagnostic capabilities.

WHO's revised International Health Regulations seek to improve worldwide disease surveillance in humans.⁵⁸ The revised Regulations were

⁵⁸The International Health Regulations are legally binding agreements on all 193 WHO member states who have not rejected them (or who have not raised reservations about them) and on all nonmember states of WHO that have agreed to be bound by them. Originally adopted in 1951 and named the International Sanitary Regulations, the Regulations were replaced by and renamed the International Health Regulations in 1969. Other than minor modifications in 1973 and 1981, the Regulations had not been revised again until the current revisions. The purpose and scope of the revised regulations are to prevent, protect against, control, and provide a public health response to the international spread of disease in ways that are commensurate with and restricted to public health risks, and which avoid unnecessary interference with international traffic and trade. Although the revised regulations do not include an explicit enforcement mechanism, WHO indicates that public knowledge and "peer pressure" within the global community are expected to provide powerful incentives for compliance.

adopted in May 2005 and effective on June 15, 2007,⁵⁹ require that member states report all events that constitute a public health emergency of international concern, such as those caused by new and reemerging diseases with epidemic potential like H5N1 influenza.⁶⁰ The Regulations set out the basic public health capacities a country must develop, strengthen, and maintain to detect, report, and respond to public health risks and potential public health emergencies of international concern. For example, at the national level a country is required to be able to assess all reports of urgent events within 48 hours. Each country must assess its ability to meet the core surveillance capacities by June 2009 and has until June 2012 to develop these capacities.⁶¹

Among activities to improve influenza surveillance in animals, in May 2005 the World Organisation for Animal Health (OIE) and the Food and Agriculture Organization of the United Nations (FAO) created the OIE/FAO Network of Expertise on Avian Influenza (OFFLU), an international veterinary counterpart to WHO's human Global Influenza Surveillance Network.⁶² OFFLU supports international efforts to monitor and control H5N1 in poultry and other bird species through the collection and sharing of influenza virus samples from infected animals. Increased animal surveillance could speed the diagnosis and reporting of novel influenza strains. One of OFFLU's goals is to put influenza sequences in the public domain for the benefit of research and development, and OFFLU is actively supported in this endeavor by the U.S. government.⁶³ Influenza sequencing reveals complete genetic blueprints of influenza

⁵⁹The revised International Health Regulations went into effect for the United States on July 17, 2007.

⁶⁰Fifty-eighth World Health Assembly, agenda item 13.1, Revision of the International Health Regulations, May 23, 2005, www.who.int/gb/ebwha/pdf_files/WHA58/A58_55-en.pdf (accessed Nov. 16, 2007).

⁶¹Despite the provisions not going into effect until June 2007, in May 2006 the World Health Assembly—the supreme decision-making body of WHO—requested that its member states comply immediately, on a voluntary basis, with provisions of the revised Regulations considered relevant to the risk posed by pandemic influenza.

⁶²OIE stands for Office International des Epizooties—the organization's original name, adopted at its founding in 1924. In 2003, the organization decided to begin using the common name World Organisation for Animal Health while retaining the OIE acronym. OIE is a multilateral organization but is not part of the United Nations.

⁶³By putting influenza sequences in the public domain rather than in restricted databases, more researchers have access to the information and can work to better understand how influenza viruses evolve, spread, and cause disease.

viruses, information which is used to develop vaccines and to monitor the emergence of antiviral-resistant influenza strains. Additionally, sequencing provides information that might indicate that a virus has changed in such a way to become more transmissible among humans. OFFLU collects animal influenza samples and shares them with NIH for sequencing and with CDC for antigenic analysis.⁶⁴ NIH sequences the samples and funds the costs of sequencing these samples. NIH then makes the completed sequences available in the public domain. Through its Influenza Genome Sequencing project, NIH makes available to the entire scientific community over the Internet the genetic sequences of human and animal influenza viruses. As of December 13, 2007, 2,807 human and animal influenza viruses have been completely sequenced. In addition to this project, CDC and NIH have provided materials to countries affected by H5N1 to test animal influenza virus strains. In the event of a pandemic, CDC and NIH have also offered them assistance in sequencing influenza viruses.

An additional effort to improve surveillance through sample sharing is the Global Initiative on Sharing Avian Influenza Data, formed in August 2006 by a group of scientists from over 40 countries. Genetic sequence data collected through this initiative will be deposited in a publicly available database and then after a specified period of time will be released automatically to publicly funded databases participating in the International Sequence Database Collaboration or in other publicly available databases. This initiative will work to overcome restrictions which have previously prevented influenza information sharing, with the hope that more shared information will help researchers understand how viruses spread, evolve, and can potentially lead to a pandemic. This initiative is open to all scientists, provided they agree to share their own data, credit the use of others' data, analyze findings jointly, and publish results collaboratively.

In addition to OFFLU, a surveillance system for animal diseases that are transmissible to humans has also been established and many countries have improved their surveillance of animal diseases. FAO, OIE, and WHO launched the Global Early Warning and Response System for Major Animal Diseases, including Zoonoses (GLEWS) in July 2006 to improve the early warning and response capacity of the three organizations to animal

⁶⁴An antigen is any foreign substance that stimulates the body's immune system to produce antibodies.

diseases, including those that can spread to humans.⁶⁵ GLEWS is the first joint early warning and response system conceived with the aim of predicting and responding to such diseases. WHO has stated that from a public health perspective, early warnings of animal outbreaks that have a known potential to spread to humans will enable the initiation of control measures that can prevent human morbidity and mortality. The United Nations System Influenza Coordinator and the World Bank have reported that many countries have improved their animal disease surveillance systems. They noted that better disease surveillance systems, along with improved laboratory capacity and increased access to epidemiological expertise, account for improved detection of H5N1 and other influenza viruses.

In April 2007, NIH announced that it was awarding \$23 million per year for 7 years to establish six Centers of Excellence for Influenza Research and Surveillance. The mission of the centers is to expand NIH's influenza research program, both in the United States and internationally, to determine how these viruses cause disease as well as how the human immune system responds to them. Specific activities include expanding animal influenza surveillance and studying how pandemic viruses emerge.

Governments, including the U.S. government, and manufacturers are undertaking efforts to increase international collaboration to monitor the evolution of influenza strains. Through a collaborative global network, CDC's WHO Collaborating Centre is monitoring the H5N1 virus to track its geographic spread and to identify and analyze changes in the virus. CDC is providing funds for the shipment of influenza samples to WHO Collaborating Centres for analysis. As part of its surveillance role, CDC conducts antiviral susceptibility testing on seasonal and novel influenza viruses and has been able to identify changes in the sequence of H5N1 virus samples that could affect their susceptibility to existing antiviral medications. For example, in January 2007 CDC testing found an H5N1 virus sample from Egypt with reduced susceptibility to Tamiflu. FDA, CDC and other WHO Collaborating Centres, other WHO laboratories, and national regulatory authorities have also used information on H5N1 strain evolution to recommend representative strains for use in the development of pre-pandemic vaccines and to develop H5N1 reference viruses which are shared with manufacturers. Manufacturers are also supporting the independent Neuraminidase Inhibitor Susceptibility Network, which

⁶⁵Zoonoses are diseases that are transferable from animals to humans.

includes government officials and works in collaboration with WHO to monitor influenza viruses for any signs of strains that have developed resistance to this class of antivirals.

Concerns regarding the failure of certain countries to share human and animal influenza samples and the availability of vaccines developed from these samples have led to efforts to promote sample sharing. In February 2007, Indonesia announced that it would no longer share H5N1 samples with WHO because the resulting vaccines produced by private companies were unlikely to be available to developing countries such as Indonesia. At times, the Indonesian government has also expressed a desire for royalties from any invention derived from an influenza sample isolated within its borders. In March 2007, WHO said that an agreement had been reached and that Indonesia would resume sharing H5N1 samples immediately. However, sample sharing did not resume until May 2007 when, at the World Health Assembly meeting, 17 developing countries introduced a resolution demanding equitable access to vaccines made from H5N1 samples the countries provide.⁶⁶ At that time, Indonesia provided three samples from two patients to WHO. Later at that meeting, the World Health Assembly requested that WHO formulate mechanisms and guidelines aimed at ensuring the fair and equitable distribution of pandemic influenza vaccines at affordable prices in the event of a pandemic. Following this, in June 2007 the health ministers of the Asia-Pacific Economic Cooperation stated they planned to share influenza virus specimens in a timely manner.⁶⁷ However, HHS officials told us that concerns remain. In July 2007, HHS reported to us that Indonesia had not shared any seasonal or H5N1 influenza samples since those it sent to WHO in May 2007. HHS also noted that the Asia-Pacific Economic Cooperation agreement is not being followed. A WHO official has also expressed concern. In August 2007, he stated that by not sharing virus samples, Indonesia is endangering the world's health as well as its own. Also in August 2007, Indonesian health officials stated that the county will continue to withhold H5N1 samples at least until a new virus-sharing agreement is developed at an international meeting in November 2007.⁶⁸ Later in August Indonesia sent two samples to CDC for testing, although

⁶⁶The World Health Assembly is the supreme decision-making body of WHO.

⁶⁷The Asia-Pacific Economic Cooperation consists of 21 economies including those of China, Indonesia, and Vietnam.

⁶⁸An official stated that the agreement must ensure that developing countries will receive equitable access to affordable vaccines made from the samples they share.

concerns remain whether Indonesia will share or continue to withhold samples in the future. At the November 2007 meeting, no agreement on sample sharing was reached. Indonesia advocated an accord stating that for every virus sample sent out of a country, there should be an agreement specifying that the sample be used only for diagnostic purposes. Commercial use of the virus would require permission of the country that provided the sample.

Improved understanding of influenza viruses could improve surveillance and, in turn, vaccine development. Scientists at NIH, along with a collaborator at Emory University, have identified mutations that would help a strain of the H5N1 virus spread easily from person-to-person. This knowledge could contribute to better surveillance of naturally occurring influenza outbreaks because efforts could be focused on identifying viruses with mutations that lead to increased transmissibility among humans. This could permit the development of vaccines prior to a pandemic, and possibly help contain a pandemic at its outset.

WHO and CDC are undertaking a number of activities in order to improve diagnostic capability worldwide. WHO reported providing equipment and training to staff working within national laboratories and is providing experts to give hands-on support. At the regional level, it reported enhancing the laboratory network with the facilities and expertise to analyze H5 samples so that every country has access to a regional H5 laboratory.⁶⁹ This H5 laboratory network has provided support to countries in shipping samples and providing confirmation of suspected H5N1 cases. According to WHO, four laboratories in Africa have been upgraded so that they can conduct H5 diagnosis. For the long term, WHO is working to build and strengthen local H5 diagnostic capability. In addition, CDC officials stated that among its activities the agency provides financial and technical assistance to 35 countries, WHO, and WHO regional offices in order to improve influenza laboratory diagnostic capability. CDC is also providing training for laboratory workers and epidemiologists in order to expand laboratory diagnostic capabilities and develop rapid response teams that could quickly detect, report, and control outbreaks caused by novel influenza viruses. CDC officials have also provided laboratory

⁶⁹H5 is 1 of 16 hemagglutinin proteins that can make up an influenza virus. It can be combined with 1 of 9 types of neuraminidase proteins to form an influenza subtype. For example, H5N1 is an influenza subtype.

support and diagnostic reagents to countries investigating H5N1 outbreaks.

Research is being conducted to improve rapid, diagnostic tests for influenza. In order to forestall a pandemic, it is critical to be able to identify people with H5N1 quickly. A reliable, rapid diagnostic test is needed for epidemiological assessments, traveler screening, and clinical care. Currently, rapid tests cannot distinguish between strains and subtypes of influenza viruses. To address this shortcoming, in December 2006, CDC awarded four companies a total of \$11.4 million in contracts to develop new viral diagnostic tests with quicker and more reliable results that could be used at, for example, a patient's bedside or a port of entry (see table 3). CDC hopes for FDA approval and commercialization of these products in 2 to 3 years. In addition, tests designed for large reference and public health laboratories are also being developed.⁷⁰ In February 2006, FDA approved a test developed by CDC that identifies H5 but not the strain within 4 hours once testing begins. Previously, it would have taken 2 to 3 days. If the virus is identified as H5, tests are then conducted to identify the strain. FDA has shared this technology with WHO and its Collaborating Centres.

Table 3: HHS Contracts Awarded to Companies in December 2006 to Develop Rapid Diagnostic Tests for Influenza

Recipient	Amount (dollars in millions)
Cepheid	\$2.4
Iquum ^a	3.8
MesoScale	.7
Nanogen	4.5
Total	\$11.4

Source: CDC.

^aAccording to HHS, the Iquum contract was terminated in May 2007 due to technical issues.

Research is also under way to improve other types of diagnostic tests for influenza. For example, using funding from NIH, scientists at the University of Colorado at Boulder and CDC have developed a test that is

⁷⁰A reference laboratory conducts tests for other laboratories. A public health laboratory is a facility with the equipment and staff needed to conduct public health assessments and respond to emergency public health issues.

based on a single influenza virus gene that could allow scientists to quickly identify influenza viruses, including H5N1. This test offers several advantages over available tests including being based on a gene that, unlike hemagglutinin and neuraminidase, does not mutate constantly. Consequently, the researchers believe that this test will be more useful than other tests because it will provide accurate results even if the hemagglutinin and neuraminidase genes mutate. However, WHO has cautioned that the availability of such tests are at least 4 years away.

Efforts Are Under Way to Increase Demand for Antivirals and Vaccines to Encourage Production and Spur Research and Development

Efforts to expand seasonal vaccination and build national stockpiles of antivirals and pre-pandemic vaccines are under way to encourage increased demand for these drugs. Demand for seasonal influenza treatment drives global production capacity for antivirals and all types of influenza vaccines. Increasing demand through government support provides incentives for manufacturers to develop more effective antivirals and vaccines.

Efforts to Increase Demand to Encourage Production

While the primary benefit of increased seasonal vaccination would be the enhanced protection against seasonal influenza, WHO has stated that increased demand for seasonal vaccines would spur manufacturers to increase their vaccine manufacturing capacity. One of WHO's goals is to increase seasonal vaccine coverage in countries that already use seasonal vaccine to 75 percent of target populations by 2010, which would require an increase in global vaccine production to 560 million doses to cover use in these countries only.⁷¹ Some countries with seasonal influenza vaccination programs had increased their use of seasonal vaccines prior to WHO setting vaccination goals, thus providing incentives for manufacturers to increase overall vaccine production capacity. In October 2007, WHO stated that seasonal influenza vaccine capacity is expected to rise to 1 billion doses annually in 2010, provided sufficient demand exists.

Increased demand for antivirals and pre-pandemic vaccines also stems from orders placed by countries to build national stockpiles. According to Roche, as of April 2007, more than 80 countries had ordered Tamiflu for their own national antiviral stockpiles. Some countries, including Australia, France, and the United States, are also ordering Relenza to

⁷¹WHO has suggested that this be one component of a larger effort to increase vaccine production capacity. See WHO, *Global pandemic influenza action plan to increase vaccine supply* (Geneva: WHO, Sept. 2006), <http://www.who.int/vaccines-documents/DocsPDF06/863.pdf> (downloaded Oct. 26, 2006).

supplement their Tamiflu stockpiles. The United States had 36.6 million neuraminidase treatment courses in its federal stockpiles as of August 6, 2007, consisting of 30.8 million treatment courses of Tamiflu and 5.8 million treatment courses of Relenza. It also had 3.6 million treatment courses of rimantadine, an adamantane, on-hand for a total stockpile of 40.2 million antiviral treatment courses. Approximately 100,000 additional Tamiflu treatment courses and 700,000 additional Relenza treatment courses are currently on order for the stockpile. The U.S. goal at the national level is to have a federal stockpile of 50 million antiviral treatment courses. In addition, states and other entities had stockpiles totaling 12.9 million treatment courses of Tamiflu and 1.6 million treatment courses of Relenza as of August 6, 2007. Similarly, Australia, Japan, the United States, and countries in Europe have been establishing stockpiles of pre-pandemic vaccines. For example, in 2005, sanofi pasteur agreed to produce 1.4 million doses of H5N1 pre-pandemic vaccine for France's stockpile. It is also providing H5N1 pre-pandemic vaccines for national stockpiling in the United States and Italy. In addition, GlaxoSmithKline Biologicals and Novartis Vaccines and Diagnostics are also producing H5N1 pre-pandemic vaccine for the U.S. national stockpile. The United States has stockpiled enough H5N1 pre-pandemic vaccine to cover about 7 million people. The United States' goal is to have a pre-pandemic vaccine stockpile of treatment courses for 20 million persons.⁷² However, developing countries may not be able to build such antiviral and vaccine stockpiles.

Antiviral manufacturers have expanded their production capabilities. Roche expanded its Tamiflu production so that it could produce 400 million treatment courses of Tamiflu by the end of 2006. Roche noted that this represents an approximate 15 fold increase over its production capacity of 27 million treatment courses in 2004. In April 2007, Roche stated that its production capacity now exceeded government and corporate orders for Tamiflu received to date.⁷³ To increase capacity,

⁷²The current HHS policy is to administer the H5N1 pre-pandemic vaccine stockpile to critical workforce members at the onset of an influenza pandemic caused by an H5N1-like virus. Studies are being conducted to determine if there may be value in immunizing more people at the onset of a pandemic. If so, the size of the pre-pandemic vaccine stockpile may be expanded. In addition, the Department of Defense is establishing, for military use, stockpiles of vaccines against H5N1 and other influenza subtypes with pandemic potential large enough to immunize approximately 1.35 million persons.

⁷³In April 2007, Roche reported that it had received orders or letters of intent from more than 80 countries for approximately 215 million treatment courses of Tamiflu. It had also received orders from more than 250 corporations for about 5 million treatment courses.

Roche expanded production from one facility to eight Roche sites, including the United States where 80 million Tamiflu treatment courses can now be produced. In addition, Roche now has 19 external manufacturing partners that perform particular functions in the manufacturing process. Roche has also granted sublicenses to selected drug companies in China and India to allow them to produce Tamiflu in its generic form, oseltamivir, which will increase the amount of that antiviral available globally. In Africa, Roche granted a sublicense to a South African company allowing it to produce oseltamivir to increase production and speed up availability of the drug for use against a pandemic strain in Africa.⁷⁴ GlaxoSmithKline, the manufacturer of Relenza, is undertaking efforts to boost Relenza production. While less than 1 million treatment courses of Relenza were produced in 2005, GlaxoSmithKline stated in May 2006 that it planned to increase production capacity in its existing facilities in North America, Europe, and Australia. It increased production to 15 million treatment courses in 2006 and plans to produce 40 million treatment courses in 2007. GlaxoSmithKline also stated that it is willing to license other manufacturers to produce Relenza in its generic form, zanamivir. In September 2006, GlaxoSmithKline announced a licensing agreement with a Chinese drug company to produce the antiviral and sell it in China, Indonesia, Thailand, Vietnam, and other developing countries.

Governments and manufacturers are also working to increase the global production of vaccines by helping to build production facilities and supplying the technology and resources necessary to produce influenza vaccines. In September 2006, WHO stated that worldwide vaccine production capacity is expected to increase by 280 million trivalent doses in the next 2 to 3 years.

- The U.S. government has offered assistance to countries trying to create the infrastructure necessary for vaccine production. For example, HHS has provided countries with reagents, the chemicals required to assess vaccine effectiveness, and training for testing vaccines. It also works with countries to help them develop their own reagents and tests for use in clinical trials and other research.
- WHO's *Global pandemic influenza action plan to increase vaccine supply*, dated September 2006, proposes building new production plants in

⁷⁴These sublicenses cannot use the Tamiflu name and Roche does not ensure the quality of the products.

both developing and industrialized countries as one means to increase production capacity.⁷⁵

- In October 2006, HHS announced a grant of \$10 million to WHO to support influenza vaccine development and manufacturing infrastructure in other countries, while Japan has contributed \$8 million. In April 2007, WHO announced that it was awarding grants to six countries to help them develop the capacity to make influenza vaccine.⁷⁶ Two of the projects will be in Latin America and four in Asia. Three of the Asian countries receiving grants—Indonesia, Thailand, and Vietnam—have had cases of persons infected with H5N1 influenza. Manufacturers have also committed substantial funds to increase their own vaccine production capacity.⁷⁷
- Additionally, sanofi pasteur signed a technology transfer arrangement with the governments of Thailand, Mexico, and Brazil.
- In June 2007, HHS awarded a \$77.4 million contract to sanofi pasteur and a \$55.1 million contract to MedImmune to renovate existing vaccine manufacturing facilities in the United States and to provide warm-base operations for manufacturing pandemic influenza vaccines. In warm-base operations, a facility does not shut down. HHS stated that these changes will increase production capacity and permit year-round production of pre-pandemic influenza vaccines for the national stockpile, which is currently limited to 3 months per year.
- In July 2007, sanofi pasteur announced that it had completed construction of a new influenza vaccine manufacturing facility in the United States. It also noted that it was expanding its influenza vaccine manufacturing capacity in France.

⁷⁵WHO has suggested that this be one component of a larger effort to increase vaccine production capacity. WHO estimates that \$2 billion to \$9 billion would be needed for all of these activities. See WHO, *Global pandemic influenza action*, <http://www.who.int/vaccines-documents/DocsPDF06/863.pdf> (accessed Oct. 26, 2006).

⁷⁶The six countries are Brazil, India, Indonesia, Mexico, Thailand, and Vietnam.

⁷⁷Sanofi pasteur has invested \$150 million to create a new manufacturing facility in the United States that will allow it to double its influenza vaccine manufacturing capacity in time for the 2008-2009 influenza season. Similarly, GlaxoSmithKline has committed more than \$2 billion to increase its vaccine and antiviral production.

Encouraging Further Research and Development

Increased demand through government support has provided incentives for manufacturers to develop more effective antivirals and vaccines. Manufacturers are conducting research on new antivirals and on improving the use of existing antivirals. Manufacturers are also working to improve the effectiveness of vaccines to combat pandemic influenza through such activities as developing pre-pandemic vaccines, examining cell-based production technology, studying substances that can be added to vaccines to improve effectiveness, and conducting research on vaccines that would provide protection against multiple influenza strains. These studies could be used to help define additional studies and resources that might be needed to assess the safety, effectiveness, and risk and benefit of products, and appropriate use of proposed new products or new uses of existing products.

Research on and Development of Antivirals

Development of new antivirals is particularly important due to concern over the emergence of antiviral-resistant influenza strains that could render existing antivirals ineffective. Manufacturers are developing and testing new antivirals, and the U.S. government is providing support to manufacturers that are developing new antivirals. In 2005, HHS announced plans to spend \$400 million to develop new antiviral drugs. In January 2007, HHS awarded a 4-year \$103 million contract to BioCryst Pharmaceuticals, Inc., to support development of a new antiviral, peramivir.⁷⁸ Sankyo Co., Ltd., of Japan and Biota Holdings Limited of Australia are working together to develop new antivirals called long-acting neuraminidase inhibitors. These companies have received a \$5.6 million grant from HHS to accelerate the development of these antivirals.

In addition to developing new antivirals, governments and manufacturers are exploring ways in which existing antivirals could be used to treat influenza more effectively and efficiently. For example, researchers are examining the potential use of antiviral combination therapy, which would entail the use of more than one antiviral to treat an influenza infection. Combination antiviral therapy may be more effective and could reduce the likelihood that an antiviral-resistant strain might emerge because, for

⁷⁸In September 2007, BioCryst Pharmaceuticals, Inc., reported the preliminary results of a study of the safety and effectiveness of peramivir in humans. The company noted that it was disappointed that the study did not meet its primary objective of reducing the time to lessen symptoms. However, it also stated that it had a plan to correct the issues identified in the study and planned to continue clinical trials.

example, there may be less chance that a strain resistant to both antivirals would emerge. Researchers are also examining the use of antivirals with other types of pharmaceuticals. NIH, the Department of Defense, and the Department of Veterans Affairs are collaborating on a study to determine if Tamiflu used in combination with the drug probenecid can stretch the supply of Tamiflu.⁷⁹ The aim of these studies is to determine whether the combination of these drugs results in Tamiflu remaining in the body longer, thus reducing the amount of Tamiflu that an individual would need to take and effectively increasing the supply of the drug. NIH has also provided funding to the South East Asian Influenza Clinical Research Network, to improve understanding and clinical management of influenza through clinical research, as well as to increase clinical research capacity in participating countries (Indonesia, Thailand, and Vietnam). One ongoing study will compare the safety and effectiveness of standard- and high-dose Tamiflu in treating animal and severe seasonal influenza in hospitalized children and adults. Planned studies include the evaluation of the safety and tolerability of the long-term use of Tamiflu and Relenza to prevent influenza in health care workers and a study of the safety and effectiveness of using intravenous Relenza for the treatment of H5N1 infection in adults and children.

Research on and Development of Pre-Pandemic Vaccines

Manufacturers, sometimes with the assistance of governments, are working to develop pre-pandemic vaccines. These vaccines might provide some protection against a pandemic strain and also give manufacturers experience in producing effective vaccines for a potential pandemic strain. The United States has been the primary government sponsor of these efforts although other countries have sponsored some studies; other studies have been conducted without government support. The United States has supported studies of vaccines developed by Baxter International, Inc., MedImmune, Novartis, and sanofi pasteur.

WHO has reported two ways in which a pre-pandemic vaccine could be used. First, such a vaccine could be used to protect selected populations at risk of being infected by viruses currently circulating among poultry. Second, it could be used to immunize general populations or selected groups (e.g., health care workers) against a potential pandemic strain. However, WHO points out that the pandemic virus may be quite different

⁷⁹Probenecid is used to treat chronic gout and gouty arthritis.

than what people are immunized against and therefore the pre-pandemic vaccine may not be protective.

Pre-pandemic vaccine might also be used as part of a “prime-boost” series in which two doses of vaccine based on different strains would be given. The first vaccine would be a pre-pandemic vaccine that would prime the immune system for a second vaccine. The second vaccine would match the pandemic strain. It is hoped that together the two doses would result in immunity. However, the data needed to support such an approach have not been fully developed.

In April 2007, FDA licensed the first pre-pandemic vaccine for human use in the United States against H5N1 based on the results of a clinical trial conducted by NIH, although the results revealed limitations. FDA approved the vaccine for the immunization of persons 18 to 64 years of age at increased risk of exposure to the H5N1 influenza subtype. The vaccine, manufactured by sanofi pasteur, will not be marketed commercially. Instead, the vaccine has been purchased by the federal government for inclusion in the United States stockpile for distribution if needed.⁸⁰ However, NIH’s clinical trial showed limitations of the vaccine. First, in previously unexposed populations, two 90 microgram doses are needed to elicit the levels of immune responses usually thought to be adequate to provide protection instead of the single 15 microgram dose of seasonal influenza vaccine that is needed for protection against a seasonal influenza strain. Second, even with this larger dosing regimen, vaccination results in an immune response thought to be protective in only 45 percent of those receiving the vaccine. Studies of seasonal vaccines in healthy persons have demonstrated that effectiveness against well-matched strains is 70 to 90 percent.⁸¹ In addition, experts have noted that such a high vaccine dose could result in an unusually high rate of adverse reactions. NIH, along with other federal agencies, sanofi pasteur, and other manufacturers, continue

⁸⁰HHS noted that this vaccine may be used during the pre-pandemic period for those at increased risk of exposure to H5N1; however, it may also be used during the pandemic period because everyone would be considered at increased risk for exposure to H5N1 if the pandemic outbreak is of the H5N1 subtype.

⁸¹The predicted effectiveness of the pre-pandemic vaccine is based on a measure of immune response. However, the measure is not a perfect surrogate for immunity and is known to be imperfect even for seasonal influenza. On the other hand, the effectiveness of seasonal influenza vaccines is based not on a surrogate measure, but on studies examining the actual level of protection offered from vaccination.

to work on the development of vaccines that will stimulate enhanced immune response at lower doses of vaccine.

GlaxoSmithKline and Novartis have both announced that they have submitted pre-pandemic H5N1 vaccines for approval in Europe.

Research on and Development of Cell-Based Production Technology

To speed development and production of new technologies for influenza vaccines, the U.S. government and manufacturers are pursuing the development of cell-based vaccine production technology as an alternative method to current egg-based production.⁸² Egg-based vaccine production cannot be scaled up quickly and egg supplies can be compromised in the event of an influenza outbreak.⁸³ According to HHS, cell-based technology could be scaled up quickly because cells can be frozen in advance and large volumes grown quickly, thus providing surge capacity in the event of a pandemic. In April 2005, HHS awarded a \$97 million 5-year contract to sanofi pasteur for development of a cell-based influenza vaccine. Subsequently, HHS awarded more than \$1 billion in contracts to accelerate development and production of cell-based production technologies for influenza vaccines within the United States. (See table 4.) HHS officials told us that this funding provided companies with the incentive to invest in this technology. In the past, companies did not want to invest in cell-based production technologies because it would not increase efficiency as both cell- and egg-based production would yield similar amounts of vaccine. FDA issued draft guidance in September 2006 to assist manufacturers in developing cell-based vaccines. In other countries, companies are making similar although smaller investments than in the United States, usually without government support.

Progress has already been made on the development of cell-based influenza vaccines. For example, Solvay Pharmaceuticals received authorization to market its cell-culture influenza vaccine in the Netherlands in 2001. However, this vaccine has not yet been marketed. In

⁸²While cell-based production methods are new for influenza vaccines, they have been used for other vaccines such as chickenpox, hepatitis A, polio, and shingles.

⁸³Eggs for vaccine manufacturing come from producers that are located mainly in Europe, as are vaccine manufacturers. This creates vulnerabilities. For example, large egg suppliers based in the Netherlands were left without eggs for vaccine production after an H7N7 influenza outbreak among chickens in that country in 2005.

June 2007, the European Union approved a cell-culture-derived seasonal influenza vaccine manufactured by Novartis. The company has stated that it expects to submit an application for approval to market the vaccine in the United States in 2008.⁸⁴

Table 4: HHS Contracts Awarded in May 2006 to Develop Cell-Based Vaccines

Recipient^a	Amount (dollars in millions)
Solvay Pharmaceuticals	\$298.59
GlaxoSmithKline Biologicals	274.75
Novartis Vaccines and Diagnostics	220.51
MedImmune	169.46
DynPort Vaccine	40.97
Total	\$1,004.28

Source: HHS.

^aIn April 2005 HHS awarded a \$97 million 5-year contract to sanofi pasteur to develop a cell-based vaccine.

Research on and Development of Adjuvants

HHS has awarded contracts to manufacturers to research and develop influenza vaccines that use adjuvants. An adjuvant is a substance added to a vaccine to improve its effectiveness so that less vaccine is needed to provide protection. When added to a vaccine, adjuvants can stretch the vaccine supply by decreasing the amount of vaccine needed per person while still providing the same level of protection. Adjuvants have been used in other vaccines, but not in influenza vaccines. GlaxoSmithKline, Novartis, and sanofi pasteur have announced study results that show that adjuvanted influenza vaccines produced possible protective immunity at lower doses than did nonadjuvanted vaccines. For example, Novartis has reported that its adjuvanted vaccine produced a strong immune response against H5N1, H5N3, and H9N2, but that its vaccine without adjuvant produced a poor response. In January 2007, HHS announced that it had

⁸⁴Researchers are also pursuing other methods to develop vaccines. For example, DNA-based vaccines contain portions of the influenza virus' genetic material. Potentially, these vaccines could be produced more quickly than egg-based vaccines and provide protection against more than one influenza strain. The first human trial of a DNA vaccine to prevent H5N1 infection in people began in December 2006. In June 2007, NIH awarded Vical Incorporated a \$6 million grant to develop a DNA vaccine manufacturing process.

awarded contracts totaling \$132.5 million to three vaccine manufacturers for the development of H5N1 vaccines using an adjuvant. (See table 5.)

Table 5: HHS Contracts Awarded in January 2007 to Develop Influenza Vaccines Containing an Adjuvant

Recipient	Amount (dollars in millions)
GlaxoSmithKline Biologicals	\$63.3
Novartis Vaccines and Diagnostics	54.8
Iomai Corporation	14.4 ^a
Total	\$132.5

Source: HHS.

^aIomai Corporation would be eligible to receive an additional \$114 million upon successful completion of Phase I trials. Phase I trials are the first stage of testing new drugs or treatments in people and normally include a small (less than 100) group of healthy volunteers.

In addition to potentially stretching the vaccine supply, there is evidence that when adjuvants are added to a vaccine, that vaccine might also provide protection against strains to which it is not fully matched. Research by Novartis demonstrated that its H5N3 vaccine generated a better immune response against H5N1 strains with an adjuvant than without it. Similarly, a GlaxoSmithKline vaccine with adjuvant provided protection against two diverse H5N1 influenza strains.

Research on and Development of Universal Vaccines and Other Vaccines That Protect Against Multiple Influenza Strains

Current efforts to develop a universal influenza vaccine are intended to address constraints on both the effectiveness and availability of vaccines. A universal vaccine would protect against multiple virus strains.⁸⁵ Availability of universal influenza vaccines would eliminate the current process required to reformulate seasonal influenza vaccines each year. Consequently, if vaccines effective against pandemic influenza could be available when a pandemic strain emerged, there would not be a 20- to 23-week period between identification of the pandemic strain and the ability to produce an effective vaccine. The recent threat of a human

⁸⁵ A universal vaccine would protect against both seasonal and pandemic influenza viruses. HHS has stated that successful development of a universal vaccine would mean that individuals would need only one influenza shot to protect them for many years (possibly for life).

pandemic arising from H5N1 has spurred new funding for manufacturers currently attempting to develop universal influenza vaccines. In October 2005, a consortium of companies and universities announced that it had received a 2-year \$1.4 million grant from the European Union to support the Universal Vaccine project. The aim of this project is to develop an easily-administered nasal vaccine that provides life-long protection against influenza. Manufacturers such as Merck and Cytos Biotechnology are also working to develop a universal vaccine. NIH is working to bring universal vaccine candidates through the pre-clinical development stage.

Despite the recent increase in funding, experts caution that a completely universal influenza vaccine is years away.⁸⁶ Therefore, some researchers and manufacturers are developing live attenuated vaccines that might protect against a matched strain as well as mutated strains that typically emerge from year to year.⁸⁷ These live attenuated vaccines would not be completely universal, but are easier to develop than universal vaccines and may provide broader protection than current vaccines that match a specific influenza strain. For example, MedImmune's current seasonal FluMist vaccine, which is a live attenuated vaccine, proved effective in children against the H3N2 strain to which it was fully matched as well as against H3N2 strains for which there was a mismatch in studies in children. However, this may not be the case in adults. Evidence suggests that a live attenuated vaccine was less effective in protecting against mismatched strains in healthy adults than was the inactivated trivalent vaccine. In September 2005, HHS announced that it would work with MedImmune to develop at least one vaccine for each of the 16 identified hemagglutinin influenza proteins. According to experts, it is not clear whether live attenuated virus vaccines matched only for the hemagglutinin protein (e.g., H5 or H7) would work as well against a pandemic strain as would a vaccine matched to the particular strain. However, as in the case of pre-pandemic vaccines, even if limited in their effect these vaccines might help reduce mortality during a pandemic while a fully matched vaccine is developed. HHS officials noted that the protection offered by live attenuated vaccines against multiple strains of different subtypes has

⁸⁶In April 2007, WHO's Strategic Advisory Group of Experts on Immunization concluded that it was realistic to expect that vaccines offering protection against multiple influenza strains could be developed; however, no specific time frame was given. In May 2007, WHO said that a universal vaccine might not be available in the next 5 to 10 years.

⁸⁷Live attenuated vaccines use a weakened form of the influenza virus to stimulate a protective immune response in the body.

yet to be established. It has also been noted that even if an acceptable live attenuated H5N1 vaccine is developed, it could not be used as a pre-pandemic vaccine. There is concern that it could reassort with a circulating seasonal influenza virus and thereby increase its transmissibility among humans.

Similarly, research has been conducted using vaccines made from whole influenza virus rather than just parts of the virus. Studies from two vaccine manufacturers, Baxter and Biken, have independently suggested that whole virus vaccines provide protection against multiple strains of the H5N1 virus and require a smaller dose than do vaccines made from parts of the virus. Consequently, the use of whole virus vaccine might not only increase the number of influenza strains against which one is protected, but also increase the number of doses available.

To Increase Availability, Governments and International Organizations Have Worked with Manufacturers to Improve Distribution of and Administration Capacity for Antivirals and Vaccines

Increasing global availability of antivirals and vaccines includes improving the global capacity for their distribution and administration. These efforts also include establishing global and regional antiviral stockpiles and addressing restrictions that different national regulations place on drug manufacture and approval.

WHO, countries, and pharmaceutical manufacturers have established global and regional antiviral stockpiles to enhance the availability and quick distribution of antivirals to the site of outbreaks. In August 2005, Roche donated 3 million treatment courses of Tamiflu to WHO for a global stockpile to contain or slow the spread of a pandemic at its origin.⁸⁸ According to Roche officials, the size of the stockpile was based on studies that indicated that 3 million treatment courses would be sufficient to stop the spread of a pandemic strain at its source. Roche will be responsible for the delivery of Tamiflu from these stockpiles to the international airport closest to the outbreak, where it will transfer the Tamiflu to WHO. It will then be the responsibility of the affected countries to distribute the donated antivirals within their country to contain outbreaks. Subsequently, in January 2006 Roche announced the donation of an additional 2 million treatment courses to WHO for the establishment of regional stockpiles. In March 2007, WHO stated that these drugs are for

⁸⁸The global stockpile is divided and located in Switzerland, the United Arab Emirates, and WHO regional offices. Prior to this, in 2004 Roche had donated 125,000 treatment courses, which were used by WHO in Asian countries affected by H5N1.

the use of countries currently experiencing human outbreaks of animal influenza. Supplies from this second donation have already been sent to those countries. Additionally, some countries have taken the lead in funding regional stockpiles. Japan has provided 500,000 treatment courses of Tamiflu for a regional stockpile for Asia. Japan is also funding the delivery of antivirals from that regional stockpile to the capitals of affected Asian nations. Discussions are under way for HHS to assist in this antiviral stockpiling. For example, there are discussions about sharing antivirals from the United States stockpile, but these drugs could be recalled for domestic use if outbreaks could not be contained or if an outbreak occurred in North America. In May 2006, HHS sent a stockpile of approximately 260,000 treatment courses of Tamiflu to Asia to be pre-positioned for international containment efforts in the event of a pandemic influenza outbreak in that region.⁸⁹

The United Nations System Influenza Coordinator and the World Bank reported in December 2007 that individual countries have also purchased or are planning to purchase antivirals but that coverage in many countries remains limited. Sixty-eight percent of countries worldwide have purchased antivirals and an additional 22 percent plan to purchase them. However, the agencies also note that 36 percent of countries report that their supply of antivirals covers less than 1 percent of their population while another 37 percent report that their antiviral supply covers from 1 to 20 percent of their populations.

Individual countries and WHO are also establishing pre-pandemic influenza vaccine stockpiles. Several industrialized countries, including the United States, have established pre-pandemic influenza vaccine stockpiles to vaccinate critical workforce and primary health care workers at the onset of a pandemic. WHO is working to establish a pre-pandemic vaccine stockpile. Such a stockpile could help to alleviate developing countries' concerns about their lack of access to H5N1 vaccines developed using virus samples provided by them. In April 2007, a WHO expert committee wrote that there is sufficient scientific support for creating a stockpile of H5N1 vaccine for use in countries without influenza vaccine production capacity or the ability to purchase stockpiles of H5N1 vaccines. The committee noted that there is some evidence that current H5N1 vaccines produce a protective immune response against other H5N1

⁸⁹However, if containment is not possible, the Tamiflu would be sent back to the U.S. stockpile of antiviral influenza medications.

viruses as well. Following this, in May 2007, the World Health Assembly passed a resolution requesting WHO to establish an international stockpile of vaccines for H5N1 or other influenza viruses of pandemic potential. In June 2007, GlaxoSmithKline announced that it would contribute 50 million doses of its H5N1 vaccine to the stockpile, enough to vaccinate 25 million people. Also in June, WHO stated that three additional companies had indicated their willingness to make some of their H5N1 vaccine available for the stockpile.

In an effort to facilitate access to various vaccines, FDA and its international counterparts, in collaboration with WHO, are developing a standard set of data requirements to support the licensure of pandemic and pre-pandemic vaccines. Each country has its own requirements for the development and licensure of vaccines for human use (which include testing in clinical trials).⁹⁰ If demand were to surge as might happen in the event of a pandemic, the time needed to go through the regulatory process to gain approval for a new vaccine could constrain its availability.⁹¹ FDA and its international counterparts, in conjunction with WHO, participate in international working groups that examine regulations for the development and manufacturing of influenza vaccines.

Some governments are also exploring other avenues to speed up their domestic regulatory process to enhance pandemic preparedness. Currently, FDA's goal is to complete the review of a "standard" application in the United States for vaccine licensure within 10 months. However, the goal for review of a "priority" license application is 6 months. Priority reviews are given to those vaccines that have the potential for providing significant preventive, diagnostic, or therapeutic advancement as compared to existing treatments for a serious or life-threatening disease. In addition, FDA has processes intended to shorten the time needed for commercial development and FDA review in certain circumstances. For example, because it can take many years to determine whether a drug provides real improvement for patients—such as living longer or feeling better—FDA has a process known as "accelerated approval." Under accelerated approval, applications are reviewed using a substitute

⁹⁰For example, different countries can have varying requirements for clinical trials.

⁹¹According to experts, global availability of antivirals and vaccines could be increased with coordination of different countries' regulatory processes. According to experts, one benefit would be that clinical trials might not have to be duplicated.

measurement of effectiveness that is considered likely to predict patient benefit.

Similarly, the European Union is pursuing approval for pre-pandemic vaccines as a mechanism to expedite approval for a pandemic vaccine.⁹² Prior to the onset of a pandemic, these pre-pandemic vaccines undergo safety and effectiveness testing and are submitted for approval. In the event of a pandemic, this approved pre-pandemic vaccine would then be reformulated to match the pandemic virus and expedited approval for the reformulated vaccine would be sought. Because the application would only pertain to a variation on the earlier, approved, pre-pandemic vaccine, regulatory approval is expected to be faster.⁹³ Both GlaxoSmithKline and Novartis have had pre-pandemic vaccines approved by the European Union under this mechanism. In addition, GlaxoSmithKline, Novartis, and sanofi pasteur have submitted additional vaccines for approval under this process.

Certain Efforts to Increase the Effectiveness and Availability of Antivirals and Vaccines Face Limitations and Will Take Several Years

While efforts are under way to alleviate constraints upon the effectiveness and availability of antivirals and vaccines, certain efforts face limitations and will take several years to complete. The strengthening of animal and human surveillance systems is vital to increasing the effectiveness of antivirals and vaccines. However, according to OFFLU officials, that network lacks sufficient funding to hire staff needed to analyze influenza strains. Officials fear that without this staff, scientists might not continue to submit samples to OFFLU—which are analyzed and presented in public databases—out of concern that they would not be analyzed. FAO, OIE, and WHO have stated that greater support of OFFLU is required in order for it to fulfill its functions. Experts have noted that public access to databases that contain influenza sequence information is vital to understanding the spread and evolution of influenza viruses and, therefore, to the research and development of influenza treatments.

⁹²Vaccines approved under this process are only approved for use in a declared influenza pandemic. They are not approved for use prior to a pandemic. The objective of this mechanism is to have a marketing authorization in place that can be changed quickly in the event of a pandemic to include the virus strain responsible, once it has been identified. These are referred to as mock-up pre-pandemic influenza vaccines.

⁹³The goal is to approve the pandemic vaccine within 4 days after the application is submitted. The United Kingdom Vaccine Industry Group estimated that overall this process would allow a pandemic vaccine to be provided 2 to 4 months faster than if a pre-pandemic vaccine had not been approved.

International support for clinical trials—necessary for developing and evaluating the effectiveness of antivirals and vaccines—is largely provided by only four countries: the United States, Australia, Japan, and the United Kingdom. The United States supports clinical trials for antivirals and vaccines being developed by global manufacturers, but experts state that more widespread and consistent international support is needed. Clinical trials are also required to test effectiveness and cross-protection provided by pre-pandemic vaccines. The United States, Australia, Japan, and the United Kingdom have provided the most support for pandemic vaccine development. However, only the United States provides substantial support to both domestic and international manufacturers for such trials. According to IFPMA representatives, the United States’ efforts are the primary governmental source for funding clinical trials for these vaccines.

Increasing demand for vaccines is likely to continue to pose difficulties because a number of countries will still need to balance concerns about a potential pandemic against other existing public health concerns. Low demand for vaccines to treat seasonal influenza is due in part to the low priority placed on seasonal influenza by many countries. As discussed earlier, current global demand for seasonal influenza vaccines is lower than global need, which is the amount required to cover individuals under medical guidelines for influenza vaccination.⁹⁴ Manufacturers have been reluctant to invest in the development and production of vaccines due to this low demand and disincentives such as low profits. One reason for low demand is that seasonal influenza programs compete with many other public health priorities for limited budgets in developing countries. For example, Indonesia, one of the countries experiencing human H5N1 outbreaks, is also dealing with other diseases as well as the aftermath of a tsunami, volcanic eruptions, and earthquakes. Some developing countries are willing to implement seasonal influenza vaccination programs but require outside funding to do so. One objective of WHO’s *Global pandemic influenza action plan to increase vaccine supply* is to increase seasonal vaccine use. According to WHO, a minimum of \$300 million is required to

⁹⁴WHO and many national health authorities recommend annual vaccination for a range of risk groups. These groups include those over a nationally defined age limit (often 65 years), those with specific chronic illnesses such as heart, lung, or kidney conditions including asthma and diabetes, and those suffering from immunosuppression, such as transplant patients and those with HIV. In addition, guidelines recommend vaccination for those who may transmit influenza to high-risk groups, such as health care workers and household contacts.

do this.⁹⁵ Similarly, efforts to increase vaccine production capacity can also be problematic. Citing Vietnam as an example, NIH officials told us that countries may have been too overwhelmed with H5N1 outbreaks to accept offers of assistance to develop vaccine production infrastructure.

Although efforts are under way to increase antiviral and vaccine manufacturers' production capacity by building new facilities, these new facilities are not expected to be ready to produce antivirals and vaccines for several years. According to manufacturers, it will take at least 5 years to build new vaccine manufacturing facilities and receive regulatory approval. WHO stated that it will take the six countries that received grants to develop vaccine production capacity at least 3 to 5 years to begin producing vaccine. Additionally, Roche granted sublicenses to selected drug companies in developing countries for the production of generic versions of Tamiflu. However, these agreements will not immediately alleviate any shortages due to the complicated production process for Tamiflu. Roche has estimated that it would take 2 to 3 years for a new facility to produce Tamiflu on a large scale. It has also stated that, even with all the materials necessary for production available, it takes 6 to 8 months to produce Tamiflu. Similarly, GlaxoSmithKline has stated that it would take a minimum of 6 to 9 months to increase production capacity for Relenza. WHO has stated that it is unlikely that sufficient quantities of antivirals will be available in any country at the onset of a pandemic. Further, in November 2006, Roche stated that because of high demand and long manufacturing lead times for Tamiflu, it is highly unlikely that it would be able to fill large Tamiflu orders on short notice. Demonstrating the importance of demand in driving production capacity, Roche announced in April 2007 that it planned to reduce Tamiflu production because it now exceeded demand for the drug. Roche officials stated that if demand were to increase, it would take 4 months to return the production level to 400 million treatment courses annually.

Although global, regional, and national stockpiles of antivirals are being established, little progress has been made in improving the capacity for

⁹⁵WHO estimates that a total of \$3 billion to \$10 billion will be required to implement its entire vaccine action plan. The other objectives of the plan are to increase influenza vaccine production capacity and to promote research and development for new influenza vaccines. In March 2007, WHO announced that in mid-2007 an independent steering committee with representation of both developing and industrialized countries would be formed to oversee implementation of the plan. Canada will provide support for the committee and its work.

distributing the stockpiled antivirals to the site of outbreaks around the world, particularly within developing countries. According to Asian Development Bank officials, the logistics of distributing antivirals in the event of a pandemic would be of greater concern than the limited supply of antivirals. Although the cost and logistics of transporting antivirals from a stockpile to a country's capital are addressed to some extent by WHO and those countries and manufacturers that have donated antivirals, issues of transportation from the capital to a province or distant region remain unaddressed by many national governments. WHO has established protocols for countries to request Tamiflu for containment purposes from its global stockpile. Roche, the donor of the WHO global stockpile, will deliver the drugs to the international airport nearest the crisis and hand them over to WHO. National authorities would then be responsible for the storage, transportation, and administration of those drugs within their borders. To do so effectively, governments must have plans in place prior to an outbreak as well as adequate resources to implement them. The U.S. government has assisted countries in developing such plans. In June 2007, WHO officials reported that over 178 countries have drafted or finalized their preparedness plans. However, WHO has noted that not all plans have incorporated its rapid containment protocol.

Agency Comments and Our Evaluation

HHS, the Department of State and WHO provided comments on a draft of this report. The comments from HHS and the Department of State are reproduced in appendixes I and II. WHO provided comments via e-mail and stated that the report was comprehensive and useful.

In its comments, HHS said that we had lost the larger context of all efforts with respect to pandemic preparedness and that HHS's antiviral and vaccine strategies and implementation plans are not captured. Expressing concern about our focus on antivirals and vaccines, HHS said that these are only one piece of the agency's broader scope of work on this topic. It cautioned that the use of antivirals and vaccines in response to a pandemic is part of a larger, integrated whole, so viewing them outside of the broader context is likely to raise other questions and issues. HHS said that we were assuming that antivirals and vaccines are the only tools necessary to forestall a pandemic. HHS commented on the uncertainty of success associated with measures such as stockpiling antivirals, stating that one must not assume that establishing antiviral stockpiles has solved the problem. HHS noted that if a potential pandemic is identified early, efforts at containment should and will be attempted. It further commented that if containment fails, the effort may still have the effect of slowing the pandemic's rate of spread while if it succeeds, a pandemic may be at least

temporarily averted. In its comments, HHS stated that as a preventive health measure only a vaccine will have the capability of dramatically changing the course of an influenza pandemic.

We do not agree that we have lost the larger context of efforts to prepare for a pandemic. This work was done in response to a congressional request that we study the role that antivirals and vaccines could play in forestalling a pandemic. While this was the focus of this engagement specifically, we are well aware that antivirals and vaccines are just two of many possible measures that could be taken in response to an influenza pandemic. As HHS notes in its comments, we have issued other reports on various aspects of pandemic preparedness (see the Related GAO Products section of this report) and we have ongoing work on numerous other aspects of this issue. We stated on page 2 of the draft report provided to HHS for comment that antivirals and vaccines may play a role in forestalling a pandemic, but we did not suggest that they were the only available response measures. Nonetheless we have added language to the report to make it clearer still that antivirals and vaccines are just two of a variety of available countermeasures that are being contemplated by WHO, HHS, and other agencies charged with the responsibility of protecting the public in the event of a pandemic. However, a discussion of the full range of possible responses to an influenza pandemic currently being contemplated by HHS and other organizations and agencies is beyond the scope of this report.

HHS also expressed concern with our discussion of “forestalling” a pandemic, suggesting that the premise that a pandemic can be forestalled is not one widely held by the public health or scientific community and is misguided and misleading. They said that few believe that a developing pandemic can be stopped in its tracks. In elaborating on this point, HHS suggested that the concept that antivirals and possibly vaccines might be used to stop an incipient pandemic or to slow the spread should be explicitly stated instead of using the word forestalled in a way that is very likely to be misinterpreted. They note that theoretically, the only way to truly forestall a human pandemic would be to eliminate the avian reservoir from which a future pandemic is likely to emerge.

In the draft of this report provided to HHS for comment, we defined the word “forestalling” to mean “preventing or at least delaying.” We use this term to suggest that, while preventing a pandemic would be the desired result of any response effort, delaying the pandemic would perhaps be the more likely yet still desired result. It is not clear why the level of concern expressed by HHS in its comments on our use of the word “forestall” is

being raised at this time. We issued a report in June 2007 that discussed efforts to forestall an influenza pandemic, including the word “forestall” in the report title, on which HHS provided written comments.⁹⁶ At that time, HHS expressed no concern with the term. In addition WHO has used the word in describing its efforts to respond to a pandemic and our definition is consistent with WHO’s use of the term.

Moreover, we fail to see significant differences in the meaning of the word “forestall” as compared to other terms and concepts contained in other parts of HHS’s comments on this report and other public comments. For example, in its comments, HHS discussed a goal to “minimize the impact” of a pandemic. They expressed the desire that we explicitly state the concept of “stopping or slowing the spread of” an incipient pandemic, rather than using the word forestall, defined as “prevent or delay,” which HHS believes is likely to be misinterpreted by the readership. Later in its comments, HHS stated that a pandemic may be “temporarily averted” or slowed. HHS stated in its letter that a vaccine could “dramatically change the course” of a pandemic. While we believe that these concepts are consistent with our use of the term forestall when describing efforts to respond to a pandemic in such a way as to avert, slow, mitigate, or change the course of a pandemic, we have revised the report and defined forestall to mean containing, delaying, or minimizing the impact of the onset of a pandemic. We have also added discussion to the report to further clarify our use of the term, making it clear that success in these efforts is uncertain and that it is unlikely that a pandemic can be entirely prevented.

HHS provided other general comments on the structure and organization of the report. HHS expressed concern that we have provided an inadequate amount of information about influenza diagnostic tests. They said that our emphasis on OFFLU is out of proportion to the role it plays in recognizing when a new virus with pandemic potential has begun to spread in humans. They further suggest that we do not adequately distinguish between seasonal, pre-pandemic, and pandemic vaccines. Finally, HHS stated that some information in the draft is out of date and that they corrected many factual errors in their technical comments.

We have evaluated HHS’s other comments on the structure and organization of the report. Both their general and technical comments suggested that we have overemphasized some issues while

⁹⁶ [GAO-07-604](#).

underemphasizing others. They also touched upon areas where HHS does not believe that we adequately distinguished between various aspects of influenza response; for example, HHS commented that we do not adequately distinguish between seasonal and pandemic influenza but also noted that much of what is believed to be true about pandemic influenza is based upon experience with seasonal influenza. We made changes to the report where HHS's general and technical comments could enhance clarity and completeness. However, this report was intended to describe the challenges and limitations of efforts to respond to an impending pandemic using antivirals and vaccines; it was not intended to capture a complete inventory of the most current scientific knowledge and developments regarding these two countermeasures. In some cases, rapid scientific advances may have outpaced the timing of this report such as, for example, the initiation of a new area of research not specifically identified in the report. In other cases, there is no consensus on the appropriate use and likely results of various medical countermeasures, including different types of antivirals and vaccines.

Further, while we updated the report to reflect changes that occurred while the draft report was with the agencies for comment, we disagree with HHS that the draft contained many factual errors. In its comments, HHS updated the information in the report in several areas, provided additional information on some points, and suggested different areas of emphasis in others. HHS suggested different wording in several instances that would have made our description of certain concepts extremely technical and not easily understood by persons not expert in the field. In those instances, we often chose not to make the change suggested by HHS. There were few instances of corrections of facts. Moreover, in a meeting discussing the draft, an HHS official was complimentary of the accuracy and completeness of the report.

The Department of State suggested in its comments that the report should be restructured to separate discussion of antivirals and vaccines. The comments state that these medical countermeasures are very different from each other in their application, utility, and the challenges the U.S. government faces in development and production of sufficient quantities. They further commented that while the report extensively discusses the challenges in production of adequate quantities of medical countermeasures, it does not give adequate consideration to the challenges of establishing protocols that would guide the international community in the use of whatever vaccines and antivirals are available. They also suggested that our use of the word "forestall" is somewhat ambiguous and should be clarified.

While we did not separate the discussion of antivirals and vaccines as the Department of State suggested, we revised the draft to ensure that discussion of antivirals and vaccines are clearly distinguished from one another. While antivirals and vaccines are very different from each other, we believe that the issues involved in identifying where they are needed, manufacturing sufficient quantities, shipping them to where they are needed, and administering them safely, are similar enough to merit discussing them together. We agree that the issue of establishing protocols to guide the international community in the use of antivirals and vaccines is an important one. However, this issue was discussed in the draft report and the Department of State did not articulate in its comments what information needs to be added.

The Department of State's concerns about our use of the word "forestall" are unclear. In making this comment, the Department of State suggests that we refer to the *North American Plan for Avian and Pandemic Influenza*, approved by the United States, Canada, and Mexico. The comments quote the plan, which states that "The North American Plan will enhance collaboration in order to ... prevent or slow the entry of a novel (pandemic) strain of human influenza to North America." We fail to see the meaningful difference between the words, "prevent or slow" in the plan and "prevent or delay," which is the meaning of the word "forestall." However, as stated earlier, we added discussion to the report to clarify our use of the word "forestall."

We incorporated technical comments provided by HHS, the Department of State, and WHO, as appropriate throughout the report.

As arranged with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution of it until 30 days after its issue date. At that time, we will send copies of this report to the Secretary of Health and Human Services, the Secretary of State, the Commissioner of the U.S. Food and Drug Administration, the Director of the Centers for Disease Control and Prevention, the Director of the National Institutes of Health, the Director of the Office of Global Health Affairs, the Special Representative on Avian and Pandemic Influenza at the U.S. Department of State, and to interested congressional committees. We will also make copies available to others upon request. In addition, the report will be available at no charge on GAO's Web site at <http://www.gao.gov>.

If you or your staff have any questions about this report, please contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov or David Gootnick at (202) 512-3149 or gootnickd@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made major contributions to this report are listed in appendix III.



Marcia Crosse
Director, Health Care



David Gootnick
Director, International Affairs and Trade

Appendix I: Comments from the Department of Health and Human Services



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Assistant Secretary
for Legislation

Washington, D.C. 20201

SEP 17 2007

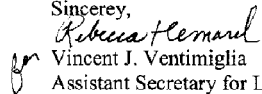
Marcia Crosse
Director, Health Care
U.S. Government Accountability Office
Washington, DC 20548

Dear Ms. Crosse:

Enclosed are the Department's comments on the U.S. Government Accountability Office's (GAO) draft report entitled, "Influenza Pandemic: Efforts Under Way to Address Constraints on Using Antivirals and Vaccines to Forestall a Pandemic (GAO 07-1052).

The Department provided several technical comments directly to your staff.

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

Sincerely,

Vincent J. Ventimiglia
Assistant Secretary for Legislation

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY'S OFFICE'S (GAO) DRAFT REPORT ENTITLED: INFLUENZA PANDEMIC: EFFORTS UNDER WAY TO ADDRESS CONSTRAINTS ON USING ANTIVIRALS AND VACCINES TO FORESTALL A PANDEMIC (GAO-07-1052)

HHS appreciates GAO's work on several different reports concerning the important topic of influenza pandemic preparedness. Although we recognize that the topics of vaccines and antivirals are very important in their own right, GAO-07-1052 clearly has lost the larger context of all efforts with respect to pandemic preparedness, and the presentation of the antiviral and vaccine strategies and implementation plans are not captured. While this context can (and should) be restored to this document, from the outset, the premise that a pandemic can be "forestalled" is not one widely held by the public health or scientific community. GAO should revisit this premise as it is misguided and misleading.

While the H5N1 influenza virus is in the news less often than it was just a year ago, we remain on alert for a human influenza pandemic (WHO Phase 3, Pandemic Alert) with the virus now responsible for animal outbreaks and killed hundreds of millions of chickens in 60 countries, up from just a dozen two years ago. Worldwide, over 300 human cases have been confirmed in 12 of those countries. For those who have been infected, the disease is very serious – overall 61 % of the human cases have been fatal. During this period, the H5N1 virus has evolved. Currently, the H5N1 viruses can be divided into two distinct clades -- clade 1 and clade 2 – with the latter branching into three subclades. While this is especially relevant to the selection of a vaccine target, it reinforces the plasticity of this RNA virus and serves as a constant reminder that with this virus becoming endemic among many avian species around the world, with each viral replication cycle comes the possibility that the next generation of virus could be the one that sparks a human pandemic.

Yet despite all that it has shown us in the past several years, scientists do not know whether this virus is capable of sparking a pandemic and if so, how severe it might be. Recent reviews of the natural history of past pandemics and our expanded investments in the scientific underpinnings of this virus provide new insights into how we might minimize the impact of a pandemic and, for the first time in history we have the potential to do this. However, unlike the SARS virus, a different respiratory virus that recently showed us the potential for rapid global spread of disease in the 21st century, unless the circumstances are ideal, few believe that a developing pandemic can be stopped in its tracks.

The majority of human cases to date can be attributed to exposure to infected poultry. However, there have been episodes where it appears likely that humans were the source of the infection in other humans, but efficient and sustained transmission from person-to-person did not occur. Although there are many uncertainties about the future of the H5N1 virus itself, based on what we have learned about pandemics in the past and what we now know about the molecular evolution of influenza viruses the only certainty about influenza pandemic is that will continue to occur since novel influenza viruses will continue to emerge and will continue to be a threat. Therefore, we must prepare. Because of what is at stake, it is appropriate that the Congress asked GAO to assess our progress.

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY'S OFFICE'S (GAO) DRAFT REPORT ENTITLED: INFLUENZA PANDEMIC: EFFORTS UNDER WAY TO ADDRESS CONSTRAINTS ON USING ANTIVIRALS AND VACCINES TO FORESTALL A PANDEMIC (GAO-07-1052)

Our preparations are broad and deep. As outlined in the National Strategy for Pandemic Influenza, they affect all Departments and Agencies, State, Local and Tribal Governments, communities, families and individuals. Therefore, we appreciate that GAO is reviewing many aspects of the nation's pandemic preparedness activities and recognize that this report, focused on vaccines and influenza antiviral drugs is only one piece of a their broader scope of work on this topic. However, we caution that analysis of vaccines and antiviral drugs is part of a larger, integrated whole, so viewing them outside of the broader context is likely to raise other questions and issues.

We believe that the current draft of GAO-07-1052 suffers from the following deficiencies:

A limited exploration, understanding and statement of fact regarding the overall U.S. Government (USG) strategy for the use of influenza vaccines and antivirals before and during a pandemic:

- The USG approach to pandemic preparedness is a very dynamic one and has advanced significantly in the last six months, in part because important substantive new data has emerged concerning the use of adjuvants with pre-pandemic vaccines. While we recognize that any report will necessarily be somewhat out of date by the time it is published, this report lacks essential information to properly inform the intended audience.
- The "mix and match" stockpiling strategy now in place must be included.

A fundamental misunderstanding concerning forestalling a pandemic using vaccines and antivirals:

- The concept that antivirals (and possibly vaccines under certain very specific circumstances) might be used to stop an incipient pandemic or to slow the spread should be explicitly stated instead of using the word forestalled in a way that is very likely to be misinterpreted by the readership. Further, GAO should acknowledge that there is not experience in preventing an incipient pandemic.
- The emergence of a virus with the ability to be transmitted from human-to-human in an efficient and sustained manner cannot be forestalled by using vaccines and antivirals.
- Because avian viruses such as H5N1 are a likely source of pandemics, without effectively eliminating the virus in avian populations, the potential threat to humans will likely persist. Thus theoretically the only way to truly forestall a human pandemic would be to eliminate the avian reservoir. This concept is not included in GAO-07-1052.

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY'S OFFICE'S (GAO) DRAFT REPORT ENTITLED: INFLUENZA PANDEMIC: EFFORTS UNDER WAY TO ADDRESS CONSTRAINTS ON USING ANTIVIRALS AND VACCINES TO FORESTALL A PANDEMIC (GAO-07-1052)

Our preparations also involve the development and analysis of new science relevant to vaccines and antivirals and a number of novel influenza viruses (including H5N1 virus). We are also concerned that this report fails to draw bright lines between what we know about seasonal influenza, the novel forms of influenza virus that have already appeared, and pandemics. What we know about how antiviral drugs and influenza vaccines perform is largely drawn from our long experience with these products during seasonal influenza. For example, the neuraminidase inhibitor drugs (oseltamivir and zanamavir) were initially licensed for use by the FDA for the treatment of uncomplicated seasonal influenza and if administered within 48 hours of the onset of symptoms, their impact was to reduce the time to freedom from illness by 1.5 days compared to placebo. How they will perform against a pandemic influenza virus cannot be predicted, but as there are currently no better options, stockpiles are being established.

In addition, we are also concerned by the expectation that GAO has set in its assumption that a pandemic can be forestalled and that vaccines and antivirals are only tools necessary to do so. While preventing a pandemic from occurring is the goal that all strive for, whether it can actually be achieved is not known. Mathematical models of the spread of a novel influenza virus hold out the hope that under the right circumstances – early identification of the emergence of a pandemic outside of a densely populated urban setting – an emerging pandemic might be contained, assuming that antiviral drugs that are used are available, effective both as treatment and as prophylaxis, are used strategically and can get to where they need to be before a pandemic spark becomes a forest fire.

Led by the World Health Organization and in concert with our global partners, the strategy for such a rapid response is being refined (WHO Pandemic Influenza Draft Protocol for Rapid Response and Containment, May 30, 2006). Antiviral drugs may well be an important component and make such an effort most effective but their availability alone is insufficient to accomplish the task. Therefore, we caution those who may conclude that the establishment of national and global stockpiles of antiviral drugs has solved the problem.

If a potential pandemic is identified early attempts at containment should and will be attempted. Such an effort would be in the best interest of both the affected country, and of benefit to global health security if it is successful in containing or slowing down the development of an emerging pandemic. Yet, there is no assurance a containment effort will succeed. In the likely event containment fails, the effort may still have the effect of slowing the pandemic's rate of spread. If containment succeeds, a pandemic may be at least temporarily averted.

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY'S OFFICE'S (GAO) DRAFT REPORT ENTITLED: INFLUENZA PANDEMIC: EFFORTS UNDER WAY TO ADDRESS CONSTRAINTS ON USING ANTIVIRALS AND VACCINES TO FORESTALL A PANDEMIC (GAO-07-1052)

In contrast, as a truly preventive health measure only a vaccine will have the capability of dramatically changing the course of an influenza pandemic. Emerging vaccine production technologies (e.g., cell culture) and new approaches to the vaccine development (e.g., vaccine adjuvants and recombinant vaccines) may well influence the time it takes to develop and produce a pandemic vaccine. Many of these approaches are very promising and studies being conducted by HHS and those of many vaccine companies will provide the data to better judge which of these approaches are the most likely to be effective, but these vaccines are not yet sufficiently advanced to prevent a pandemic in its tracks if it occurred tomorrow.

The addition of a very small amount of information about influenza diagnostic test development is confusing within the context of the subject and structure of the document:

- The efforts to develop diagnostic tests go well beyond the information presented here which is not factually correct as noted in the editorial comments. This section should be excised or expanded to be complete and factually correct.

The emphasis on OFFLU is totally out of proportion to the role they play in recognizing when a new virus with pandemic potential has begun to spread in humans. This recognition will occur on the international and domestic human influenza arena, not in the veterinary context:

- OFFLU is given great emphasis in this document on page 33 and again on page 52. It must be understood that OFFLU does not monitor human infections and plays a limited role in international surveillance for influenza viruses that infect humans.
- The role of human influenza surveillance is neglected in this document relative to the importance of the detection and monitoring of person-to-person spread of a new pandemic virus. This detection will trigger the use of vaccines and antivirals. HHS will append a spreadsheet outlining all of the international activities for influenza surveillance and capacity building relevant to human health accomplishments which dwarf what OFFLU has done in the context of pandemic preparedness.
- The emphasis on OFFLU is just one example where the auditors spoke with an articulate person from this organization but were unable to put the information into the proper context of the threat of pandemic influenza and what the USG and others are doing globally.

Structural weakness in the document that will confuse the Congressional audience about the differences between seasonal and pre-pandemic or pandemic vaccines:

- The concept that vaccines could be used to help with limiting the spread of an incipient influenza pandemic is a rather new one and has not been fully explored and over emphasis is placed on vaccines within this context.

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY'S OFFICE'S (GAO) DRAFT REPORT ENTITLED: INFLUENZA PANDEMIC: EFFORTS UNDER WAY TO ADDRESS CONSTRAINTS ON USING ANTIVIRALS AND VACCINES TO FORESTALL A PANDEMIC (GAO-07-1052)

- The use of pre-pandemic vaccines is also controversial but one that is not explored factually in this document.

Although seasonal, pre-pandemic and pandemic vaccines are defined on page 10, the authors are not consistent throughout the document in defining for their audience the use and target populations for these vaccines.

Information that is out of date:

- Some information dates from 2005 and other dates from 2006 and these pieces of information are out of date and misrepresent the current status.

Many factual errors are in GAO-07-1052:

- Many errors of fact are corrected in the technical comments which are provided to GAO in a separate document. In addition, we have attempted to point out areas where additional fact finding should be done by the auditors in order to present to Congress an accurate and more complete picture of USG activities.

We hope that this information as well as the technical comments attached to this response is useful to you. Please do not hesitate to contact us if we can be of further assistance.

Appendix II: Comments from the Department of State



United States Department of State

*Assistant Secretary for Resource Management
and Chief Financial Officer*

Washington, D.C. 20520

Ms. Jacquelyn Williams-Bridgers
Managing Director
International Affairs and Trade
Government Accountability Office
441 G Street, N.W.
Washington, D.C. 20548-0001

SEP 18 2009

Dear Ms. Williams-Bridgers:

We appreciate the opportunity to review your draft report, "INFLUENZA PANDEMIC: Efforts Under Way to Address Constraints on Using Antivirals and Vaccines to Forestall a Pandemic," GAO Job Code 290618.

The enclosed Department of State comments are provided for incorporation with this letter as an appendix to the final report.

If you have any questions concerning this response, please contact Dan Singer, Senior Policy Advisor, Office of Avian Influenza Action Group, at (202) 312-9780.

Sincerely,

A handwritten signature in black ink, appearing to read "S. Kaplan".

Sid Kaplan (Acting)

cc: GAO – Thomas Conahan
G/AIAG – John Lange
State/OIG – Mark Duda

Department of State Comments on GAO Draft Report

**INFLUENZA PANDEMIC: Efforts Underway to Address Constraints
on Using Antivirals and Vaccines to Forestall a Pandemic**
(GAO-07-1052, GAO Code 290618)

Thank you for the opportunity to review and comment on the draft report "*Influenza Pandemic: Efforts Underway to Address Constraints on Using Antivirals and Vaccines to Forestall a Pandemic.*"

The report in its current draft would benefit from major restructuring. One particular problem is the frequent jump in the text from discussion of antivirals to discussion of vaccines. These medical countermeasures are very different from each other in their application, utility, and the challenges the U.S. Government faces in development and production of sufficient quantities. The paper would be clearer if all issues pertaining to antivirals were discussed, then all issues pertaining to vaccines, with appropriate sections before and after to deal with a few cross-cutting issues.

The use of the word "forestall" is somewhat ambiguous and should be clarified, since the definitions of forestall include such distinct concepts as to prevent or to hinder (delay). It may be useful to note that the *North American Plan for Avian and Pandemic Influenza*, approved by the United States, Canada and Mexico, makes clear the distinction between: (1) containing an incipient pandemic and thereby preventing a global pandemic; and, if containment fails, (2) delaying the arrival of the pandemic influenza in this region. The *Plan* states, "The North American Plan will enhance collaboration in order to...prevent or slow the entry of a novel strain of human influenza to North America."

The report discusses extensively the challenges in production of adequate quantities of medical countermeasures. Proportionally, it does not give adequate consideration to the challenges of establishing protocols which would guide the international community in the use of whatever vaccines and antivirals are available. At the moment, there is not an international consensus on how antivirals or vaccine would be deployed, at what stage, and to whom, and this is a larger issue than the problem of clinical trials, which is addressed in the report. The development of international guidance for the use of antivirals and especially pre-pandemic vaccines could be addressed in the document, along with what the U.S.

2

Government is doing to promote the development of such guidance (such as funding the World Health Organization (WHO) to write the guidance, providing staff to WHO, and directly promoting our own views, such as the guidelines on community mitigation during a pandemic.)

Appendix III: GAO Contacts and Staff Acknowledgments

GAO Contacts

Marcia Crosse, (202) 512-7114 or crosssem@gao.gov

David Gootnick, (202) 512-3149 or gootnickd@gao.gov

Acknowledgments

In addition to the contacts above, Thomas Conahan, Assistant Director; Celia Thomas, Assistant Director; Robert Copeland; Etana Finkler; David Fox; Cathy Hamann; R. Gifford Howland; Michael McAtee; Jasleen Modi; Syeda Uddin; and George Bogart made key contributions to this report.

Related GAO Products

Influenza Vaccine: Issues Related to Production, Distribution, and Public Health Messages. [GAO-08-27](#). Washington, D.C.: October 31, 2007.

Influenza Pandemic: Opportunities Exist to Address Critical Infrastructure Protection Challenges That Require Federal and Private Sector Coordination. [GAO-08-36](#). Washington, D.C.: October 31, 2007.

Influenza Pandemic: Further Efforts are Needed to Ensure Clearer Federal Leadership Roles and an Effective National Strategy. [GAO-07-781](#). Washington, D.C.: August 14, 2007.

Influenza Pandemic: DOD Combatant Commands' Preparedness Efforts Could Benefit from More Clearly Defined Roles, Resources, and Risk Mitigation. [GAO-07-696](#). Washington, D.C.: June 20, 2007.

Influenza Pandemic: Efforts to Forestall Onset Are Under Way; Identifying Countries at Greatest Risk Entails Challenges. [GAO-07-604](#). Washington, D.C.: June 20, 2007.

Avian Influenza: USDA Has Taken Important Steps to Prepare for Outbreaks, but Better Planning Could Improve Response. [GAO-07-652](#). Washington, D.C.: June 11, 2007.

The Federal Workforce: Additional Steps Needed to Take Advantage of Federal Executive Boards' Ability to Contribute to Emergency Operations. [GAO-07-515](#). Washington, D.C.: May 4, 2007.

Financial Market Preparedness: Significant Progress Has Been Made, but Pandemic Planning and Other Challenges Remain. [GAO-07-399](#). Washington, D.C.: March 29, 2007.

Influenza Pandemic: DOD Has Taken Important Actions to Prepare, but Accountability, Funding, and Communications Need to be Clearer and Focused Departmentwide. [GAO-06-1042](#). Washington, D.C.: September 21, 2006.

Influenza Pandemic: Applying Lessons Learned from the 2004-05 Influenza Vaccine Shortage. [GAO-06-221T](#). Washington, D.C.: November 4, 2005.

Influenza Vaccine: Shortages in 2004-05 Season Underscore Need for Better Preparation. [GAO-05-984](#). Washington, D.C.: September 30, 2005.

Influenza Pandemic: Challenges in Preparedness and Response. [GAO-05-863T](#). Washington, D.C.: June 30, 2005.

Influenza Pandemic: Challenges Remain in Preparedness. [GAO-05-760T](#). Washington, D.C.: May 26, 2005.

Flu Vaccine: Recent Supply Shortages Underscore Ongoing Challenges. [GAO-05-177T](#). Washington, D.C.: November 18, 2004.

Emerging Infectious Diseases: Review of State and Federal Disease Surveillance Efforts. [GAO-04-877](#). Washington, D.C.: September 30, 2004.

Emerging Infectious Diseases: Asian SARS Outbreak Challenged International and National Responses. [GAO-04-564](#). Washington, D.C.: April 28, 2004.

Global Health: Challenges in Improving Infectious Disease Surveillance Systems. [GAO-01-722](#). Washington, D.C.: August 31, 2001.

Flu Vaccine: Supply Problems Heighten Need to Ensure Access for High-Risk People. [GAO-01-624](#). Washington, D.C.: May 15, 2001.

Influenza Pandemic: Plan Needed for Federal and State Response. [GAO-01-4](#). Washington, D.C.: October 27, 2000.

GAO's Mission

The Government Accountability Office, the audit, evaluation, and investigative arm of Congress, exists to support Congress in meeting its constitutional responsibilities and to help improve the performance and accountability of the federal government for the American people. GAO examines the use of public funds; evaluates federal programs and policies; and provides analyses, recommendations, and other assistance to help Congress make informed oversight, policy, and funding decisions. GAO's commitment to good government is reflected in its core values of accountability, integrity, and reliability.

Obtaining Copies of GAO Reports and Testimony

The fastest and easiest way to obtain copies of GAO documents at no cost is through GAO's Web site (www.gao.gov). Each weekday, GAO posts newly released reports, testimony, and correspondence on its Web site. To have GAO e-mail you a list of newly posted products every afternoon, go to www.gao.gov and select "E-mail Updates."

Order by Mail or Phone

The first copy of each printed report is free. Additional copies are \$2 each. A check or money order should be made out to the Superintendent of Documents. GAO also accepts VISA and Mastercard. Orders for 100 or more copies mailed to a single address are discounted 25 percent. Orders should be sent to:

U.S. Government Accountability Office
441 G Street NW, Room LM
Washington, DC 20548

To order by Phone: Voice: (202) 512-6000
TDD: (202) 512-2537
Fax: (202) 512-6061

To Report Fraud, Waste, and Abuse in Federal Programs

Contact:

Web site: www.gao.gov/fraudnet/fraudnet.htm

E-mail: fraudnet@gao.gov

Automated answering system: (800) 424-5454 or (202) 512-7470

Congressional Relations

Gloria Jarmon, Managing Director, jarmong@gao.gov, (202) 512-4400
U.S. Government Accountability Office, 441 G Street NW, Room 7125
Washington, DC 20548

Public Affairs

Chuck Young, Managing Director, youngc1@gao.gov, (202) 512-4800
U.S. Government Accountability Office, 441 G Street NW, Room 7149
Washington, DC 20548