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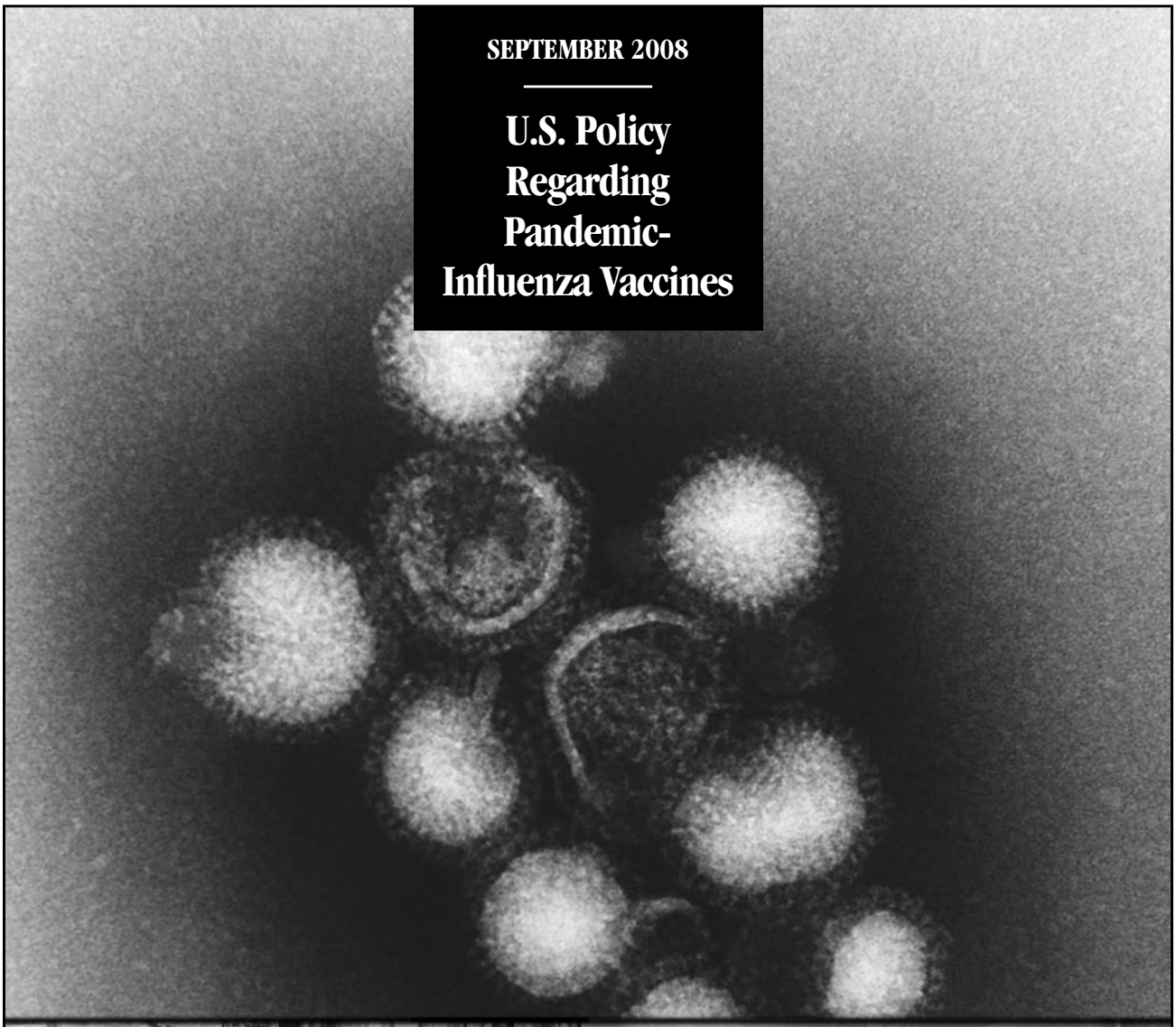
U.S. Policy Regarding Pandemic-Influenza Vaccines



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The Congress of the United States ■ Congressional Budget Office

Notes

Unless otherwise indicated, all years refer to fiscal years. Numbers in the text and tables may not add up to totals because of rounding.

On the cover: Top, transmission electron micrograph of a small grouping of influenza A virions; image courtesy of the Centers for Disease Control and Prevention, Public Health Image Library. Bottom right, eggs are inoculated to produce vaccine; photo by Peggy Greb; image courtesy of the Department of Agriculture, Agriculture Research Service, News & Events Image Gallery. Bottom left: Vaccine production, photo by A. Grillet; image courtesy of Marcy l'Etiole France V4, copyright 2006 Sanofi Pasteur.

Preface

The possibility of an influenza pandemic is cause for concern among policymakers, public health experts, and the world's populations. Against that prospect, in 2005, the Department of Health and Human Services (HHS) published a plan that includes a series of measures, first to monitor the spread of disease in the event of a worldwide outbreak and then to facilitate a rapid response. That second step includes developing influenza vaccines and expanding the nation's capacity for producing influenza vaccine; creating stockpiles of antiviral drugs and other medical supplies (to avert an influenza pandemic or minimize its effects); coordinating federal, state, and local preparations; and planning for public outreach and communications.

HHS's plan has two specific goals that relate to vaccines. The first goal is to have in place by 2011 domestic production capacity sufficient to supply vaccine to the entire U.S. population within six months of the onset of a pandemic. The second goal is to stockpile enough doses of vaccine to inoculate 20 million people as soon as possible after the onset of a pandemic.

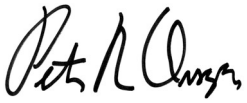
This Congressional Budget Office (CBO) paper, which was prepared at the request of the Senate Majority Leader, focuses on the government's role in the vaccine market that stems from HHS's plan. It provides information on the current state of readiness, the additional expenditures likely to be necessary to achieve HHS's vaccine-related goals, the expenditures that are likely to be needed to maintain preparedness, and the approaches of other countries as they too face the prospect of an influenza pandemic. In keeping with CBO's mandate to provide objective, nonpartisan analysis, this paper makes no recommendations.

The report was written by Julie Somers and Philip Webre of CBO's Microeconomic Studies Division under the supervision of Joseph Kile and David Moore. Bob Arnold, David Auerbach, Bob Dennis, Keith Fontenot, Renee Fox, Carla Tighe-Murray, and Jeanne De Sa (formerly of CBO) provided thoughtful comments on drafts.

Helpful comments also came from outside CBO. Thanks go to David Fedson, M.D.; Christopher Adams, Federal Trade Commission; Peter Dunnill, University College London; Robert Giffin and Margaret Hamburg, Institute of Medicine; Sarah Lister, Congressional Research Service; Peter Khoury, Baxter BioScience; the Food and Drug Administration's (FDA's) Immediate Office of the Director, Office of Vaccines Research and Review in the Center for Biologics Evaluation and Research; the FDA's Office of Compliance and Biologics Quality; the FDA's Office of Counter-Terrorism and Emerging Threats; the Biomedical Advanced Research and Development Authority; and the National Vaccine Program Office in

HHS. (The assistance of external reviewers implies no responsibility for the final product, which rests solely with CBO.)

Angela McCollough prepared the tables for publication. Kate Kelly edited the manuscript, and Loretta Lettner proofread the paper. Maureen Costantino prepared the figures for publication and designed the cover. Lenny Skutnik produced the printed copies, Linda Schimmel coordinated the print distribution, and Simone Thomas produced the electronic version for CBO's Web site (www.cbo.gov).



Peter R. Orszag
Director

September 2008

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Public health officials are concerned that a particular strain of influenza, known as H5N1, or "avian flu," which has caused widespread infection of poultry flocks in Asia, Europe, the Near East, and Africa, might become easily transmissible among humans, causing illness and death at rates unseen at least since the early 20th century. In the "Spanish flu" pandemic of 1918 and 1919, more than 500,000 people died in the United States and some 50 million perished worldwide. By contrast, in a typical year, seasonal influenza causes about 36,000 deaths in the United States. Public health officials worry that an influenza pandemic today could cause some 2 million deaths in the United States. It also could lead to substantial adverse economic consequences both here and abroad (CBO 2005, 2006a).

Against the prospect of such an event, the Department of Health and Human Services (HHS) has developed a plan to prepare for and combat an influenza pandemic and has budgeted about $7.9 billion since 2004 for influenza preparedness activities (HHS 2005b). Most of that money—about $5.6 billion—was provided through supplemental appropriation bills in 2006 in response to the HHS plan. About $3.2 billion of the supplemental funds, along with some additional funds that are part of HHS's annual appropriation, is being spent for vaccine-related activities, reflecting the strong consensus among public health officials that vaccination is the best tool for reducing the consequences—and the costs—of an influenza pandemic.[1]

HHS planners initially confronted two problems: inadequate capacity for vaccine production and delays in producing vaccine. The emergence of H5N1 as a human health risk found a U.S. production base that had been reduced to a single domestic manufacturer, using an egg-based process developed in the 1940s to produce the vaccine. The current process for delivery of seasonal-influenza vaccine takes about six months from the initial step of isolating the virus strain to the final delivery of the vaccine to the clinic or doctor's office.

Step one in HHS's plan was to promote an increase in capacity as rapidly as possible by encouraging the expansion and refurbishing of existing plants. The second, and current, step is to introduce cell-based manufacturing technology to the domestic production of influenza vaccine. (That method uses cells rather than chicken eggs as the medium in which to grow the active ingredient in the vaccine; it is a standard method for manufacturing most vaccines against childhood diseases, for example.)

Because production requires about six months, and an influenza pandemic could spread much faster than that, HHS's plan includes short- and longer-term approaches to the problem of making vaccines available quickly. In the short run, a small stockpile of vaccines could be used for a limited initial response. Longer-term plans call for the development of "next-generation vaccines," which will draw on advances in biotechnology to speed production. Because developing safe and effective vaccines could take years—perhaps a decade or more—HHS is encouraging pharmaceutical manufacturers to start development now.

In parallel with the efforts to scale up production of egg- and cell-based vaccines, HHS is funding the development of new adjuvants, substances that can be added to influenza vaccines to reduce the amount of active ingredient (also called antigen) needed per dose of vaccine. The use of adjuvants for egg-based and cell-based vaccines could allow domestic manufacturers to produce more doses in

1. The remainder of the spending in HHS's plan is for developing and stockpiling antiviral drugs that might prevent the spread of a pandemic or diminish the severity of illness in people who become infected; creating stockpiles of other medical supplies, such as surgical masks, respirators, ventilators, and syringes; coordinating state and local preparedness; and monitoring the spread of disease.

existing facilities, and so fewer new facilities would be needed to manufacture cell-based formulations. Moreover, smaller stockpiles could be used to protect larger numbers of people. But adjuvanted vaccines can induce more pronounced side effects than ordinary vaccines can, a definite downside because vaccines, unlike most other pharmaceuticals, are given to healthy people. To date, the Food and Drug Administration has not approved an adjuvanted vaccine for influenza. In contrast, adjuvanted influenza vaccines have been approved for use in Europe.

This paper from the Congressional Budget Office (CBO) focuses on the government's role, under HHS's plan, in the development of new vaccines and the capacity to manufacture them. It provides information on progress and on the potential cost of achieving HHS's vaccine-related goals, the continuing expenditures that are likely to be needed to maintain preparedness, and the experience of other countries in preparing for a possible pandemic. It also presents options for modifying HHS's 2005 plan. The work is based on a review of the academic literature, on industry data, and on interviews with government and industry experts who are working to improve the response of vaccine producers to a potential influenza pandemic.

Findings

The manufacturers of currently approved influenza vaccines made in the United States cannot produce vaccines of sufficient effectiveness, in sufficient quantities, or in the time required to meet public health needs in the event of an influenza pandemic. Several companies, some with funding from HHS, are developing adjuvants that could boost the effectiveness of influenza vaccines and thus reduce the amount of active ingredient needed per dose. In the short term, adjuvants offer the best hope for achieving HHS's goal of inoculating 300 million people within six months of the onset of an influenza pandemic; adjuvants could allow manufacturers to increase the number of doses produced in existing domestic manufacturing facilities, and their development would substantially affect the cost of most other aspects of HHS's plan. The extent to which manufacturers can develop safe and effective adjuvanted vaccines will have a major effect on the scope of preparations for a possible pandemic.

Additional Capacity and New Cell-Based Vaccines

By 2011, companies that receive funding from HHS plan to more than triple domestic capacity for production of egg-based influenza vaccines. To augment private investment, HHS has obligated $176 million to provide a year-round egg supply and to retrofit existing facilities. If, in addition to the increased capacity, manufacturers also can develop adjuvanted egg-based vaccines, it is possible that they could make enough to inoculate 225 million people or more. If not, the same facilities could be expected within six months to produce enough vaccine for only 38 million people.

HHS intends to support the modernization of influenza vaccine production by helping manufacturers shift from egg-based to cell-based technology, which HHS believes is more reliable. HHS has obligated $1.3 billion, an amount experience suggests is sufficient to support development of cell-based influenza vaccines.

New facilities would have to be built to produce the vaccines—although less capacity would be necessary for adjuvanted vaccines. CBO estimates that it would cost between $1.2 billion and $1.8 billion to build new production facilities for adjuvanted cell-based vaccines and between $7.6 billion and $11.4 billion for facilities for cell-based vaccines without adjuvants. Pharmaceutical manufacturers are not likely to create that much new capacity on their own because the capacity would exceed that necessary to meet demand for seasonal-influenza vaccine. Moreover, because building those facilities is a complex matter, it is not likely any would be finished in time to meet HHS's goal of 2011.

The additional capacity would be in excess of that needed in years when there is no pandemic. To keep the factories ready to operate, continuing federal support—in the form of purchases for the stockpile or direct payments—would probably be necessary.

Stockpiles

If safe and effective adjuvanted vaccines can be developed, the current stockpile could be stretched to vaccinate well more than HHS's initial goal of 20 million people. (Information from HHS indicates that it would cost about $350 million annually to replace expired vaccine and adjuvants.) Even if the development of adjuvants is not successful, the stockpile holds enough to vaccinate about 6 million people, and it would cost about $1.1 billion to purchase the remainder necessary to inoculate 20 million people. Once the stockpile is full, annual replenishment of expired vaccine should cost about $1.1 billion. Continued spending to maintain the

stockpile could occupy excess manufacturing capacity and obviate much of the need for direct government payments to pharmaceutical manufacturers. However, because it was manufactured with a virus strain that differs from that likely to cause a pandemic, no one knows how effective the vaccine in the stockpile will be for protecting people in the event of a pandemic.

Next-Generation Vaccines

In the long-term, the public health community hopes that entirely new vaccines and production technologies will substantially reduce vaccine production times and create vaccines that offer broad protection against many—or all—strains of influenza virus. Developers expect to use recombinant DNA techniques to manufacture next-generation vaccines that might someday approach the lifetime effectiveness of currently available vaccines against many childhood diseases. HHS's plan has relatively few incentives for manufacturers to develop new products or production technologies because its funds go largely to support the expansion of existing production facilities for egg-based vaccines and for the development of new cell-based vaccines. Moreover, HHS's plans now call for supporting the creation of more production capacity than can be sustained by current demand. The excess supply could easily saturate the market, substantially driving down prices for influenza vaccine. Low prices could make the market look unattractive to companies developing next-generation vaccines. Consequently, government funding is likely to be needed to help bring next-generation vaccines to the marketplace.

Activities in Other Nations

Several European countries are entering into advance supply agreements with manufacturers to provide vaccines in the event of a pandemic; those governments agree to make advance payments to guarantee the supply of vaccine in the event of an influenza pandemic. It is unknown whether the companies can produce the vaccines promised under their agreements. Several European countries also are stockpiling vaccines, although the size of the stockpiles relative to national populations varies substantially. International organizations and other nations' governments also are funding the development of influenza vaccines, although not to the extent seen in the United States.

Options

In at least one important regard, the world's circumstances have changed since HHS published its plan in 2005: Several manufacturers have reported success using adjuvants in influenza vaccines, and some of them have been approved in Europe. Adjuvants have the potential to substantially reduce the amount of antigen needed per dose. That development raises questions about whether the current policy is the most cost-effective approach to meeting HHS's goals. CBO examined several other options, briefly outlined here.

Scale Back Support for Cell-Based Manufacturing Technology

One option that HHS might consider if adjuvanted vaccines prove successful is to reduce the capacity targeted for manufacturing cell-based influenza vaccine. A reduction could save the $600 million that HHS currently has budgeted for the construction of facilities for producing cell-based vaccines, and it would reduce the amount of spending needed to maintain the new facilities. The resulting reliance on a small number of manufacturers and facilities and on poultry flocks, however, could increase the risk of supply disruptions.

Add Resources to Develop Next-Generation Vaccines

Success with adjuvanted vaccines could have implications for the use of resources devoted to development of the next generation of vaccines and for the mechanisms the government uses to accomplish its objectives. Specifically, if adjuvanted vaccines reduced the near-term risk posed by pandemic influenza because they stretched available and planned production capacity, more resources might be made available to support the development of next-generation vaccines.

Alternative mechanisms for providing that support also could be considered for next-generation vaccines. HHS could use demand-side rather than supply-side incentives to accomplish its goals. For example, HHS could commit to stockpiling next-generation vaccines that proved successful rather than choosing which specific companies and technologies to support. Such an approach would help HHS reduce the likelihood of encountering pitfalls associated with active government intervention in decisionmaking about private investment and commercial production.

Early success in developing next-generation influenza vaccines is unlikely, however. Most of the formulations are in early stages of development, at the start of a long and risky path to approval.

Consider Advance Supply Agreements

HHS could consider entering into advance supply agreements like those used in Europe for procuring the quantities of vaccine necessary to immunize the U.S. population in the event of a pandemic. Such agreements could provide a contractual obligation for manufacturers to supply vaccines to public health officials or physicians in the United States. Although the current U.S. approach of directly subsidizing vaccine development and additional production capacity could result in a more abundant supply of vaccine, it does not ensure that the United States would be able to buy enough vaccine to meet its need in a pandemic. Manufacturers could exhaust their supplies when fulfilling their European agreements before they have the chance to sell any to the United States. If the United States does pursue advance supply agreements, it might be necessary to structure them to recognize that other nations' governments could temporarily restrict or prohibit exports of pandemic-influenza vaccine until their own populations have been immunized.

The Size of the Vaccine Stockpile

The current goal of 20 million doses for the stockpile could be too large or too small: If, for example, the strain that causes the pandemic influenza does not respond to the stockpiled vaccine formulation, the stockpile could be wastefully large. But it could be too small if a pandemic were to spread through the population more quickly than new vaccines could be manufactured.

Successful development of adjuvanted vaccines could alter the balance of risks in determining the size of the stockpile and potentially reduce the cost of mitigating those risks. Some recent research indicates that adjuvanted vaccines could provide protection against more than one strain of virus, thereby improving the chances that the vaccines in the stockpile would be effective in a pandemic. Moreover, because adjuvants would reduce the amount of antigen required, HHS either could retain its current goal of maintaining a stockpile sufficient to inoculate 20 million people while reducing the amount of stockpiled antigen or it could plan to expand the population it would inoculate with prepandemic vaccine.

CHAPTER

1

The Market for Seasonal-Influenza Vaccine and the Challenge of Providing Vaccine in a Pandemic

The prospect of an influenza pandemic—a global outbreak of influenza that leads to serious illness or death in large numbers of people—is cause for concern among policymakers, public health experts, and the public at large. Pandemics are not new: There were three in the 20th century, the deadliest of which, the "Spanish flu" of 1918, caused global devastation, killing more than 500,000 people in the United States and about 50 million people worldwide. According to the World Health Organization (WHO), an influenza pandemic requires three conditions: First, a new virus emerges to which people have little natural immunity. Second, infection leads to significant rates of illness or death. And third, the virus is transmitted efficiently from one person to another (WHO 2006, p. 1).

Although a pandemic could be caused by any of several influenza strains, policymakers and public health experts are particularly worried about the persistence of the currently circulating H5N1 strain (the "avian flu" or "bird flu"), which has caused high mortality among poultry in Asia and has spread in poultry from Southeast Asia to Central Asia, Europe, and Africa.[1] The H5N1 virus meets two of the three conditions for a pandemic: First, people have little natural immunity to H5N1 because it has not widely circulated among the human population. And second, it has caused significant illness in the 385 people who have become infected, and 243 of those people have died. The mortality rate from the H5N1 virus is thus in excess of 60 percent of known cases (WHO 2007a).[2] So far, WHO's third condition has not been met: The H5N1 virus is not transmitted efficiently from one person to another. Close contact with infected poultry is thought to be required for human infection. However, the danger exists that the virus will evolve in a way that allows for efficient human-to-human transmission, perhaps leading to a pandemic. Depending on the virulence of the particular strain of influenza, a pandemic could have substantial consequences for human health and for economic activity around the world (CBO 2005, 2006a). Because infectious diseases are unpredictable, public health authorities cannot say for sure when a pandemic will arise, whether it will involve H5N1 or some other strain, or whether it will be mild or virulent.

Against the prospect of a pandemic like the 1918 Spanish flu, the Department of Health and Human Services (HHS) since 2004 has budgeted about $7.9 billion for activities to support a research and preparedness plan for an influenza pandemic (see Table 1-1). A large portion of that amount—nearly $5.6 billion—came in supplemental appropriations for 2006 to fund HHS's plan for coping with an influenza pandemic (HHS 2005b).[3] The department's national response plan includes support for research and development in new vaccines and new vaccine formulations, an increase in production capacity, and the establishment of vaccine stockpiles. The plan also encompasses the stockpiling of existing antiviral drugs as

1. Influenza viruses that affect humans, birds, and other animals are named for two surface proteins, hemagglutinin and neuraminidase. The surface of H5N1, accordingly, has one type 5 (of the possible 16) hemagglutinin protein and one type 1 (of 9) neuraminidase protein (CDC 2005).

2. The mortality rate, however, might in fact be substantially lower. Public health authorities do not know how many people with milder cases did not seek medical care or how many received care that was not reported.

3. A supplemental appropriation is an act of Congress appropriating funds in addition to those already contained in the usual annual appropriation legislation.

Table 1-1.

HHS's Funding for Influenza Preparedness, 2004 to 2008

(Budget authority, in millions of dollars)

	2004	2005	2006	2006[a]	2007	2008	Total, 2004–2008
Office of the Secretary	43	101	4	5,152	0	76	5,377
Centers for Disease Control and Prevention	198	323	295	400	73	73	1,361
Food and Drug Administration	3	5	5	20	33	38	103
National Institutes of Health	113	164	207	18	271	271	1,044
Total	**357**	**592**	**511**	**5,590**	**377**	**458**	**7,885**

Source: Congressional Budget Office based on data collected from HHS.

Note: HHS = Department of Health and Human Services.

a. Additional funds were provided in the form of emergency supplemental appropriations.

well as other medical supplies (including surgical masks, respirators, ventilators, and syringes) and the development of new antiviral drugs. In addition, HHS's recommendations address the coordination of state and local preparedness and response and methods for monitoring influenza viruses that have the potential to cause a pandemic.

HHS has budgeted $3.2 billion of its 2006 supplemental appropriations (plus some of its appropriated funds from other years) for vaccines (see Table 1-2). Relying mainly on the supplemental funding provided in 2006, HHS has obligated almost $2.6 billion to promote the development of vaccines, increase the investment in new production capacity, and procure vaccine stockpiles (see Table 1-3). According to agency officials, HHS has yet to obligate about $1.3 billion of the supplemental appropriations provided in 2006. About $900 million of that amount is budgeted for vaccine-related activities. Officials at HHS note that although those funds have not yet been obligated, there are plans for their use.

The President's budgetary proposals for 2009 include $820 million for HHS to pursue its pandemic-influenza activities. Of that amount, $467 million is to procure vaccines for the stockpile and to fund vaccine production capability, $40 million is to stockpile other medical supplies, and $313 million is to fund preparedness activities at the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the National Institutes of Health (NIH), and the Office of the Secretary in HHS.

The vaccine component of HHS's plan is motivated by concerns about the capacity and capabilities of the current group of manufacturers of seasonal-influenza vaccine to respond to the threat of a pandemic. Because current vaccines and manufacturing capacity are inadequate to protect the U.S. population in the event of a pandemic, HHS is devoting much of its effort to developing new vaccines and expanding existing manufacturing capacity. Specifically, the first goal is to have in place by 2011 domestic production capacity sufficient to supply vaccine to the entire U.S. population within six months of the onset of a pandemic. The second goal is to stockpile enough doses of prepandemic vaccines to inoculate 20 million people. (Prepandemic vaccines are developed from strains that public health officials believe have the most potential to cause an influenza pandemic.) First priority for vaccination will be given to children and to people who are critical to maintaining security, health care, and essential services.

This Congressional Budget Office (CBO) paper examines several questions:

- What steps have been taken and what is the status of HHS's plan to improve manufacturers' response to an influenza pandemic?

Table 1-2.

Supplemental Funding for HHS's Pandemic-Influenza Plan, 2006

	Budget Authority	
	Millions of dollars	Percentage
Vaccines	3,233	58
Antiviral Drugs	911	16
Medical Supplies	170	3
State and Local Preparedness[a]	770	14
Monitoring[b]	455	8
Other	51	1
Total	**5,590**	**100**

Source: Congressional Budget Office based on data from HHS (2006a).

Note: HHS = Department of Health and Human Services.

a. Includes funding for state subsidies for antiviral drugs.

b. Includes international and domestic activities.

- What changes have occurred in the vaccine industry, particularly as a result of expanded government involvement in the influenza vaccine market?

- What is the continuing role for the government in developing and producing influenza vaccines to meet the performance objectives specified under current policy, and how will that role affect federal spending?

The Market for Seasonal-Influenza Vaccine

The first line of defense against seasonal influenza, which results in the hospitalization of about 200,000 people and causes about 36,000 deaths each year in the United States, is annual vaccination.[4] About 100 million U.S. residents were inoculated in the 2006–2007 season. Vaccination is considered a principal strategy to combat pandemic influenza as well, but a pandemic will create huge surges in demand. The nation's response to an influenza pandemic will depend to a great extent on whether the manufacturers of seasonal-influenza vaccine can meet the challenge of providing a far larger number of doses of the correct vaccine quickly enough to inoculate the whole population.

As it is currently formulated, the seasonal-influenza vaccine contains 15 micrograms (a microgram is one one-millionth of a gram) of active ingredient, or antigen (the protein that elicits an immune response in the body) from each of three strains of influenza virus, for a total of 45 micrograms per dose. (By contrast, a pandemic vaccine would contain antigen from a single strain.) Since the 1940s, manufacturers have made vaccines by injecting seed viruses into hens' eggs, growing them there, and then using the viruses grown in the fluids inside the eggs as the starter for the vaccine.

The FDA has licensed two main types of vaccine: One, called a subunit vaccine, uses purified proteins from killed viruses. The subunit vaccine is delivered by injection and accounts for 97 percent of the vaccine used in the United States. The other type uses a weakened live form of the influenza virus (often called live, attenuated virus). The vaccine made from the weakened live virus is administered in an intranasal spray, and just one company produces it for the U.S. market.

Because the genetic makeup of influenza viruses can change rapidly, the vaccine must be reformulated each year to confer immunity against the strains researchers

Table 1-3.

HHS's Obligations for Pandemic-Influenza Vaccine Projects

	Obligations[a] (Millions of dollars)	Duration
Develop New Vaccines	1,435	2005 to 2012
Increase Capacity	176	2004 to 2012
Stockpile Vaccine	950	2004 to 2008
Total	**2,561**	

Source: Congressional Budget Office based on data from Robinson (2008).

Note: HHS = Department of Health and Human Services.

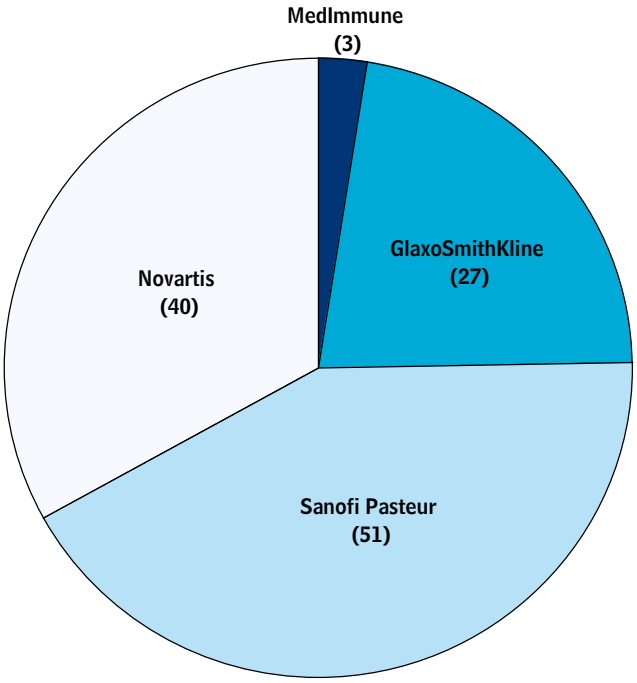
a. As of December 2007.

4. According to CDC, "Influenza is a respiratory illness. Symptoms of flu include fever, headache, extreme tiredness, dry cough, sore throat, runny or stuffy nose, and muscle aches. Children can have additional gastrointestinal symptoms, such as nausea, vomiting, and diarrhea, but these symptoms are uncommon in adults. Although the term 'stomach flu' is sometimes used to describe vomiting, nausea, or diarrhea, these illnesses are caused by certain other viruses, bacteria, or possibly parasites, and are rarely related to influenza" (CDC 2008).

Figure 1-1.

Vaccine Production for the 2006–2007 Influenza Season in the United States

(Millions of doses)



Total Production = 121 million doses

Source: Congressional Budget Office based on Health Industry Distributors Association (2007) and Novartis (2007).

believe will circulate that year. In February or March, the FDA announces the strains, which are chosen on the basis of surveillance data from CDC and WHO. Manufacturers then produce vaccine for delivery between November and March, the peak influenza season in the Northern Hemisphere. It takes about six months from the time the virus strains are isolated for the process to play out: manufacturing, purification, testing, filling, packaging, and delivery to clinics and physicians' offices.

The production of seasonal-influenza vaccine is characterized by high fixed costs—costs that do not change whether a manufacturer produces one dose of vaccine or millions. The most widely cited analysis puts the fixed cost of producing any vaccine at 60 percent of the total costs (exclusive of research and development costs), regardless of volume (Mercer Management Consulting 2002). Among the fixed expenses are depreciation, administration, quality assurance, and personnel. Another 25 percent of the cost is fixed at the batch level regardless of batch size. Only 15 percent of the cost is truly variable, fluctuating directly with the number of doses produced.

The proportion of fixed costs suggests that the manufacturers with the largest market share will enjoy lower average costs—a condition that is conducive to market concentration among vaccine producers. As the number of producers declines, the potential for supply disruptions caused by contamination or other problems rises.

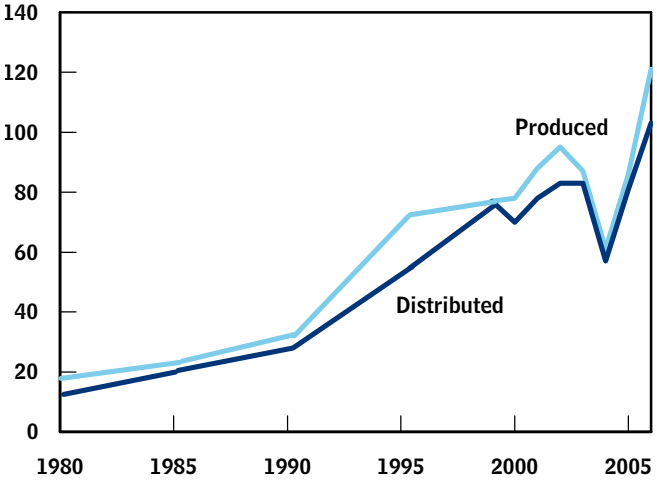
For the 2006–2007 season, there were only four manufacturers of influenza vaccine for the United States: GlaxoSmithKline (GSK), Sanofi Pasteur, Novartis, and MedImmune (see Figure 1-1). And only one of those, Sanofi Pasteur, actually produces the vaccine domestically. In all, those manufacturers produced about 120 million doses of vaccine for the 2006–2007 season, of which about 100 million were distributed (see Figure 1-2). (Because seasonal-influenza vaccine is reformulated each season, manufacturers must discard undistributed vaccine every year.)

The supply of seasonal-influenza vaccines has been disrupted several times in the recent past. In 2000–2001,

Figure 1-2.

Seasonal-Influenza Vaccine for the U.S. Market

(Millions of doses)



Source: Congressional Budget Office based on data from the Centers for Disease Control and Prevention.

manufacturers had difficulty growing one of the three influenza strains, and some facilities were shut down because of the FDA's concerns about compliance with good manufacturing practices (Danzon, Sousa Pereira, and Tejwani 2005; Government Accountability Office 2007). In the 2003–2004 season, Wyeth's decision to exit the market rather than incur the cost of upgrading its facility left just two manufacturers of injectable influenza vaccine. One of the two was unable to deliver any vaccine to the U.S. market for the 2004–2005 season because of contamination at its facility in the United Kingdom.

Between 1999 and 2006, list prices (which are set by manufacturers and reported to CDC) for influenza vaccine jumped from about $2 to about $11 per dose. In general, individual clinicians, clinics, and hospitals pay list price or close to it; large groups, state consortia, and health plans often can negotiate for rebates and discounts (Institute of Medicine 2004, pp. 127–128). The number of doses distributed rose from 77 million in 1999 to 100 million in 2006 (see Figure 1-2).

WHO has estimated that, in 2007, manufacturers produced 565 million doses for the global market (WHO 2007d). That quantity would still fall well short of the number needed to inoculate the world's 6.6 billion people; by 2010, new production capacity could raise the global supply to 1 billion doses of seasonal-influenza vaccine.[5]

Supplying Vaccine in a Pandemic

If an influenza pandemic were to occur today, it would be impossible to meet HHS's goal of vaccinating the entire U.S. population of about 300 million people within the next six months. To begin with, current capacity for domestic production would be completely inadequate. (Only 50 million of the approximately 120 million doses produced for the domestic market during the 2006–2007 influenza season were manufactured in the United States.) In the event of a pandemic, moreover, it could be difficult to obtain supplies from overseas, especially if there are shortages in vaccine-producing countries or if those countries vaccinate their own populations before permitting exports to the United States (Osterholm and Branswell 2005).

It also is anticipated that the pandemic-influenza vaccine would have to be stronger than the seasonal version. Because of the lack of previous exposure to the H5N1 virus, humans would be expected to have no immunity at all. The only H5N1 vaccine currently approved for the U.S. market requires a course of two doses at 90 micrograms per dose (FDA 2007). (The seasonal vaccine is administered in a single dose of 45 micrograms of antigen—15 micrograms against each of three strains. Most adults are exposed regularly to seasonal-influenza viruses and thus have some immunity, so the seasonal vaccine is in effect a booster shot. The course for children, who generally have less exposure and hence less immunity, typically is two doses.)

When all of those factors—uncertain availability of imports, higher content per dose, and more doses per course—are taken into consideration, current U.S. capacity to produce pandemic vaccine is only about 12.5 million courses (see Table 1-4). That estimate could be high; in the past, manufacturers have had difficulty growing pandemic-influenza strains. Moreover, given the six months it takes to produce and distribute current vaccines, experts fear that the pandemic-influenza vaccine would not be available until after the first wave of a pandemic had passed.

An influenza pandemic therefore would present a significant challenge for public health authorities and for manufacturers. About one-third of the U.S. population was vaccinated in the 2006–2007 season. If a pandemic were to occur, demand for vaccine would be much greater, even if vaccinating the entire U.S. population were not a policy goal. It would be a significant undertaking to increase output by so much, so quickly.

Overview of HHS's Plan

Because domestic vaccine manufacturers right now could not quickly provide enough vaccine to meet the threat of an influenza pandemic, HHS has focused on increasing domestic capacity for production. In the future, the agency plans to focus on reducing production time.

5. Recommendations for meeting potential global demand for pandemic vaccine are discussed by David Fedson (2003).

Table 1-4.

Domestic Production Capacity for Seasonal- and Pandemic-Influenza Vaccine

	Adjustment Factors	Assumptions
Seasonal-Influenza Vaccine	50 Million Doses	
Adjustments for		
Strains per dose of pandemic vaccine	× 3	One strain instead of three
Antigen per dose of pandemic vaccine[a]	÷ 6	90 micrograms instead of 15 micrograms against a single strain[b]
Doses per course of pandemic vaccine	÷ 2	Two doses per course[c]
Pandemic Vaccine for U.S. Market	12.5 Million Courses	

Source: Congressional Budget Office.

a. Antigen is the active ingredient in a vaccine.

b. A microgram is one one-millionth of a gram.

c. For seasonal vaccines, a course generally consists of a single dose. Researchers believe the pandemic-influenza vaccine will require a course consisting of two doses.

The emergence of H5N1 as a human health risk found a U.S. manufacturing base reduced to a single domestic manufacturer, producing the vaccine in an egg-based process developed in the 1940s. The first step in the HHS plan was to promote an increase in capacity as rapidly as possible by encouraging the expansion and refurbishing of existing plants. The second, and current, step is to introduce cell-based manufacturing technology to the domestic production of vaccine. Cell-based production uses animal cells to culture the virus, and it is a standard method for producing other vaccines, including several against childhood diseases.

It would be more expensive and time-consuming to initiate cell-based manufacturing than it would be to add capacity for egg-based production. But, HHS contends, adding cell-based capacity reduces the risk that is inherent in egg-based technology—that the laying hens could become infected with H5N1. HHS also argues that it allows for the possibility of producing the quantities of vaccine that would be needed in a pandemic.

HHS's plan includes short- and longer-term approaches to solving the problem of how to make the vaccine available quickly in the event of an influenza pandemic. In the short run, the procuring of a limited stockpile of vaccines would permit the government to expedite an initial response. But because stockpiled vaccines are made before a pandemic virus emerges, the formulations are not expected to perfectly match the pandemic virus, and they might not provide adequate protection. Moreover, the size of the current stockpile would permit inoculation of only a limited number of people.

HHS's long-term plans to promote the development of the next generation of vaccines—perhaps taking advantage of new methods in biotechnology—would address the problems of capacity shortage and of long production times. However, because developing safe and effective vaccines could take years, perhaps a decade or more, HHS's plan would encourage pharmaceutical manufacturers to start development now so that they are more likely to be able to produce vaccines quickly if a pandemic occurs in the future.

In parallel with those efforts, HHS is funding the development of adjuvants, substances that could boost the potency of the antigen in vaccines, thus reducing the amount of active ingredient needed per dose. Their successful development could affect many areas of HHS's plan. The use of adjuvants for egg-based and cell-based vaccines could allow for the production of more doses of vaccine from existing facilities, and fewer new manufacturing facilities would need to be built. Moreover, smaller stockpiles could be set aside to protect larger numbers of people.

Risks Associated with HHS's Plan

Any program that targets a problem as complex as an influenza pandemic entails risks and costs. The technology for cell production, for example, has been expensive to develop, and building the necessary facilities will require yet more resources. Yet, should technology develop successfully for the next generation of vaccines, the newly refurbished production facilities for egg-based products and the newly constructed facilities for cell-based vaccines would no longer be needed for producing influenza vaccine. The egg-based production facilities could become obsolete and perhaps be discarded while the facilities for cell-based production could be put to other uses.

A strategy of building up egg-based capacity while focusing on next-generation technology could avert some of the expense associated with modernizing the manufacturing technology. The trade-off would come with the possible exposure of the country to risk if the development of next-generation technology vaccines were delayed or never occurred at all.

Governments abroad have chosen different strategies in the face of the possibility of an influenza pandemic. Several member states of the European Union have entered into advance supply agreements with vaccine manufacturers. The governments agree to pay the manufacturers in advance, and the vaccine makers guarantee they will provide a specified number of doses of vaccine within a set period, such as six months. The governments' expectation is that the manufacturers (or the U.S. government) will develop the requisite vaccines and manufacturing technology. Other governments have given much less support for technology development than has the U.S. government. Given that seasonal-influenza vaccine is largely privately purchased in the United States, some analysts have asked whether substantial federal support for technology development is appropriate, especially compared with other governments' investments.

Although the threat of a pandemic on the scale of the Spanish flu of 1918 looms large in public health calculations, public health officials also recall the prospect in 1976 of an outbreak of what was known as the swine flu. In that instance, there was a widely perceived threat, and a federal vaccine program was initiated rapidly (Allen 2007, p. 261; Kolata 1999, pp. 121–185). The government determined it would inoculate 200 million U.S. residents within six months. In the end, some 40 million people received the vaccine, double the number ever vaccinated in a single year. However, the pandemic never appeared, and within months the vaccine became associated in public opinion—possibly incorrectly—with Guillain-Barré syndrome, a rare neurological disorder. The federal government ended up paying $100 million in compensation. Because of that history of premature response and backlash, and because vaccines are drugs that are given to healthy people, the public health community is cautious about introducing new vaccines into the market even in anticipation of a global health threat.

Additional Public Health Questions

The government's role in the vaccine market under HHS's plan also raises important questions for the medical and public health communities about whether the plan provides adequate protection against the threat of a pandemic. For example, HHS will need to ensure that it has mechanisms in place to identify the recipients and distribute the vaccines from the stockpile and from manufacturers as the vaccines are being produced. Policymakers must decide who will pay for pandemic vaccines. Currently, most influenza vaccine is purchased by the private sector. Would the same conditions obtain during a pandemic? Those issues are beyond the scope of this paper, which focuses on the development of new vaccines and the capacity to manufacture them.

CHAPTER

2

Developing New Vaccines

Unlike a good deal of federally funded biomedical research, the work supported by the Department of Health and Human Services to develop new vaccines and new types of vaccine production is product-oriented. The objective of that applied work is to produce vaccines that are more effective and produced faster, more reliably, and in larger volumes than in the past. Rather than seeking to advance knowledge in the general hope that a cure or treatment might eventually emerge, HHS's efforts are directed at taking vaccines through clinical trails to approval for use.

HHS is concentrating on three specific development areas: The first involves the constraints imposed by limited capacity for production, which could be overcome by the use of adjuvants, substances that can be added to a vaccine to boost its ability to produce an immune system response. If manufacturers can develop and use adjuvanted vaccines, they should be able to produce more doses of vaccine with current domestic capacity because each dose can contain a smaller amount of antigen, or active ingredient. The second area of research involves manufacturing influenza vaccines through cell-based technology, which now is in wide use for other kinds of vaccines. The third area focuses on long-term alternatives to current vaccines and their manufacturing processes. That work aims to develop next-generation vaccines, and it includes efforts to reduce the time necessary to produce large quantities of vaccine that would be needed in the event of an influenza pandemic.

Projects supported by HHS are in various stages of development. Some projects have not entered the clinical-trial phase; others in Phase III (the final stage of clinical trials) in the United States have been approved in Europe. HHS hopes to accelerate the typical drug approval process by funding clinical trials and testing to arrive more quickly at the licensing phase. Typically, clinical trials can last five to seven years (see Box 2-1). HHS is encouraging the development of vaccines based on H5N1 (the "bird flu" virus) and other currently circulating virus strains with pandemic potential so that manufacturers gain experience producing pandemic-like vaccines. Then, if a pandemic occurs, HHS hopes that within six months of onset, manufacturers will be in a position to deliver vaccines based on the correct virus strain.

Although this paper considers them separately, in practice it is difficult to distinguish the development of a vaccine from the development of its production facility. The regulatory process requires at least some of the vaccine used in Phase III clinical trials to be manufactured at full-scale production volumes in facilities that meet industry standards for manufacturing. The Food and Drug Administration must approve both the vaccine and the manufacturing facility.

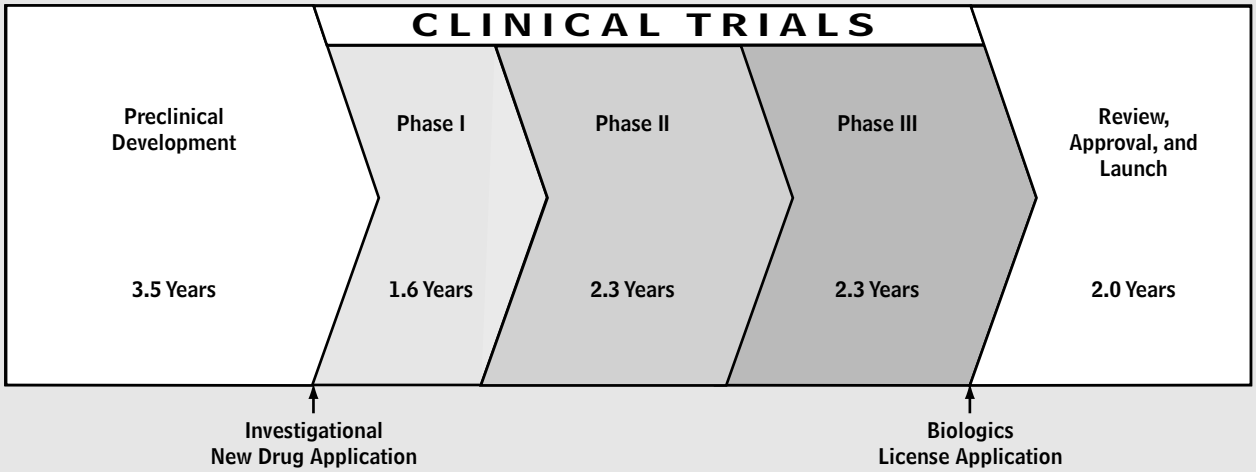
Adjuvanted Vaccines

The pandemic-influenza vaccine that is currently licensed in the United States at best offers poor to moderate protection against the H5N1 virus, even though a course contains 12 times the amount of antigen used to combat a single seasonal-influenza virus strain (Poland 2006). HHS therefore considers the H5N1 vaccine a good candidate for research in adjuvanted vaccines, which offer the promise of requiring smaller amounts of antigen per dose and provide some hope of protection against virus strains that are different from but related to the strain used to make the vaccine.

Successful development of adjuvanted vaccines could affect many aspects of HHS's plan. If they are used with the older egg-based vaccines or with those produced by cell-based techniques, the success of adjuvanted vaccine could mean that a smaller stockpile could protect a larger number of people and that existing manufacturing capacity might be stretched to provide enough vaccine for a larger share of the population.

Box 2-1.

Vaccine Development: Typical Time and Cost



Source: Congressional Budget Office based on Adams and Brantner (2006, 2008); DiMasi and Grabowski (2007); DiMasi, Hansen, and Grabowski (2003); and Struck (1996).

On average, it takes a little over a decade for a drug to move from preclinical development to the marketplace, and it is an expensive undertaking. The cost for clinical trials alone—only a portion of the process—can exceed $100 million. The analysis presented here assumes that the schedules and costs of developing pharmaceutical drugs and vaccines are similar, although industry observers often focus on pharmaceutical drugs, which are chemically synthesized, rather than on biopharmaceuticals, which are derived from living sources. (Influenza vaccines, for example, come from viruses grown in hens' eggs). The Web site of the Food and Drug Administration (FDA) explains the development process for vaccines.[1]

Development Timeline for a Vaccine

Before a vaccine enters human testing, the developer conducts laboratory (in vitro) and laboratory animal (in vivo) testing to determine whether the product will be safe enough for researchers to proceed to clinical trials. The developer must obtain the FDA's approval to begin clinical trials through the submission of an investigational new drug, or IND, application.

Clinical trials typically have three phases. Phase I focuses on the vaccine's safety and generally involves fewer than 100 human subjects. The purpose of Phase II, which typically involves several hundred subjects, is to expand Phase I safety data and identify whether and at what dose the vaccine elicits a protective immune response. Phase III typically involves thousands of people and is used to document effectiveness and develop additional safety data (notably concerning the incidence and severity of side effects) required for licensing. Clinical trials generally last five to seven years. If all three phases of the clinical development are successful, the developer may submit a biologics license application, or BLA, to the FDA for review. If the FDA approves the application, the developer launches the new vaccine, a process that includes training its sales force and increasing production capabilities to meet the anticipated demand.

1. See "Vaccine Product Approval Process," www.fda.gov/Cber/vaccine/vacappr.htm.

Continued

Box 2-1. Continued

Vaccine Development: Typical Time and Cost

Costs of Clinical Trials

Researchers at the Federal Trade Commission have analyzed the cost of clinical trials (Adams and Brantner, 2008). They report that drug trials can cost from $12 million annually at the 25th percentile to $26 million annually at the 75th percentile. That is, in 25 percent of the cases, the manufacturers spent $12 million or less; in 25 percent of the cases, they spent $26 million or more; and in 50 percent of the cases, they spent between $12 million and $26 million per year for a drug in clinical trials. The researchers also reported average spending per drug of $38 million per year (see the table to the right).

The researchers calculated that the total cost to take a drug through clinical trials ranges from $78 million at the 25th percentile to $166 million at the 75th percentile. They also reported that average spending (of $239 million) exceeded spending at the 75th percentile, which suggests that average spending is heavily influenced by a relatively small share of drugs that are very expensive to develop. (The Congressional Budget Office converted the published estimates, which were expressed in 1999 dollars, to 2007 values using the consumer price index for all urban consumers for medical expenditures. That index was used instead of the gross domestic product deflator or the producer price index because medical costs, including the costs of clinical trials, have risen much faster than the rate of inflation.)

The cost of developing influenza vaccines is more likely to fall in the range between the 25th and 75th percentiles than it is to be comparable to average spending for drug development. Other types of clinical trials (those for some cancer drugs, for example) require expensive hospital stays for study participants or involve drugs that are expensive to manufacture. Clinical trials for influenza vaccines, by contrast, are relatively simple: In Phases I and II, subjects are given the flu shot; after a few weeks, laboratory tests determine the blood concentrations of antibodies to the virus, and subjects are assessed for side effects. In Phase III, subjects are given the injection and assessed later to determine whether they have become sick with influenza or have developed any health complications.

Clinical trials account for something between one-fifth and one-third of the total costs of developing a drug. Other expenses include research and preclinical development; opportunity costs incurred by forgoing the return a developer might receive from a different investment; and the costs of drugs that do not proceed through the development and approval process. See CBO (2006b) for a review of pharmaceutical research and development costs.

The Cost of Clinical Trials for an Investigational New Drug, by Percentile

(Millions of dollars)

	Percentile			
	25	50	75	Average
Annual Spending	12	21	26	38
Total Spending	78	127	166	239

Source: Congressional Budget Office based on data reported by Adams and Brantner (2008).

The adjuvanted vaccines currently licensed for use in the United States—against diphtheria, tetanus, hepatitis A, and hepatitis B—are made with aluminum (Vogel and Hem 2004, p. 70). But aluminum adjuvants do not reduce the amount of antigen needed by enough to substantially increase the amount of vaccine that would be available during a pandemic. Some other influenza vaccines formulated with proprietary adjuvants—mainly emulsions containing special oils in water—have shown the ability to allow significant reductions in the amount of antigen required, however, and they might be sufficient to confront the challenge of an influenza pandemic. Even though some of those influenza vaccines formulated with proprietary adjuvants have been approved in Europe,

Table 2-1.

Egg-Based Pandemic-Influenza Vaccines, With and Without Adjuvants

	HHS Obligations (Millions of dollars)	Adjuvant	Dose (Micrograms)[a]	Approval Status[b]
Sanofi Pasteur	0	None	90.0	Approved in U.S.
Iomai	14	Proprietary	45.0	Phase II
GlaxoSmithKline	0	Aluminum	15.0	Approved in EU
Novartis	55	Proprietary	7.5	Approved in EU
GlaxoSmithKline	63	Proprietary	3.8	Approved in EU
Sanofi Pasteur	0	Proprietary	1.9	Phase I
Total	**133**			

Source: Congressional Budget Office based on European Medicines Agency (2007a, b; 2008), HHS (2007a), Iomai (2008a, b), NIH (2008c), and Sanofi Pasteur (2007a, c).

Note: HHS = Department of Health and Human Services; EU = European Union.

a. All vaccines other than that produced by Iomai (which is administered as a combination of a patch and a single injection) are administered in two injected doses. A microgram is one one-millionth of a gram.

b. See Box 2-1 for a discussion of the various steps in the approval process.

the FDA's approval is likely to require the manufacturers to supply additional data on the safety of adjuvanted vaccines. The FDA has not approved a human vaccine containing a new type of adjuvant in many years. Other types of adjuvants have thus far produced too many side effects to meet the FDA's standards, and, in at least one case in Europe, an approved adjuvanted influenza vaccine had to be withdrawn because of its association with Bell's palsy (Kenney and Edelman 2004, pp. 215–216).[1] The FDA's requirements for additional data are likely to increase the costs of development and delay approval.

HHS has awarded contracts, for a total of $133 million, to three companies (GlaxoSmithKline, Novartis Vaccines and Diagnostics, and Iomai Corporation) to support the development of H5N1 influenza vaccines with adjuvants (see Table 2-1). The contracts support work through Phase III clinical trials in the United States aimed at obtaining U.S. licensure for the products. Each company must provide its proprietary adjuvant for government-sponsored, independent evaluation with influenza vaccines from other manufacturers.

Novartis is working on a proprietary adjuvanted H5N1 influenza vaccine that has demonstrated an acceptable immune response when administered in a course of two doses of 7.5 micrograms of antigen each, about one-twelfth the dose of the currently licensed H5N1 vaccine. In May 2007, the European Commission approved the vaccine for use in the event that a pandemic is officially declared by the World Health Organization or the European Union (European Medicines Agency 2007b). The manufacturer will produce a formulation that contains the influenza strain causing the pandemic. Novartis also sells a seasonal-influenza vaccine that contains the same adjuvant that is in its H5N1 vaccine. That formulation is licensed for use in most of Europe in people over the age of 64. Since its approval, about 30 million doses have been distributed (Novartis 2007, p. 39).

GSK also formulated a prepandemic H5N1 influenza vaccine with its proprietary adjuvant. (The vaccine, developed from a virus strain that has the potential to cause a pandemic, is called prepandemic because it would be produced before a pandemic begins. It is intended for use before or in the early stages of a pandemic.) The adjuvanted vaccine was documented to elicit an acceptable immune response when administered in two doses of 3.8 micrograms of antigen each, a 24-fold decrease in the amount of antigen required relative to the currently licensed pandemic vaccine (GSK 2007). In May 2008, the European Commission approved the vaccine (European Medicines Agency 2008). By the end of 2008, the

1. The adjuvant in question belonged to a different family of adjuvants than those discussed for use in a pandemic-influenza vaccine (Couch 2004; Mutsch and others 2004).

company plans to submit the vaccine to the FDA for U.S. approval (Whalen 2008a).

GSK also has a pandemic-influenza vaccine formulated with an aluminum adjuvant.[2] That adjuvanted vaccine, which was approved by the European Commission in March 2007, elicited an acceptable immune response when administered in two doses of 15 micrograms of antigen each, which is one-sixth the dosage of the currently licensed H5N1 vaccine (European Medicines Agency 2007a).

Iomai is developing a skin patch that contains an adjuvant for use in tandem with an injected vaccine formulation; the product is still in the early stages of clinical trials. According to the company, in a recently completed Phase I/II clinical trial, the combination vaccination elicited an acceptable immune response when administered in a single dose of 45 micrograms of antigen, a fourfold decrease in the amount of antigen required relative to the currently licensed pandemic vaccine (Iomai 2008b).[3] Iomai announced in April 2008 that it is working with HHS on a budget for a new Phase II trial (Iomai 2008a).

Sanofi Pasteur currently is funding its own early clinical trials for a vaccine formulated with its proprietary adjuvant. The company stated that, in Phase I clinical trials, the compound elicited an acceptable immune response when administered in two doses of 1.9 micrograms of antigen each (Lewcock 2007c).

HHS has budgeted more funding for the development of adjuvanted vaccines even though only about $5 million of the $133 million obligated to date has been spent. Specific amounts have not been announced, but an agency press release stated that Iomai may receive an additional $114 million in funding upon successful completion of Phase I trials (HHS 2007).

Manufacturers could decide to develop two distinct vaccines: a seasonal vaccine without adjuvants and a pandemic-influenza vaccine with adjuvants. The benefit–risk calculus, and therefore the regulatory landscape, is likely to change in the event of a pandemic. Because of the lower risk associated with seasonal influenza, those vaccines are held to high standards: They must be absolutely safe; extremely well-tolerated; and elicit few, if any, side effects. By contrast, because the risk of illness and death from whatever virus causes a pandemic is much higher, a higher risk of side effects from a vaccine could be acceptable. Adjuvanted vaccines might also be used in the United States, as in Europe, for patient groups that do not respond well to the conventional vaccines against seasonal influenza (for example, elderly people).

Cell-Based Vaccines

HHS's funding for the development of cell-based influenza vaccines is motivated by the potential drawbacks of egg-based production, particularly the need for large supplies of eggs (and the hens to produce them) and specialized manufacturing facilities. According to HHS, the domestic supply would be inadequate in the event of a pandemic, and the specialized manufacturing facilities are not easily duplicated. The egg supply also could be threatened by influenza viruses, including H5N1, that infect poultry flocks.

Cell-based vaccines use antigens from viruses grown in purified strains (or lines) of cells, for example, from the kidneys of dogs. Cell-based production technology is widely used to manufacture vaccines against polio, chicken pox, measles, mumps, and rubella. Policymakers at HHS believe that cell-based production could offer a more reliable and flexible method of producing influenza vaccines that can be scaled up to meet pandemic needs. Unlike eggs, which are perishable and must be ordered months in advance, cell lines can be kept frozen indefinitely, a benefit should it prove necessary to scale up a major manufacturing capability on short notice (HHS 2006c, p. 7).

Some industry analysts believe that HHS's planning emphasis should not be on cell-based production because it does not substantially reduce production times (Matthews 2006). Rather, they believe HHS should focus on bringing next-generation vaccines to market. In addition, some of the cell lines that have the potential to produce large volumes of influenza vaccine also could cause tumors (Homeland Security Council 2006, footnote 16, p. 105).

2. That vaccine is a whole-virus vaccine; seasonal-influenza vaccines licensed in the U.S. are subunit vaccines. Vaccines formulated from whole viruses can be more effective at lower doses, but they also generally cause more side effects (Fukuda and others 2004, pp. 346–347).

3. Phase I/II clinical trials combine the objectives of Phases I and II to examine both the safety of the vaccine and its ability to elicit a protective immune response.

Table 2-2.

HHS's Contract Awards and Development Status for Cell-Based Influenza Vaccines

	Obligations (Millions of dollars)	Vaccine	
		Seasonal	Pandemic
DynPort Vaccine and Baxter[a]	242	Phase III	Phase I
GlaxoSmithKline	275	Preclinical Development	Preclinical Development
MedImmune	169	Phase I	Preclinical Development
Novartis Vaccines and Diagnostics	221	Phase III	Preclinical Development
Sanofi Pasteur	97	Phase II	Phase I
Solvay Pharmaceuticals	299	Phase I	Phase I
Total	**1,302**		

Source: Congressional Budget Office based on Computer Sciences Corporation (2007), HHS (2005a, 2006b), NIH (2008b), Novartis (2007, p. 35), Program for Appropriate Technology in Health (2007, p. 13), Sanofi Pasteur (2007b), and WHO (2007c).

Notes: HHS = Department of Health and Human Services.

See Box 2-1 for a discussion of the various steps in the development and approval process.

a. DynPort Vaccine is the prime contractor; it manages the clinical trials. Baxter is developing the candidate vaccines; it will manufacture the vaccines and own all clinical data and licenses.

To date, HHS has obligated $1.3 billion to promote the development of new influenza vaccines based on cell culture (see Table 2-2). The agency is contracting with several manufacturers in the hope of diversifying and expanding the supply of influenza vaccine for the United States. In the past, dependence on a few suppliers has contributed to shortages of seasonal vaccine when one or another has experienced disruptions in supply. In May 2006, HHS added to the $97 million contract signed earlier with Sanofi Pasteur when it awarded five contracts worth $1 billion in all. To reinforce the commitment, in November 2007 HHS extended its contract with DynPort Vaccine and Baxter International for another $201 million.

The manufacturers are at various points along the path toward approval for cell-based vaccines (see Table 2-2). Some have products that are still in preclinical development; others have cell-based vaccines moving through Phase III clinical trials. Novartis expects to submit an application for a U.S. license in 2008 for a seasonal-influenza vaccine, already approved in the European Union, and to make it available in Europe for the 2008–2009 influenza season (Lewcock 2007a). DynPort Vaccine is managing a Phase III clinical trial for a cell-based seasonal-influenza vaccine and a Phase I clinical trial for a cell-based pandemic-influenza vaccine, both developed and manufactured by Baxter (Computer Sciences Corporation 2007).

Rather than using an adjuvant to cut the amount of antigen needed per dose of vaccine, Baxter's pandemic-influenza vaccine uses the whole virus. Whole-virus vaccines have been shown to be more effective than subunit vaccines that consist of just the purified proteins from the virus. However, because whole-virus vaccines also have been more prone to cause adverse reactions, all injectable seasonal-influenza vaccines licensed in the United States are subunit vaccines.

Baxter is developing another whole-virus, cell-based, pandemic-influenza vaccine that, according to the company, can be produced in three months instead of the typical six months (Ehrlich and others 2008; Wright 2008). Baxter's production process for that vaccine is faster largely because it uses a "wild-type" virus (one that circulates in nature). Other companies first modify the H5N1 virus so it can be grown in eggs without killing the embryo; that modification and the associated safety testing take about two months. The disadvantages of using the wild-type virus include increased risks of infection among production workers and of the virus's escaping the production facility. Thus, facilities for manufacturing wild-type vaccines must meet stricter safety standards than are required for seasonal-influenza-vaccine manufacturing. HHS's contracts support the development of cell-based pandemic vaccines using modified H5N1, but not wild-type, viruses (see Table 2-2).

In general, the vaccines for which HHS is providing support are somewhere between Phase I and Phase II clinical trials (see Table 2-2). Phase II and Phase III studies take a little over two years each (see Box 2-1 on page 10); submitting the product for the FDA's review and launching it in the marketplace can add another year or two.[4] So it is likely to be another six years before most of the companies that were awarded contracts from HHS can complete development of their cell-based influenza vaccines and bring them to market.

Results of a study by researchers at the Federal Trade Commission suggest that manufacturers' expenditures for a single drug in clinical trials typically range between $12 million and $26 million per year, although clinical trials for some drugs can cost much more (see Box 2-1). Those estimates do not include the cost of failures or return on private investment. On that basis, for each successful vaccine, the additional costs incurred in the remaining four years for Phase II and Phase III clinical trials would add between $48 million and $104 million to what is already spent, with a median value of $84 million. On the basis of that calculation, the estimated remaining cost to develop 12 vaccines—one seasonal and one pandemic version of a cell-based vaccine for each of the six companies—is likely to range between $600 million and $1.2 billion.

The $1.3 billion obligated to date could be sufficient to ensure the development of cell-based vaccines. As of January 2008, the contracting companies had requested that HHS reimburse them for $160 million (roughly 12 percent of the total contracts). The contracts' balance of $1.1 billion would cover the remaining costs of clinical trials, as long as those costs do not approach or exceed the high end of the estimated range.

4. Several research groups have examined drug development times, including Adams and Brantner (2006, 2008); DiMasi and Grabowski (2007); DiMasi, Hansen, and Grabowski (2003); and Struck (1996). However, some of that work tracked the development of drugs from as early as 1983, before the enactment in 1992 of the Prescription Drug User Fee Act (PDUFA), which has since been reauthorized several times, most recently in 2007. Many analysts, including Berndt and colleagues (2005) and Abrantes-Metz, Adams, and Metz (2006), concur that PDUFA and its reauthorizations have sped development.

Next-Generation Vaccines

The six months that it takes to produce egg-based or most cell-based vaccines could be too long to respond to an influenza pandemic: Past outbreaks have reached the United States within two to five months of emerging in Asia, and some experts believe that the increase in international travel could facilitate an even faster transmission from abroad. After the egg-based and cell-based techniques, the next generation of vaccine manufacturing, based on the use of recombinant-DNA technology, offers the prospect of increased efficacy, shorter production times, and perhaps broader protection against some or all influenza strains for years or even a lifetime (see Box 2-2), although the vaccines could be 10 years or more away from the market. HHS has yet to fund their development for use against influenza, in part because it has chosen to build on the decades of experience in using cell culture to produce other vaccines.

However, HHS plans to award contracts worth $155 million for the development of next-generation vaccines (Robinson 2007). Even without contracts from HHS, several companies have been working on next-generation vaccines, sometimes with help from agencies within HHS, including the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC). One article in a medical journal in 2007 enumerated 29 next-generation influenza vaccines in development, concluding that the "pipeline for new influenza vaccines is robust" (Belshe 2007, pp. 746, 748). With one exception, however, next-generation vaccines have not advanced past early-stage clinical trials.

The funding of the development of cell-based vaccines and the expansion of egg-based capacity (discussed in Chapter 3) could solidify the hold of those technologies on the market for seasonal-influenza vaccine. Once plants open, it will be difficult for new entrants to compete, unless their costs are markedly below those of existing producers. Increases in capacity could saturate the market and drive down the price of seasonal vaccine, making the market less attractive to newcomers. New technology alone will not be sufficient to increase market share. The newer live influenza virus vaccine, for example, has not captured a significant portion of the market, even though it offers greater cross-protection against different virus strains. It also is administered as a nasal spray, rather than by injection, which can be a benefit to people who find shots unpleasant or painful.

Box 2-2.

What Constitutes the Next Generation of Influenza Vaccines?

Vaccine manufacturers hope to make extensive use of recombinant DNA techniques to produce large amounts of vaccine more quickly than is possible with egg-based or cell-based production. Universal vaccines that protect against a range of strains—or perhaps all strains—could protect the population in advance of an influenza pandemic.

Recombinant Vaccines

Recombinant vaccines are made by splicing antigen-producing genes into the DNA of another organism. The modified organisms then reproduce to provide bulk quantities of antigen (the active ingredient in the vaccine). Recombinant techniques are already in use to make vaccines against hepatitis B and human papillomavirus (CDC 2006, FDA 2006). The hepatitis B vaccine is made by splicing the genes that produce the antigen into plasmids—viruslike DNA molecules—inserting the modified plasmids into yeast cells, and then growing the recombinant yeast cells to produce more antigen. One manufacturer has a recombinant seasonal-influenza vaccine in Phase III clinical trials (NIH 2008a). However, most recombinant influenza vaccines have not yet advanced past early-stage clinical trials.

Universal Vaccines

Even though many vaccines last years or a lifetime, people now must be vaccinated every year to maintain immunity against seasonal influenza. Current influenza vaccines target hemagglutinin, a protein on the surface of the virus, and the vaccines "train" the immune system to react to that protein. Because the hemagglutinin protein changes rapidly as influenza viruses mutate, however, the pattern the immune system tries to recognize is not the same from year to year. Scientists are investigating vaccines that target other proteins that do not change so rapidly and that are present in all strains of influenza. At least one company has reported promising results in Phase I clinical trials (Gray 2008).

To be sure, next-generation vaccines could replace egg- or cell-based formulations if they proved substantially better than current formulations. In some years, the seasonal vaccine does not confer good protection against seasonal influenza because the strains in the vaccine are different from the strains that happen to be circulating that year. The mismatch is the result of the long production timeline, which requires manufacturers and public health officials to choose the strains far in advance of the season. Some next-generation vaccines in development hold the promise of much-shortened production timelines, allowing for the decision about which strains to include in a given year's vaccine to be made much closer to the flu season so as to reduce the probability of strain mismatches.

Even more desirable would be a vaccine that protects against all influenza strains. The hope is that someday it will be possible to be vaccinated just once for a lifetime of immunity against all strains of influenza.

If, in the end, the private sector does not find that next-generation vaccines are an attractive investment, then the federal government probably would need to supply well more than $155 million to bring the new formulations to market. The discussion of development costs in Box 2-1 illustrates the point: Getting one next-generation vaccine through clinical trials could cost well over $100 million, exclusive of the costs of capital or of the costs associated with the failure of a given vaccine to advance to the regulatory finish line of FDA approval. Because the principal characteristics of next-generation vaccines are still largely unknown, it is likely that there will be many failures, which will in turn drive up the costs of bringing those products to market. Moreover, because most next-generation vaccines are still in the earlier stages of development, additional research will be necessary before clinical trials can begin.

International Efforts at Funding the Development of Vaccines

The European Commission funds research on the development of influenza vaccines under its Sixth Framework Programme, which supports a multinational consortium of vaccine specialists who are trying to develop an H5N1 vaccine (Cordis 2007; European Commission 2007). The program announced a grant of $5.5 million.[5] The schedule for the four-year effort calls for clinical trials to begin within two years. The effort is part of a longer program that has spent $102 million on all aspects of influenza research, not just vaccines, since 2001. Of that amount, $55 million has gone to research on vaccines, including some veterinary vaccines. Although CBO has not been able to ascertain the specific funding by individual countries' ministries of health, a BBC News (2006) report stated that Germany is spending $313 million on vaccine development.

5. Values shown are converted from euros at an exchange rate of 1.57 dollars to the euro, the average for May, June, and July 2008.

CHAPTER

3

Investing in New Capacity for Production

Current manufacturing capacity for the only licensed pandemic-influenza vaccine in the United States is about 25 million doses, or enough vaccine to protect about 12.5 million people (see Table 1-4 on page 6). The goal the Department of Health and Human Services set for vaccine production in an influenza pandemic is 24 times the amount available in the United States—manufacturers would have to produce enough vaccine for each of the nation's 300 million people. (In an influenza pandemic, a course of immunization would consist of two doses for each person). Policymakers at HHS do not believe the goal can be achieved solely by expanding capacity for egg-based production. However, because it is the dominant technology, the agency has awarded contracts to domestic manufacturers of egg-based influenza vaccines to substantially expand capacity (see Table 3-1).

Another goal is to shift the production of influenza vaccine from egg-based to cell-based technology. Manufacturers of cell-based vaccines developed under the advanced-development contracts will be eligible for additional funding from HHS to build new facilities. Cell-based technology does not work substantially faster than egg-based methods, however, and shortened production time is another goal of HHS's plan. In the ideal case, HHS calls for the new egg- or cell-based capacity that is being funded today to be retired when next-generation vaccines are ready to come to the market or, in the case of capacity for cell-based production, put to some other use. It is expected that the new vaccines will be produced more quickly than are current formulations and that they will provide broader protection against many or even all strains of influenza viruses.

The process of putting manufacturing capacity into place is more difficult for vaccines than it is for most other drugs. During the final phases of clinical development, the manufacturer must seek approval of the proposed manufacturing facility from the Food and Drug Administration. The vaccine maker also must expand the capacity of its production processes from that used for quantities required in clinical trials to that appropriate for commercial production. The FDA's approval process includes facility inspections and it requires the company to demonstrate that its product elicits immune responses that are consistent from batch to batch. That requirement for dual certification limits manufacturers' flexibility in altering either the process or the facility to boost production. HHS hopes to provide manufacturers with incentives to begin now to assemble new facilities in advance of an influenza pandemic. Then, if a pandemic occurs, the new vaccines can be produced within six months of the onset.

Egg-Based Manufacturing Capacity

HHS has taken several actions to increase domestic capacity for egg-based manufacturing of influenza vaccine. In 2004, the agency signed a $43 million contract with Sanofi Pasteur to ensure a year-round supply of eggs for that company's domestic manufacturing facility, to stockpile other vaccine-manufacturing supplies, and to supply pandemic-influenza vaccine for clinical trials. A year-round supply of eggs makes it possible for Sanofi Pasteur to produce pandemic vaccine even if a pandemic occurs outside of the company's annual production cycle. Because that contract expires in 2008, HHS has requested $42 million for 2009 to maintain a year-round egg supply for the next five years.

In 2007, HHS signed contracts totaling $133 million with two companies (about $77 million to Sanofi Pasteur and $55 million to MedImmune) to retrofit their domestic vaccine-manufacturing facilities. The facility upgrades will allow Sanofi Pasteur to produce prepandemic vaccine for the stockpile year-round. Currently, Sanofi Pasteur

Table 3-1.

HHS's Funding for Capacity to Produce Influenza Vaccine

	Obligations (Millions of dollars)	Duration
Provide Year-Round Egg Supply	43	2004–2008
Retrofit Existing Egg-Based Manufacturing Facilities	133	2007–2012
Build New Cell-Based Manufacturing Facilities	TBD	TBD
Total	**176**	

Source: Congressional Budget Office based on Robinson (2008).

Notes: HHS = Department of Health and Human Services, TBD = to be determined. HHS has not yet awarded contracts to build new facilities for manufacturing cell-based vaccines. HHS has stated that it will award $600 million for that purpose.

produces prepandemic vaccine for the stockpile only during the three months of the year that it is not producing seasonal vaccine. MedImmune does not produce prepandemic vaccine for the stockpile. Its live, attenuated vaccine (made with a weakened form of the virus) against H5N1 has not been successful in early clinical trials (WHO 2008). Furthermore, there is fear that stockpiling prepandemic vaccine made with a live, attenuated virus could increase the chances of a pandemic's occurring by providing the opportunity for a virus with pandemic potential to mix with a seasonal strain, creating a deadly transmissible virus (McKenna 2007a).

Sanofi Pasteur is working to triple its production capacity by 2011. The company is set to pay $25 million of the $102 million cost of retrofitting an existing facility, and it has added a second facility, at a cost of $150 million, to its complex in Swiftwater, Pennsylvania (*Vaccine Weekly* 2007). When both facilities are approved by the FDA—which is expected by 2011—the company's annual production capacity for seasonal-influenza vaccine will approximately triple, from 50 million to 150 million doses of 45 micrograms each. That expected capacity could allow the manufacturer to produce 75 million doses of its licensed pandemic-influenza vaccine, or enough vaccine for about 38 million people (at 90 micrograms per dose for a two-dose course). If the company's experimental adjuvanted vaccine proves safe and effective, then its capacity would increase because the amount of antigen (the active ingredient in a vaccine) it had to produce would drop. For example, its expected capacity would be 450 million doses of an adjuvanted pandemic vaccine (at 15 micrograms of antigen per dose), enough to inoculate 225 million people, but even larger capacity increases are also possible. However, additional manufacturing facilities would still have to be built to produce the adjuvants.

By 2011, MedImmune is expected to have emergency capacity to produce 50 million doses of pandemic vaccine.[1] MedImmune's manufacturing facility in the United Kingdom produces bulk seasonal-influenza vaccine for the U.S. market, but it prepares the seasonal seed strain at its facility in California. MedImmune will use its award to retrofit its California facility to produce bulk quantities of pandemic-influenza vaccine in case of an emergency. The company will contribute $14 million to the project.

The contract also included options in later years that would keep the new capacity in reserve and ready to produce in the event of a pandemic by manufacturing at least one commercial-scale lot of vaccine each year to maintain licensure. The size of a lot depends on the facility, but typically it would be hundreds of thousands of doses. The cost of production in the contract is about $15 million per year for a capacity of 50 million doses of pandemic-influenza vaccine.

Cell-Based Manufacturing Capacity

Each of the six companies that won advanced development contracts for cell-based vaccines was required to commit to establishing a U.S.-based cell-manufacturing facility with a production capacity of at least 150 million doses of pandemic-influenza vaccine within the first six months after the onset of a pandemic, although the awards do not cover the cost of building new manufacturing facilities.

HHS does not expect that each of the six contracts will lead to additional capacity that can produce 150 million doses of pandemic-influenza vaccine. Instead, it forecasts the possibility of a total of 475 million doses from the

1. MedImmune is not developing an adjuvant. That company's vaccine uses a live, attenuated virus (a weakened form of the virus), which reduces the amount of antigen needed per dose.

additional domestic capacity, and it plans to award additional contracts totaling $600 million to the most successful companies. That funding will defray the costs of building new facilities for cell-based manufacturing.

Because the expanded capacity would not be needed to meet the demand for seasonal vaccine, some government funding would probably be required to induce producers to build more factories. The contracts for retrofitting the egg-based production facilities involve cost sharing between the government and the two companies, each of which would provide at least 25 percent of the total cost. HHS has said that the contracts for cell-based vaccine facilities will require manufacturers to provide a higher percentage.

Initial Costs

Production facilities for cell-based influenza vaccine are newly under construction, so estimates of the cost to build and obtain the FDA's approval should be considered preliminary. According to the company, the Novartis plant in North Carolina will cost more than $600 million and will have a production capacity of 50 million doses of seasonal vaccine (Lewcock 2007b; Whalen 2006). That estimate includes the cost of bringing the plant online and the cost of seeking the FDA's approval for the facility, which can take two years. Other industry sources have estimated a cost of about $320 million—bringing the plant online and obtaining the FDA's approval would add to that total—to build a plant with an annual capacity of 50 million doses of cell-based seasonal vaccine. On the basis of discussions with industry experts, CBO anticipates that bringing the plant online and submitting to the FDA's approval process would add 25 percent to the capital cost of that plant, making the total cost about $400 million.

Most vaccine producers are developing adjuvants, substances that can be added to vaccine formulations to reduce the amount of antigen needed per dose. (The first calculations that follow assume that the use of adjuvants will cut the amount of antigen needed from 90 micrograms to 15 micrograms per dose for the pandemic-influenza vaccine.[2]) That amount, which equals the amount of antigen for each strain of seasonal-influenza vaccine, is easily being bested in published clinical trials (see Table 2-1 on page 12). To the extent that producers achieved a larger antigen savings than assumed, the costs described here would overstate the cost of the program.

A plant with a capacity of 50 million seasonal-influenza doses (45 micrograms per dose) could produce 150 million pandemic-influenza doses at 15 micrograms per dose. It would take about three plants with that capacity to produce 475 million doses. If the cost of construction, bringing the plant online, and obtaining the FDA's approval averaged $400 million per plant, the total cost of the expanded capacity would be $1.2 billion. If each plant cost $600 million, the total would be $1.8 billion.

HHS's goal of diversifying the sources of the U.S. influenza vaccine supply would be met if, in addition to the existing domestic plants that produce egg-based vaccines, three plants were built for cell-based manufacturing. The nation's reliance on a small number of manufacturers has resulted in several recent disruptions in supply. If adjuvants fulfill the promise of sharply cutting the amount of antigen needed for pandemic-influenza vaccines, policymakers might face a choice between reducing the cost of the program and ensuring a diversity of supply.

If no adjuvanted vaccine proves safe and effective, then the initial costs of construction would rise substantially. It would take 19 plants, rather than 3, to produce 475 million doses (at 90 micrograms of antigen per dose). The initial costs of construction would rise proportionately, to between $7.6 billion and $11.4 billion.

In either case, it is unlikely that enough capacity could be available in time to meet the target date of 2011. Only Novartis has begun construction of a domestic facility for making cell-based vaccine. The company anticipates its plant will be in operation by 2012 and will have an annual production capacity of 50 million doses of seasonal vaccine (Pink Sheet 2007). MedImmune has announced its intention to convert an existing plant in Frederick, Maryland, that currently manufactures monoclonal antibodies into a manufacturing facility for seasonal-influenza vaccine that would serve domestic and international markets with an expected capacity of 50 million to 60 million doses of cell-based seasonal vaccine. The influenza vaccine operations are unlikely to begin before 2012–2013. GlaxoSmithKline has purchased a vaccine-manufacturing facility in Pennsylvania that it plans to modernize to develop and produce

2. HHS uses that assumption in its contracts for expanding egg-based capacity (HHS 2006a). However, in other planning, HHS has assumed that different amounts of antigen would be required for pandemic-influenza vaccine (Robinson 2008).

cell-based seasonal- and pandemic-influenza vaccines (Megget 2007). Sanofi Pasteur, Baxter, and Solvay have not announced plans to manufacture cell-based vaccine in the United States.

Continuing Costs

If U.S. demand for seasonal-influenza vaccine grows by 4 percent per year (continuing the trend observed from 1999 to 2006; see Figure 1-2 on page 4), demand will reach nearly 130 million doses of vaccine by 2011. By itself, Sanofi Pasteur's projected capacity for egg-based vaccine, at 150 million seasonal doses by 2011, would exceed projected U.S. demand. So if all the new capacity for manufacturing egg-based and cell-based vaccines were built as called for by HHS, there would be excess capacity to serve the domestic demand for seasonal vaccine.

Cell-based technology might have technical advantages over egg-based production, but its economic advantages are less clear; the resulting vaccines could be more expensive for the near term (Lash and Wang 2006). Plants that manufacture cell-based vaccines will have alternative uses; plants that make egg-based formulations do not. Consequently, unless they have some federal incentives to remain, the excess capacity in the seasonal-influenza vaccine market could drive manufacturers of cell-based vaccine from the market first. If the costs for cell-based production facilities to remain in reserve are similar to those for producers of egg-based vaccines—$15 million annually per 50 million doses—then the capacity to produce 475 million cell-based doses of pandemic-influenza vaccine would cost about $140 million per year to remain operational at 15 micrograms per dose. If no company developed adjuvanted vaccines, the continuing costs would be about $850 million at 90 micrograms per dose.

Purchases of vaccine for the stockpile could go a long way toward supporting the reserve capacity. It could cost between $350 million and $1.1 billion annually to purchase replacement vaccine for the stockpile as the contents expired (as described in Chapter 4). The new manufacturing capacity also could be supported through exports of seasonal vaccine and through increased domestic demand for seasonal vaccine.

Some experts have suggested that the additional cell-based production facilities could be used to manufacture other products during years when there is not an influenza pandemic. Then, if a pandemic did occur, a plant could switch to manufacturing vaccine against the pandemic-influenza strain. The caveat about dual-use facilities involves safety. Manufacturing facilities would have to be cleaned to prevent cross-contamination and then subjected to a new FDA approval process, which could easily take months. If HHS's objective of a maximum delay of six months from the identification of a pandemic to the inoculation of the public is to be met, the recertification process could prove impractical. It also might not be cost-effective to build dual-use facilities that required specialized equipment and processes for the manufacture of different products.

International Efforts to Build Capacity

An alternative way to encourage private-sector construction of capacity is for governments to sign advance supply agreements with producers. The Department of Health in the United Kingdom has agreements with several suppliers to deliver 150 million doses of vaccine as soon as possible in the event a pandemic is identified (Donaldson 2006). The French government has an agreement with Sanofi Pasteur to deliver 28 million doses of vaccine in the event of a pandemic, and Italy has signed agreements for 36 million doses of vaccine (BBC News 2006; Sanofi Pasteur 2006). Several other countries also have signed such agreements. Although the terms have not been revealed, the Canadian government has signed an agreement with GSK, which has a plant producing influenza vaccine in Quebec. There is no public information about whether the companies have the capacity to produce the vaccines promised in the advance supply agreements.

The European and U.S. strategies for developing and maintaining capacity entail costs and risks. Under the European approach, the manufacturers might not have the capacity to fulfill the advance supply agreements in the event of a pandemic. And despite the U.S. subsidies for vaccine development and capacity building, in the event of a pandemic, the United States would not have a committed supply and would have to spend additional money to buy vaccine. Moreover, the manufacturers could exhaust their supplies in the act of meeting their obligations under the European advance supply agreements and have nothing left to distribute in the United States.

The World Health Organization has made several small grants to help build vaccine-manufacturing capacity in very poor countries (P. Taylor 2007). The funding is limited ($2 million to Thailand, for example) and is not

likely to be adequate to support new production facilities. Total funding for such construction in all countries is $18 million, $11 million of which is provided by HHS.

Private companies also are increasing their investments in other countries in response to the growing demand for seasonal-influenza vaccines. Microbix, a Canadian company, has just signed a contract to build a $200 million manufacturing facility in China (N. Taylor 2008a). The project will be jointly financed by the company and the government of China, which has indicated an interest in increasing its seasonal vaccination rate from the current 2 percent to 20 percent of its population. Sanofi also recently completed building a manufacturing plant in China (Whalen 2008b), and press reports indicate that the other major companies hope to garner a share of that market. More generally, Sanofi is expanding its worldwide capacity and has launched a multiyear, multi-billion-dollar construction effort to create vaccine-manufacturing capacity against a variety of diseases, including influenza (N. Taylor 2008b).

CHAPTER

4

Stockpiling Vaccine

One goal of the Department of Health and Human Services' plan for an influenza pandemic is to stockpile—as soon as possible and within the constraints of industrial capacity—enough vaccine to immunize 20 million people against the strains that present a pandemic threat (HHS 2005b, p. 24). It is far-fetched to think that a prepandemic vaccine—so called because it is produced before the onset of a pandemic—would be a perfect match for the virus causing the pandemic, but policymakers and public health officials hope that it would offer at least some protection to people who are essential to maintaining security; to health care providers; to those who provide essential products and services; and to infants, young children, and pregnant women before a vaccine specific to the pandemic can be produced.[1]

Since 2004, HHS has obligated more than $950 million to procure roughly 26 million doses of prepandemic-influenza vaccine (90 micrograms of antigen per dose) for the stockpile (see Table 4-1). The stockpile is intended to meet changing threats to public health; as new influenza strains are identified as having the potential to cause a pandemic, they will be added to the stockpile. So far, HHS has stockpiled vaccines against two variants of the H5N1 virus, the "bird flu." The first variant, called clade 1, consists of the virus that is circulating in Cambodia, Thailand, and Vietnam. The second, clade 2, consists of the virus circulating in China and Indonesia (WHO [no date]). (A clade is a group of viruses descended from a single ancestor.) Although HHS currently is treating the stockpile as one entity, the cost of stockpiling vaccine would rise if it was determined that each strain required a separate stockpile with enough vaccine to immunize 20 million people.

At two doses per course (the recommendation for pandemic-influenza vaccine), the stockpile would hold enough to inoculate about 13 million people. Because there already are standards for how long seasonal-influenza vaccines can be stored, HHS has begun studies to determine how long the stockpiled prepandemic vaccines can be counted on to be safe and effective. Currently, HHS assumes a two-year shelf life, which is consistent with industry data for the shelf life of seasonal-influenza vaccine. About 15 million of the 26 million doses in the stockpile have already expired or are now reaching expiration, so the approximately 11 million doses left in the stockpile would be enough to inoculate only about 5.6 million people.

Production of vaccine for the stockpile currently is limited to the three months of the year when the manufacturers are not making seasonal-influenza vaccine. However, HHS has signed a contract with Sanofi Pasteur to retrofit its domestic vaccine-manufacturing facility so it can produce prepandemic-influenza vaccine year-round for the stockpile.

Cost to Complete and Maintain the Stockpile

Several factors drive the cost of completing and maintaining the stockpile: the ability of adjuvants to reduce the amount of antigen needed in a dose of vaccine, the shelf life of stockpiled antigen and adjuvants, and the number of virus strains against which stockpiles must be established.

1. For a listing of the priority groups, see "Draft Guidance on Allocating and Targeting Pandemic Influenza Vaccine," www.pandemicflu.gov/vaccine/prioritization.html.

Table 4-1.

U.S. Stockpile of H5N1 Vaccine, by Year of Purchase

(Millions of doses)

	2004	2005	2006	2007	Total
Clade 1	0.5	7.1	0.9	0	8.4
Clade 2	0	0	6.4	11.2	17.6
Total	**0.5**	**7.1**	**7.4**	**11.2**	**26.0**

Source: Congressional Budget Office based on Robinson (2008).

Note: H5N1 is the virus that causes the "bird flu." A clade is a group of viruses descended from a single ancestor. One dose contains 90 micrograms of antigen. (A microgram is one one-millionth of a gram; antigen is the vaccine's acitve ingredient). Influenza vaccine typically expires after two years; 15 million doses have expired or will expire soon.

Stockpiling Adjuvanted Vaccines

Most of the vaccine in the stockpile is being stored in bulk at company sites. From there, it must be put into its final formulation and packaged for shipping to doctors' offices and clinics. Part of HHS's plan for a response to an influenza pandemic includes the use of any available adjuvants; the agency wants to be able to consider adjuvanted vaccines as it determines optimal dosage.

If the use of adjuvants substantially reduced the need for antigen, the current stockpile could surpass HHS's goal of providing enough for 20 million people. If adjuvants made it possible for a dose to consist of 15 micrograms of active ingredient—which would match the amount for each strain of seasonal-influenza vaccine—rather than the 90 micrograms called for with the pandemic-influenza formulation, then the 11 million doses remaining in the stockpile could be stretched to 66 million, or enough to inoculate about 33 million people. In that event, the stockpile would not need to be made larger, although adjuvant would have to be produced and purchased.

Like the vaccines they augment, adjuvants have a limited shelf life—HHS assumes that adjuvants will expire after three years. On the basis of information from the agency, CBO estimates that it would cost $350 million per year to replace expiring antigen and adjuvants with enough new material to maintain a stockpile for 20 million people through 2020, assuming 15 micrograms of antigen per dose. However, the costs would be less if HHS determined that the stockpiled antigen had a longer shelf life: If it lasted three years instead of two, the cost of annual maintenance would drop to about $300 million.

Because adjuvants are not stand-alone drugs, approval by the Food and Drug Administration for adjuvanted versions of the vaccines already in the stockpile would be contingent on completion of additional clinical trials (some are in the planning stages). If the stockpiled vaccines and the adjuvants were made by different companies, however, additional hurdles could arise concerning intellectual property rights (McKenna 2007b). However, if an influenza pandemic were to occur, the FDA could permit the use of unlicensed adjuvanted vaccines even if they had not completed the full cycle of clinical trials. Unlicensed vaccines could be administered under an emergency use authorization or under FDA's Investigational New Drug provisions (Lister 2007, p. 30).

Stockpiling Vaccines Without Adjuvants

If there is no success in using adjuvants to substantially cut the amount of antigen required, then about 29 million doses of vaccine will be needed to complete the stockpile. Information from HHS indicates that the cost would be about $1.1 billion. However, if HHS found that the stockpiled antigen had a shelf life longer than two years, that cost would be reduced. For example, if antigen could be kept in the stockpile for three years, the cost of completing the stockpile would fall to about $790 million. After completion, it would cost about $1.1 billion annually to replace expired antigen and to maintain a stockpile for 20 million people through 2020.

Additional Considerations

The vaccine in the stockpile is a combination of vaccines made from different strains of the H5N1 virus. Vaccine made from one strain might not provide protection against viruses from different strains. If HHS maintained a stockpile of vaccine for 20 million people for each circulating strain then the cost of the stockpiles would rise. For example, it would cost about $2.2 billion annually for HHS to maintain a complete stockpile for two circulating strains without adjuvants and about $700 million annually with adjuvants.

The results of recent studies show that adjuvants can increase the ability of influenza vaccines to protect against viruses from different but related virus strains that are not contained in the vaccine (WHO 2008). Thus, if adjuvants can be used with the stockpile, the number of virus

strains against which stockpiles must be built can be reduced (WHO 2007b).

The annual cost of maintaining the stockpile would be greater than the cost of funding reserve capacity. Instead of paying $160 million to $870 million per year in subsidies to keep the additional capacity for egg-based or cell-based production ready, most of that excess capacity could be used to produce vaccine for the stockpile, at an additional annual cost of $350 million to $1.1 billion.[2] However, not all of the reserve capacity would be suitable for making vaccine for the stockpile (see Chapter 3).

International Efforts to Stockpile Vaccine

The World Health Organization has proposed a global stockpiling plan that would focus on developing nations, mostly those without domestic manufacturing capacity or sufficient resources, to purchase vaccines from abroad (Lewcock 2007d). Several manufacturers (Baxter, GlaxoSmithKline, and Sanofi Pasteur) have pledged to donate or sell at a discount millions of doses of pre-pandemic vaccine over the next several years. As with the domestic stockpile, the success with adjuvants will determine the number of people who can be immunized. In addition, like policymakers in the United States, WHO will have to decide what to do about stored, but expired, vaccines.

Individual countries are procuring stockpiles, although many more are planning to rely on advance supply agreements (Mounier-Jack, Jas, and Coker 2007, p. 925). The United Kingdom's Department of Health (2008) has announced that it is stockpiling 3 million doses; France and Italy have announced plans for stockpiling 2 million doses each (Mackenzie 2005). In all, those supplies would contain enough vaccine to inoculate about 2 percent of the populations of those countries. By contrast, Ireland has announced its intention of creating a stockpile of 8.5 million doses, and Austria has signed a contract for 16 million doses; enough in each case to inoculate the entire population of the country (Raymond 2006). The amount in the stockpiles, relative to the size of the population, varies greatly from one nation to another, and different countries could be purchasing vaccine with different amounts of antigen per dose.

2. Of the total, $15 million per year would go to subsidize capacity for producing egg-based vaccine; the balance of roughly $140 billion to $850 billion annually would support expanded capacity for production of cell-based vaccine (see Chapter 3).

CHAPTER

5

Options for Modifying HHS's Plan

The vaccine component of the plan developed by the Department of Health and Human Services in 2005 would provide some amount of immediate insurance against an influenza pandemic, more protection when vaccines produced with cell culture technology are approved and facilities are built, and at some point in the indefinite future a much-reduced risk if next-generation vaccines are successful. This analysis by the Congressional Budget Office indicates that additional spending will be necessary for the indefinite future and that it is unlikely that the objective of providing enough vaccine to immunize 300 million people will be met by 2011. The environment in which the original plans were made has changed in at least one important regard: Policymakers have more information today than they did in 2005 when the plan was formulated. In particular, the likelihood has increased that adjuvants could be used to reduce the amount of antigen needed to provide immunity. That information raises several questions about whether the course of current policy is the most cost-effective and whether it should be altered:

- Does progress in developing adjuvanted vaccines suggest that the current plan supports too much expansion of production capacity?
- In light of the prospects for adjuvanted vaccines, would providing more support for early and advanced development for next-generation vaccines ultimately provide more protection against an influenza pandemic?
- Should the United States consider adopting a strategy similar to that of several governments in the European Union? (Instead of giving direct government support to new production facilities, some European governments have entered into advance supply agreements to purchase vaccine in the event of an influenza pandemic.)
- Does the prospect of successfully developing an adjuvanted vaccine change the optimal size of the stockpile of prepandemic vaccines?

Adjuvanted Vaccines and Adequate Capacity

One option HHS might consider if adjuvanted vaccines fulfill their promise is to reduce targets for domestic cell-based manufacturing capacity. Such a reduction could initially save $600 million that HHS has budgeted for the construction of the facilities, and it could reduce the spending that will be necessary to keep manufacturers in a state of readiness.[1]

European regulatory authorities have approved adjuvanted vaccines against seasonal and pandemic influenzas. Drug companies are reporting encouraging results for other adjuvanted influenza vaccines in clinical trials in Europe and the United States. The arithmetic of pandemic vaccination changes dramatically, as discussed in Chapter 2, if adjuvanted vaccines are developed and approved. An extrapolation of the results from clinical trials leads to the preliminary conclusion that, by 2011, domestic egg-based manufacturing could produce enough antigen within six months of the onset of a pandemic to immunize 225 million people with adjuvanted vaccines at 15 micrograms per dose. Data from the most successful clinical trials for adjuvanted vaccines show that the projected U.S. capacity would make it possible to produce enough antigen within six months of the onset of a pandemic to immunize the U.S. population several times over. However, if adjuvanted vaccines were not used, the projected capacity could produce enough antigen

1. Although HHS has budgeted $600 million to offer capital subsidies to manufacturers to build cell-based production facilities, no contracts have been signed as of this writing.

only to inoculate about 38 million people (see Table 2-1 on page 12).

In light of that wide range of estimates of the possible domestic volume of production for egg-based vaccines, it might be prudent for the federal government to slow its support for additional capacity and focus more effort on developing adjuvants. If adjuvant development is successful, the capacity for egg- or cell-based production that is currently available or under construction would be enough to meet HHS's goal of vaccinating every U.S. resident within six months of the onset of a pandemic. If development is not successful, however, the current plan for $600 million in subsidies would be just a fraction of the $7.6 billion to $11.4 billion needed to build enough cell-based production capacity to meet HHS's goal.

Current and announced capacity already exceeds what could be supported by demand for seasonal vaccine. Creating additional (possibly unneeded) capacity could compound the risk that the industry would expand too much and then would need to contract, with the result that some companies would exit the market, as has occurred in the past.

Such a change in policy would come with risks, however. The decision not to support the building of new plants for cell-based production would leave the domestic supply still concentrated in a few facilities that are producing egg-based vaccine. Contamination of just one facility or of associated poultry flocks during an influenza pandemic could grievously hamper the federal response and leave the U.S. population at risk. Although manufacturers adhere to strict practices to ensure that their flocks are protected from disease, the risk remains. Adjuvants would lessen that risk, however, because their use would mean there is less capacity and fewer flocks to protect.

Creating additional capacity to produce cell-based vaccines would improve the government's ability to immunize people who cannot be vaccinated with adjuvanted vaccines. If even a fraction of people required the unadjuvanted vaccine, the supply of antigen could be quickly exhausted. Policymakers could conclude that the side effects from adjuvants, which to date have been minor, are outweighed by the need to immunize a majority of the population. But such a decision would be likely to reduce compliance.

HHS could be optimistic in its goals for manufacturing capacity for cell-based vaccine, in any event. The manufacturers have had incentives to develop adjuvanted prepandemic vaccines in order to win premium-priced contracts from governments around the world for vaccine stockpiling. Absent a market in which to sell the additional seasonal cell-based vaccine, large federal subsidies are likely to be needed to support construction of such facilities, an eventuality that might require additional appropriations.

Next-Generation Vaccines

Next-generation vaccines are needed to reduce the production time required to manufacture the current set of vaccines. Development of adjuvanted vaccines also could have implications for the resources devoted to next-generation vaccines and for the mechanisms the government chooses to accomplish its objectives. Specifically, if adjuvanted vaccines reduce the near-term risk posed by an influenza pandemic by stretching the available and the planned capacity, then resources might be available to support more development of next-generation vaccines. Moreover, there might be enough time to work through markets to use guaranteed purchases or other mechanisms to promote the development of next-generation vaccines, where manufacturers with successful products would be ensured sales into the stockpile.

However, policymakers cannot count on easy and rapid success with next-generation vaccines. Those formulations are, in many cases, based on truly novel concepts and are largely in the early stages of development. It is likely that there will be many failures, which will prolong the process and increase the costs of bringing those products to market.

Advance Supply Agreements

European governments have chosen to enter into advance supply agreements with companies to provide vaccine in the event of a pandemic. The U.S. approach differs: Policymakers here have chosen to provide direct support to manufacturers for the development of vaccines and the construction of new production facilities. The U.S. government could consider entering into advance supply agreements, which are seen in Europe as economically attractive because each side can concentrate on what it does best: Governments track public health needs, and businesses develop vaccines and manufacturing facilities.

Also, with the advance supply agreements, the governments actually purchase some specified amount of vaccine for their populations. The U.S. government, in contrast, would not have a committed supply of vaccine and would need to spend additional funds to acquire vaccine for an influenza pandemic. Companies may have to fulfill the European advance supply agreements first before selling vaccine to the United States, possibly exhausting their supplies. It might be necessary for the United States to structure agreements to recognize that other nations' governments could temporarily restrict or prohibit exports of pandemic-influenza vaccine until their own populations have been immunized. Even if the United States enters into advance supply agreements, there remains the risk that manufacturers will not have the capacity to fulfill those agreements.

Some analysts question the ability of advance supply agreements to stimulate the development of technology, especially given the lengthy process of ushering vaccines through approval. The European governments, they argue, are beneficiaries of U.S. efforts in technology development. Other analysts point to Sanofi Pasteur's independent development of an as-yet-unapproved adjuvant as one example of technology development that occurs in response to government demand (in this case for the national stockpiles) but without direct subsidies.

The Size of the Stockpile

The potential success of adjuvanted vaccines could provide a rationale for HHS to reconsider the size of the stockpile. The current policy calls for building and maintaining a stockpile of prepandemic vaccines large enough to immunize 20 million people. In the event of a pandemic, that supply would be distributed first to health care workers and first responders; to providers of public safety and critical infrastructure; and to infants, young children, and pregnant women.

Determining the optimal size of the stockpile poses a challenge for a variety of reasons that are related to the public health risks that the stockpile is designed to reduce. The current goal of 20 million doses for the stockpile could be too large or too small: If, for example, the strain that causes the pandemic influenza does not respond to the stockpiled vaccine formulation, the stockpile could be wastefully large. But it could be too small if a pandemic were to spread through the population more quickly than new vaccines could be manufactured. The size of the stockpile, moreover, is linked to other elements of the HHS plan that are related to antiviral drugs, medical supplies, and state and local preparedness measures.[2]

Successful development of adjuvanted vaccines could alter the balance of risks in determining the size of the stockpile and potentially reduce the cost of mitigating those risks. Some recent research indicates that adjuvanted vaccines could provide protection against more than one strain of potential pandemic virus, thereby improving the chances that the vaccines in the stockpile would be effective in a pandemic. Moreover, because adjuvants would reduce the amount of antigen required to immunize any target population, HHS either could retain its current goal of maintaining a stockpile sufficient to inoculate 20 million people while reducing the amount of stockpiled antigen or expand the number of people that could receive the prepandemic vaccine. Doing the latter would reduce the risk that a pandemic would move through the population more quickly than new vaccines could be manufactured, and it might provide enough protection in the population to reduce the severity of the pandemic.

2. For a discussion of the likely interactions of various public health policies during a pandemic, see Ferguson and colleagues (2006).

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