CONGRESSIONAL BUDGET OFFICE
U.S. Congress
Washington, DC 20515

May 22, 2006; revised July 27, 2006

Honorable William H. Frist, M.D.
Majority Leader
United States Senate
Washington, DC 20515

Honorable Judd Gregg
Chairman
Committee on the Budget
United States Senate
Washington, DC 20510

Dear Senators:

In December 2005, at the request of the Senate Majority Leader, the Congressional Budget Office (CBO) prepared an assessment of the possible macroeconomic effects of an avian flu pandemic. In its assessment, CBO also described the nation's preparedness for addressing a possible pandemic.

In response to your request, CBO has updated its December assessment, focusing in particular on changes in the level of preparedness. The details of CBO's current analysis are contained in the attachment to this letter.

CBO would be pleased to address any further questions you might have. I can be reached at (202) 226-2700, and Joseph Kile, who is the staff contact on this project, can be reached at (202) 226-2940.

Sincerely,

Donald B. Marron

Donald B. Marron
Acting Director

Attachment

cc: Honorable Kent Conrad
Ranking Minority Member
Committee on the Budget

Honorable Harry Reid
Minority Leader
United States Senate

Honorable J. Dennis Hastert
Speaker
U.S. House of Representatives

Honorable Nancy Pelosi
Minority Leader
U.S. House of Representatives

A Potential Influenza Pandemic: An Update on Possible Macroeconomic Effects and Policy Issues

May 22, 2006; revised July 27, 2006

This revision incorporates corrected estimates of the overall impact of a potential flu pandemic on gross domestic product: about 4-1/4 percent in the severe scenario and about 1 percent in the mild scenario.

The Congress of the United States ■ Congressional Budget Office

In December 2005, at the request of the Senate Majority Leader, the Congressional Budget Office (CBO) prepared an assessment of the possible macroeconomic effects of an avian flu pandemic.[1] In its assessment, CBO also described the nation's preparedness for a pandemic and options for increasing preparedness. At the request of the Majority Leader and the Chairman of the Senate Budget Committee, CBO has undertaken this update to its earlier work, focusing on changes in the budgetary and economic aspects of the nation's preparedness.

Although a pandemic could be caused by any of several influenza strains, scientists are particularly worried about H5N1, a strain that has caused repeated epidemics with high mortality among poultry in Asia; has spread from Southeast Asia to flocks in Central Asia, Europe, and Africa; and has made the jump from birds to humans, causing the deaths of over 120 people. Infectious diseases are unpredictable, so it is impossible to say for sure whether a new pandemic will arise; whether it will involve the H5N1 virus; and, if it does, when it will happen and whether it will be mild or severe. The H5N1 virus could mutate in a way that causes a severe pandemic next year or a mild epidemic in a decade or two. Or it could evolve in a way that renders it harmless. Or a pandemic could arise from an entirely different virus subtype.

Since CBO's earlier assessment in December 2005, a number of developments have occurred:

- Several studies of the macroeconomic impact of an influenza pandemic have been released, providing estimates that span a wide range and thereby highlight the considerable uncertainty involved. In December, CBO estimated that a severe influenza pandemic (similar to the one that began in 1918) might cause a decline in U.S. gross domestic product (GDP) of about 4-1/4 percent and that a milder pandemic (similar to those that occurred in 1957 and 1968) might reduce GDP by about 1 percent, relative to what would have happened otherwise. One recent study, notable in that it analyzes economic data from past pandemics, suggests that the impact of a 1918-style pandemic would be milder than what CBO and others have estimated.

- The Congress provided $3.8 billion in funding for pandemic influenza preparedness for fiscal year 2006 through an emergency supplemental appropriation added to the defense appropriation bill in December 2005. Of that amount, $3.3 billion was provided to the Department of Health and Human Services (HHS). For the most part, those funds have been allocated in line with the Administration's request, although more than the amounts

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1. See Congressional Budget Office, *A Potential Influenza Pandemic: Possible Macroeconomic Effects and Policy Issues* (December 8, 2005).

requested have been provided to state and local governments to plan their responses to an outbreak of a pandemic influenza. The Congress has not yet made decisions about an additional $3.5 billion requested by the Administration for 2007 and 2008.

- The Administration's policy continues to emphasize efforts to produce enough vaccine within six months of a pandemic outbreak to inoculate the entire U.S. population. By May 2006, HHS had taken the first steps to meet that goal by 2011 by contracting with six vaccine manufacturers to plan and develop new production capability.

- The Administration's *National Strategy for Pandemic Influenza: Implementation Plan*, issued in May 2006, reaffirms plans to stockpile vaccines sufficient to inoculate 20 million people against pandemic influenza.[2] At the current time, 4 million courses of H5N1 prepandemic vaccines have been ordered. Preparedness activities also include steps to increase the domestic production capacity of vaccines, increase the availability of antiviral and other drugs, and improve the response of state and local governments and the health system.

- The Public Readiness and Emergency Preparedness Act, enacted in December 2005, provides broad liability protection for manufacturers and others with regard to products to combat pandemic influenza and extends those protections to other medical countermeasures.

Macroeconomic Effects

In December, CBO estimated that a severe influenza pandemic (similar to the one that began in 1918) might cause a decline in U.S. GDP of about 4-1/4 percent and that a milder pandemic (similar to those that occurred in 1957 and 1968) might reduce GDP by about 1 percent, in comparison to what it would have been in the absence of a pandemic. In each case, economic activity would probably snap back once the pandemic ended, as consumers increased spending and businesses increased production to meet pent-up demand.

Several estimates of the macroeconomic impact of an influenza pandemic have been released since CBO's assessment was published. Some find effects that are larger than CBO's. For example, a study by Steven Kennedy, Jim Thompson, and Petar Vujanovic estimates that a pandemic with total mortality of roughly one-third of what occurred in 1918 would reduce Australian GDP by nearly 6 percent,

2. Homeland Security Council, *National Strategy for Pandemic Influenza: Implementation Plan* (May 2006).

relative to a base case without a pandemic.[3] Moreover, some medical experts, stressing the uncertainty about the exact characteristics of the potential virus, suggest that the worst-case scenario could be much worse than the severe scenario that CBO considered, especially if the H5N1 virus acquires the ability to spread efficiently among humans without losing its extreme virulence.

Other studies estimate effects on the economy that are roughly the same size as CBO's. For example, Warwick McKibbon and Alexandra Sidorenko, using an econometric model of the world economy, estimate that a severe influenza pandemic might reduce GDP in the United States by 5.5 percent, relative to a base case without a pandemic.[4] Another study, by Sherry Cooper of the investment firm BMO Nesbitt-Burns, adopted CBO's estimate of the impact under a severe scenario but boosted it to account for greater disruption in international trade (and the resulting effect on global supply chains), which resulted in an estimate of a 6 percent decline in GDP.[5]

One recent study, however, estimates effects that are much milder than those reported by CBO and the others. Steven James and Timothy Sargent estimate that a severe pandemic, with mortality similar to that seen in 1918, would reduce Canadian GDP by an amount that ranged from 0.3 percent to 1.1 percent in the year of the pandemic.[6] The authors note that those effects would be typical of other advanced economies, such as that of the United States.

The James-Sargent study is notable for its use of economic data from the three 20th century pandemics and the SARS (severe acute respiratory syndrome) episode in 2003. For example, on the basis of monthly data on industrial production in the United States, the authors estimate that real GDP declined by roughly 0.5 percent during 1918 as a result of the pandemic. In addition, though retail sales declined during the month of the pandemic, that decline was not unusual given the normal monthly variation in the data series. The authors found no evidence that international trade flows were disrupted or that financial markets were affected. Moreover, information gleaned from other sources reveal only mild

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3. See Steven Kennedy, Jim Thompson, and Petar Vujanovic, *A Primer on the Macroeconomic Effects of an Influenza Pandemic*, Working Paper 2006-01 (Parkes, Australia: Treasury of Australia, February 2006). Similarly, a study by the New Zealand Treasury estimated that a severe pandemic would reduce GDP in New Zealand by between 5 percent and 10 percent in the year that it occurred. See James Douglas, Kam Szeto, and Bob Buckle, *Impacts of a Potential Influenza Pandemic on New Zealand's Macroeconomy*, Policy Perspectives Paper 06/03 (Wellington: New Zealand Treasury, March 2006).

4. See Warwick McKibbin and Alexandra Sidorenko, *Global Consequences of Pandemic Influenza*, (Washington, D.C.: Brookings Institution, Lowy Institute for International Policy, February 2006).

5. See Sherry Cooper, *The Avian Flu Crisis: An Economic Update* (BMO Nesbitt-Burns, March 13, 2006).

6. See Steven James and Timothy Sargent, "The Economic Impact of an Influenza Pandemic" (mimeo, Department of Finance—Canada, May 9, 2006).

effects on such indicators as the number of passenger miles traveled on railroads and the number of trips taken on New York City subways and streetcars as a result of the pandemic. The authors conclude that the 1918 pandemic caused a mild reduction in supply due to illness and a very small reduction in demand and that the economic effects of the 1957 and 1968 pandemics were even smaller.

James and Sargent also conclude that the SARS outbreak did not cause a significant disruption in supply in the affected areas (primarily Hong Kong, Singapore, and Toronto). Economic activity slipped, but that was largely because of a temporary reduction in international travel to the affected areas, along with a decline in the lodging and restaurant industries. The authors found little evidence of wider impacts on retail sales, shipping tonnage, or airfreight—leading them to conclude that supply chains were largely unaffected.

Preparedness Policy

Current policy and options to mitigate the human and economic costs of an avian flu pandemic continue to evolve in three critical areas: developing vaccines and vaccine production capacity, developing treatments with antiviral drugs and other medications that would play a key role in reducing the impacts of a pandemic, and preparing state and local government and public health responses to the problems presented by an outbreak (see Table 1).

- As part of its plan, the Department of Health and Human Services is taking steps for sufficient capacity to exist by 2011 to produce vaccine for the entire U.S. population within six months of an outbreak.

- Clinical trials are being conducted to see if the industry's limited capability to produce vaccine in the next several years can be stretched by "dose-sparing" techniques. Information from those trials is expected to be available by late 2006 or early 2007.

- Since December 2005, plans have been put in effect to expand federal and state stockpiles of antiviral drugs. Manufacturers have taken the first steps toward increasing their capacity. If all goes as planned, the national supply of antiviral drugs should be about 80 million doses by the end of 2008. Public health officials are also looking to other existing medicines that might be effective in treating people who are sick with the flu—for example, statins and other drugs that address the inflammatory symptoms that accompany an influenza infection.

- The national response to a pandemic influenza would rely on state and local governments and the private sector as well as the federal government. For 2006, the Congress appropriated $680 million to improve response, including funding for state and local planning, state purchases of antiviral drugs for stockpiles, and purchases of medical supplies.

Table 1.

Supplemental Appropriations for the Department of Health and Human Services for Preparedness Against Pandemic Influenza, Fiscal Year 2006

(Millions of dollars)

	Budget Authority
Vaccines	
H5N1 prepandemic vaccine stockpile	80
Egg-based vaccines	531
Cell-based vaccines	1,004
Dose-sparing vaccines	150
Other	16
Subtotal	**1,781**
Antiviral Drugs	
Federal stockpile	361
State stockpiles	170
Development	200
Subtotal	**731**
State and Local Preparedness	350
Medical Supplies	162
Other Domestic Activities[a]	133
Communications	38
International Activities[b]	125
Total	**3,320**

Source: Congressional Budget Office based on Department of Health and Human Services, *Pandemic Planning Update: A Report from Secretary Michael O. Leavitt* (March 13, 2006), p. 2.

a. Includes activities related to surveillance, quarantine, lab capacity, and rapid tests.

b. Includes activities related to international preparedness, surveillance, and response.

Vaccine Supply

One challenge in providing vaccine for a pandemic is that the production of a vaccine specifically matched to the pandemic strain requires a sample of that strain itself. Therefore, production could begin only after the outbreak. With current egg-based technology, a pandemic vaccine would require at least six

months to produce. Current domestic production capacity might provide enough pandemic vaccine for only about 3 percent of the population.[7]

Production Lag. The Administration's implementation plan directs HHS to "establish and maintain stockpiles of prepandemic vaccines adequate to immunize 20 million persons against influenza strains that present a pandemic threat, as soon as possible within the constraints of industrial capacity."[8] The vaccine produced before a pandemic would not be a perfect match with the strain of virus causing the outbreak, but the hope is that it would offer at least some protection for first responders, at-risk populations, and military personnel before a vaccine specific to the pandemic could be produced. Furthermore, producing prepandemic vaccines increases manufacturers' experience in producing vaccines with potential against a pandemic. Clinical trials are under way now to determine how much cross-protection an H5N1 vaccine based on one strain will provide against different H5N1 strains, with results expected at the end of 2006.

HHS has awarded about $240 million in contracts to two manufactures, Sanofi Pasteur and Chiron, to produce nearly 8 million doses of H5N1 prepandemic vaccine for strategic stockpiling.[9] About $80 million of the funds are from the $3.3 billion appropriated to HHS for 2006. Recently published results of clinical trials indicate that a person will require two doses of that vaccine to induce an effective immune response against the H5N1 virus.[10] The initial stockpile would thus be sufficient to fully vaccinate about 4 million individuals. But some experts argue that to provide the greatest protection for a population, giving a lower dose to each person may be better in order to vaccinate more people.[11]

The vaccine counted in the Strategic National Stockpile is stored in bulk form by the companies that produced it until the government requests that it be formulated (the vaccine is stored at Sanofi Pasteur's facility in Swiftwater, Pennsylvania, and Chiron's facility in Liverpool, England). The rate of stockpiling will be slow,

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7. The estimate assumes that each person requires two doses of 90 micrograms of antigen (the raw material from which vaccines are made) and that yields for a pandemic strain are 20 percent to 50 percent lower than yields for seasonal strains. See Congressional Budget Office, *A Potential Influenza Pandemic*, pp. 22-23.

8. See Homeland Security Council, *National Strategy*, p. 120.

9. A dose is 90 micrograms of antigen, and a treatment course is two doses per person. See Department of Health and Human Services, *Pandemic Planning Update: A Report from Secretary Michael O. Leavitt* (March 13, 2006), p. 5.

10. See John J. Treanor and others, "Safety and Immunogenicity of an Inactivated Subviron Influenza A (H5N1) Vaccine," *New England Journal of Medicine*, vol. 354, no. 13 (2006), pp. 1343-1351.

11. See David S. Fedson, "The Global Pandemic Vaccine Challenge" (presentation at the WHO Consultation for the Development of a Global Action Plan for Increasing Pandemic Vaccine Supply, May 2 and 3, 2006), to be posted at www.who.int/csr/disease/influenza/vaccinesconsult2006/en/index.html.

however, because the companies can produce prepandemic vaccines only in the "off-season" (that is, the time of the year when they are not producing vaccine for seasonal influenza). Moreover, the vaccine stockpile will have to be restocked because the shelf life for influenza vaccine stored in bulk is about 12 to 18 months. As the vaccine approaches the end of its shelf life, it could be destroyed. Alternatively, it could be used to vaccinate volunteers under the Food and Drug Administration's (FDA's) Investigational New Drug provisions, even though a pandemic outbreak has not yet occurred.[12] However, as discussed in CBO's December 2005 assessment, the experience with the swine flu in 1976 suggests that such a mass immunization campaign for a potential pandemic is an enterprise not without challenges and risks.[13]

Capacity Limitation. The Administration's implementation plan directs HHS to work with the pharmaceutical industry toward the goal of developing, within 60 months, domestic production capacity sufficient to provide vaccine for the entire U.S. population within six months of a pandemic outbreak.[14] According to the Secretary of Health and Human Services, 20 percent of the production capacity would come from traditional egg-based vaccine manufacturing facilities and 80 percent would come from new cell-based vaccine manufacturing facilities.[15]

Egg-Based Vaccine Production. Domestic production capacity of egg-based vaccine would have to increase sevenfold from the current level in order to produce an H5N1 vaccine for 20 percent of the U.S. population. Sanofi Pasteur (which recently broke ground on a new facility in Swiftwater, Pennsylvania) anticipates doubling the current domestic capacity for seasonal influenza vaccine, from 60 million doses to 120 million doses, by the 2009 influenza season.[16] However, the company's current domestic production capacity for H5N1 vaccine is only about 8 million to 10 million courses (or 16 million to 20 million doses) in a six month period, because much more H5N1 vaccine is needed per dose and because yield for the H5N1 strain is 20 percent to 50 percent lower than it is for seasonal flu strains.[17] Therefore, doubling Sanofi Pasteur's current capacity would

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12. Those provisions include strict requirements for inventory control, recordkeeping, and informed consent. See Sarah Lister, *Pandemic Influenza: Domestic Preparedness Efforts*, CRS Report for Congress RL33145 (Congressional Research Service, November 10, 2005), p. 27.

13. See Congressional Budget Office, *A Potential Influenza Pandemic*, p. 26.

14. See Homeland Security Council, *National Strategy*, p. 120.

15. Statement of Michael O. Leavitt, Secretary of Health and Human Services, *Pandemic Influenza*, before the Subcommittee on Labor, Health and Human Services, and Education, Senate Committee on Appropriations (November 2, 2005), available at http://appropriations.senate.gov/hearmarkups/Leavitt.htm.

16. E-mail correspondence with Sanofi Pasteur, November 11, 2005.

17. See Congressional Budget Office, *A Potential Influenza Pandemic*, pp. 22 and 23; and "Vaccines: HHS's Role," *National Journal* (April 1, 2006), p. 34.

provide only about 16 million to 20 million courses (or 32 million to 40 million doses) of H5N1 vaccine, enough for only 5 percent to 7 percent of the U.S. population.[18]

HHS plans to spend $531 million of its 2006 funding on the development of new manufacturing facilities for egg-based vaccine and the expansion of existing facilities. The department expects to issue requests for proposals soon.

Cell-Based Vaccine Production. As part of an effort to develop domestic production capacity of cell-based vaccine sufficient to cover 80 percent of the U.S. population, HHS has awarded contracts totaling about $1.1 billion over five years to six companies.[19] In addition to facilitating development leading to licensing by FDA, the contracts include commitments to U.S. manufacturing facilities and may be used to scale up development and to design manufacturing facilities but not to construct them. Most of those funds come from the $3.3 billion that the Congress appropriated to HHS for 2006 for influenza preparedness. The remaining funds were awarded in March 2005 from previous appropriations.

Some observers estimate that a facility to manufacture cell-based flu vaccine would require four years to build and qualify for FDA approval.[20] That estimate is for the design and construction of the plant alone. Because the contracts to develop cell-based influenza vaccines have just been signed, several years of development and clinical trials will probably be required before ground is broken. HHS believes that timeline can be expedited by performing many steps in parallel. The department expects that, with the current awards and private funds, at least some of the six companies will prove successful in accelerating the

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18. Since September 2004, HHS has also had a contract with Sanofi Pasteur (for $41 million through 2008) to ensure a year-round supply of eggs and other essential vaccine production supplies. Before 2004, flocks were killed at the end of the flu season. The contract would make producing a pandemic influenza vaccine in the off-season possible if an outbreak were to occur. Under the contract, Sanofi Pasteur also supplies investigational lots of pandemic influenza vaccine for clinical study. See Sanofi Pasteur, "Aventis and U.S. Department of Health and Human Services Enter into Third Pandemic Influenza Vaccine Agreement" (press release, November 9, 2004).

19. The first contract, for $97 million, was awarded in March 2005 to Sanofi Pasteur. The other five, totaling about $1 billion, were awarded in May 2006 and went to GlaxoSmithKline ($274.75 million), MedImmune ($169.46 million), Novartis Vaccines and Diagnostics ($220.15 million), DynPort Vaccine ($40.97 million), and Solvay Pharmaceuticals ($298.59 million). See Department of Health and Human Services, "HHS Awards Contracts Totaling More Than $1 Billion to Develop Cell-Based Influenza Vaccine" (press release, May 4, 2006), available at www.hhs.gov/news/press/2006press/20060504.html), and "HHS Awards $97 Million Contract to Develop Cell Culture-Based Influenza Vaccine" (press release, April 1, 2005), available at www.hhs.gov/news/press/2005pres/20050401.html.

20. See Etienne Malhaize, GlaxoSmithKline, "Cell Culture Based Vaccine Production: Engineering Bottlenecks" (presentation at the National Academy of Engineering/Institute of Medicine meeting "Vaccine Production: Potential Engineering Approaches to a Pandemic," Cleveland, Ohio, April 10 and 11, 2006), available at www.vaccine2006.org/program.html.

development of their cell-based influenza vaccines. Presumably, for the companies that are successful in the first round, HHS plans additional awards from anticipated funding in 2007 and 2008—leading to enough cell-based vaccine production capacity to cover 80 percent of the population by 2011.

Other stakeholders have argued that the regulatory process to approve manufacturing methods that are not egg-based is long and involved and would require large clinical trials to demonstrate a vaccine's safety and efficacy.[21] The Administration's implementation plan notes "that certain issues must be addressed by extensive testing and characterization prior to the banking and use of mammalian cells for vaccine production."[22]

The Administration's motivation to shift from egg-based to cell-based production capacity results primarily from the fact that egg-based production capacity can not be scaled up in times of emergency, mostly because of its reliance on specially prepared and treated eggs. In fact, according to some estimates, the supply of eggs would have to increase from the roughly 100 million currently required to meet the U.S. demand for seasonal influenza vaccine to almost 2 billion to produce enough vaccine for the entire U.S. population during a pandemic.[23]

By contrast, cells can be frozen in advance and large numbers grown quickly. In addition, capacity can be increased in a modular fashion by adding fermenting equipment. Cell-based influenza vaccines would also provide an option for people who are allergic to eggs and therefore unable to receive the currently licensed vaccines. Some proponents of cell culture technology also argue that it provides security against the risks associated with egg-based production, such as the potential for the supply of eggs to be contaminated by various poultry-based diseases. However, others argue that cell lines can easily become contaminated by viruses or bacteria. The Administration's implementation plan notes that "cells may be at risk of contamination with various disease-causing organisms, . . . and there may be tumorigenicity concerns with cells that may be useful for high-yield manufacturing."[24]

Alternative Vaccines and Production Technologies. Production of a cell-based vaccine, although readily scalable, would still require about the same amount of

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21. E-mail correspondence with Vical, May 12, 2006. Vical is a biopharmaceutical company working on a DNA (deoxyribonucleic acid) vaccine that could provide protection against all influenza viruses.

22. See Homeland Security Council, *National Strategy*, p. 105, footnote 16.

23. For requirements for seasonal influenza, see Michael Osterholm, "Preparing for the Next Pandemic," *New England Journal of Medicine*, vol. 352, no. 18 (2005), pp. 1839-1843; for requirements for pandemic influenza, see Department of Health and Human Services, "Vaccine Production in Cells," available at www.pandemicflu.gov/vaccine/vproductioncells.html.

24. See Homeland Security Council, *National Strategy*, p. 105, footnote 16.

time as that of an egg-based vaccine. Thus, although cell-based production addresses the capacity limitation, it does not address the production lag. Vaccines that confer immunity to a broader range of influenza strains and other novel vaccine technologies have the potential to increase the industry's capacity to produce sufficient quantities and to address the lag in production during a pandemic. If more people receive vaccines with broader powers of protection, then the need for a speedy production response may be lessened. Moreover, people vaccinated in previous years may retain some level of protection.

One vaccine delivered by nasal spray, rather than injection, may provide some immunity across influenza strains.[25] And because the production process is different, it may also offer the opportunity for large numbers of doses from much smaller numbers of eggs. Although the nasal vaccine for protection against seasonal influenza is already on the market, most alternative vaccines are still in clinical trials or even at the research stage. A recent survey of clinical trials of flu vaccines offering broader protection found seven such trials occurring in 2006 and 2007.[26]

Recombinant genetic techniques may also produce vaccines that can be manufactured in much greater quantities than those using egg- or cell-based production. Because such technologies are already widely used in industry, tapping into them could modernize the production of flu vaccines.[27] In HHS's first round of technology development contracts, none of the candidates using recombinant genetic techniques was awarded a contract, although some have other contracts for technology development or testing with other government agencies. However, HHS is preparing to issue requests for proposals to develop flu vaccines relying on recombinant genetic techniques, just as it did for cell-based technology.

Ongoing Government Support. The current level of market demand for the seasonal influenza vaccine is not sufficient to attract private investors to finance the development and design, construction, and ongoing operation of a domestic industry that can provide 300 million courses within six months of an outbreak. The federal funds currently appropriated will add to private investment in the development of new production technology and the design of new plants. The Administration's request for 2007, and its likely plans for 2008, would provide

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25. The broadened immunity may come because the vaccine uses a weakened live virus, rather than component parts, as other seasonal flu vaccines do.

26. See Jocelyn Kaiser, "A One-Size-Fits-All Flu Vaccine?" *Science* (April 21, 2006).

27. See David Estell, Genencor International, "Adapting Industry Practice for Rapid Large Scale Manufacture of Pharmaceutical Proteins," and Lada Rasochova, "A Microbial Expression System as a Possible Route to Antigen Production for Use as Vaccines" (presentations at the National Academy of Engineering/Institute of Medicine meeting "Vaccine Production: Potential Engineering Approaches to a Pandemic," Cleveland, Ohio, April 10 and 11, 2006), available at www.vaccine2006.org/program.html.

public funds to complement private financing of new construction and renovation of existing plants. But even when the construction and renovation are completed sometime after 2010, maintaining the surge capability to meet the potential demands of an influenza pandemic and continuing to develop new production technologies and vaccines may require public support. Success in increasing the egg-based and cell-based production of currently available vaccines will probably diminish the incentive for the private sector to invest in more-advanced processes and products, so a possible policy option could be additional government support for those technologies.

Currently, the federal government creates demand for seasonal influenza vaccines by recommending vaccination for certain groups—the elderly, for example—and by providing funds for many people receiving vaccinations each year—largely, Medicare and Medicaid recipients. One approach to building and maintaining the capability to produce large amounts of a pandemic vaccine is to encourage demand for the seasonal vaccines. In February 2006, the Centers for Disease Control's Advisory Committee on Immunization Practices added children ages 24 months to 59 months and their healthy household contacts to the list of people encouraged to get a flu shot.[28] Some observers have called for a universal recommendation for everyone to receive a seasonal flu shot. The movement toward such a recommendation and concerns about the seasonal flu that have been created by the threat of a pandemic virus have led to predictions that manufacturers will deliver 120 million doses of vaccine for the 2006-2007 season, which is well above last year's level of 85 million doses.[29] The Administration's implementation plan also calls for HHS to support the industry through purchasing and maintaining stockpiles of 20 million courses of vaccine against each circulating influenza virus with pandemic potential. In the future, support of two or three manufacturers with the capacity to produce, collectively, enough pandemic vaccine for the entire U.S. population could require even larger direct purchases than those now provided for by Medicare and Medicaid and the currently planned stockpiles, depending on the global market for influenza vaccine.

Dose-Sparing Efforts. To address the immediate production capacity limitation, researchers are looking for ways to make the current vaccine more effective at lower doses, stretching the available supply to serve more people and thus increasing the value of stockpiling. Adding an adjuvant to the pandemic vaccine is one dose-sparing technology currently under investigation.[30] However, clinical

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28. "Flu Vaccine Production Soars, Setting up Debate on Universal Recommendation," *Pink Sheet* (April 24, 2006), p. 18.

29. Ibid.

30. Adjuvants are substances used to enhance the ability of antigens to stimulate the immune system. Adjuvants may also provide cross-protection; that is, they may enhance the ability of a vaccine to offer protection against influenza viruses of a different strain than that used to make the vaccine.

trials of adjuvanted vaccines against avian influenza have generally shown mixed results. Most recently, Sanofi Pasteur completed a clinical trial of a prepandemic H5N1 vaccine using adjuvants.[31] In the trial, an adjuvant was able to reduce the amount of vaccine by two-thirds and still achieve requisite levels of immune response. The formulation of stockpiled vaccine and the production capacity necessary to provide vaccine for the entire population will depend in part upon how successful adjuvants are in reducing the amount of vaccine required to provide immunity.

To assess the safety of adjuvants and other dose-sparing techniques and their ability to improve the immune response, HHS and the National Institutes of Health are supporting several manufacturers to produce dose-sparing vaccines for clinical testing. Results are expected to be available by the end of the year. HHS also plans to spend $150 million from 2006 funds on contracts to support advanced-stage development of dose-sparing strategies.

Liability Protection. Legislation enacted in December 2005 provides broad liability protection for manufacturers and others with regard to products to combat pandemic influenza and extends those protections to other medical countermeasures.[32] That legislation, the Public Readiness and Emergency Preparedness (PREP) Act, prohibits suits under federal and state law against manufacturers and health care workers for injuries caused by certain medical products used to counter pandemic influenza, other epidemics, and diseases caused by acts of terrorism. The liability protections apply only to products used during a period that the Secretary of Health and Human Services declares a public health emergency. The law provides an exception to immunity if a manufacturer engaged in willful misconduct.

The PREP Act also authorizes the Secretary to develop a compensation program for individuals injured by those products that will be similar to a program for individuals injured by the smallpox vaccine. Funding compensation under that program depends upon future appropriations.

Antiviral Drugs and Other Medicines to Treat the Sick

HHS plans to spend $731 million appropriated for 2006 on currently available antiviral drugs and research to develop new antiviral agents. The funds are allocated for both federal and state initiatives. Specifically, the federal government will spend $361 million to purchase approximately 20 million doses of Tamiflu and Relenza for the Strategic National Stockpile. Those doses are

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31. "Influenza: Prepandemic Flu Vaccine Candidate with Adjuvant Shows Good Immune Response in Trial," *Vaccine Weekly* (January 18, 2006), p. 59.

32. The Department of Defense, Emergency Supplemental Appropriations to Address Hurricanes in the Gulf of Mexico, and Pandemic Influenza Act, 2006 (Public Law 109-148), was enacted on December 30, 2005. The Public Readiness and Emergency Preparedness Act is included as division C of that legislation.

expected to be delivered by the first quarter of 2007. States will be given $170 million in matching funds to use toward the purchase of 31 million doses of antiviral drugs for their stockpiles. And finally, HHS plans to spend $200 million on the development of additional antiviral drugs aimed at combating the effects of pandemic and seasonal influenza.

Stockpiles. To date, the Strategic National Stockpile includes about 5.1 million courses of Tamiflu and 84,000 courses of Relenza.[33] HHS has ordered another 16.2 million courses of Tamiflu and 3.9 million courses of Relenza, which will raise the total national stockpile to about 25 million courses of those drugs by the first quarter of 2007, if deliveries are made on time.[34] HHS intends to purchase an additional 24 million courses of Tamiflu and Relenza with funds requested for 2007 and 2008.[35] As noted above, HHS has also allocated $170 million of 2006 funds to cover 25 percent of the cost of states' purchases of an additional 31 million courses. State governors have been asked to notify HHS if they plan to purchase their allocated antivirals by July 1, 2006.[36] Ultimately, the department's goal is to have 81 million courses of antiviral drugs in the Strategic National Stockpile (50 million from federal spending and 31 million from a combination of federal and state funds) by the end of 2008.[37]

Effectiveness. When effective, an antiviral drug reduces the severity, duration, and likelihood of death associated with a viral infection. But there are not solid data about how effective currently available antiviral drugs are against the H5N1 virus. It is commonly believed that viral resistance to the older and less expensive class of antiviral drugs called adamantanes would limit their usefulness during a pandemic.[38] (The Strategic National Stockpile includes 5 million courses of

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33. For Tamiflu, a course of treatment consists of 10 capsules; for Relenza, 20 inhalations of 5 milligrams each. See Department of Health and Human Services, *Pandemic Influenza Plan* (November 2005), Supplement 7, "Antiviral Drug Distribution and Use," and Appendix F, "Current HHS Activities," available at www.hhs.gov/pandemicflu/plan; and "Investing in Bird Pandemic Flu," *Baltimore Sun*, April 30, 2006.

34. See Department of Health and Human Services, "HHS Buys Additional Antiviral Medication as Preparations for Potential Influenza Pandemic Continue (press release, March 1, 2006), available at www.hhs.gov/news/press/2006pres/20060301.html, and "HHS Buys More Antiviral Medication for the Strategic National Stockpile" (press release, March 22, 2006), available at www.hhs.gov/news/press/2006pres/20060322.html; and e-mail correspondence with the Centers for Disease Control, May 16, 2006.

35. Statement of John O. Agwunobi, Assistant Secretary of Health, Department of Health and Human Services, *Working Through an Outbreak: Pandemic Flu Planning and Continuity of Operations*, before the House Committee on Government Reform (May 11, 2006).

36. See Department of Health and Human Services, "Antivirals—State Allocations," available at www.pandemicflu.gov/state/antivirals.html.

37. See Department of Health and Human Services, *Pandemic Planning Update*.

38. See Department of Health and Human Services, *Pandemic Influenza Plan*, Appendix D. However, a study expected to appear in a coming issue of the *Journal of Infectious Diseases* suggests the possibility that adamantanes can be used selectively alongside Tamiflu to treat people infected with

rimantadine, which is a drug of that type.) Accordingly, HHS has focused its recent antiviral stockpiling efforts on purchasing Tamiflu and Relenza even though recent reports have surfaced that some strains of the H5N1 virus are becoming resistant to Tamiflu.[39] In response, HHS has changed its stockpiling strategy to decrease the target share of Tamiflu held in reserve from 90 percent to 80 percent and increase the share of Relenza from 10 percent to 20 percent.

Production of Existing Antiviral Drugs. In 2003, the production capacity for Tamiflu was 6 million courses. Roche, the patent holder and manufacturer of the drug, said it will be capable of producing 400 million courses in 2007—the result of contracts that it has recently signed with more than 15 companies, each of which will help carry out a step in the production process.[40] The firm has also granted sublicenses to Shanghai Pharmaceutical Group and HEC group, both in China, and to Hetero Drugs in India to produce generic versions of Tamiflu for use in China, India, and other developing countries. In addition, other companies are producing generic versions of Tamiflu without sublicenses from Roche in India, Taiwan, Bangladesh, and Algeria.[41] In the United States, Roche is currently producing 80 million courses of Tamiflu per year in six facilities.[42]

In response to the growing demand, GlaxoSmithKline has also increased production of Relenza from less than 1 million courses in 2005 to 15 million courses in 2006.[43] Currently, Relenza is not produced in the United States; however, the company says that it will begin production in North Carolina in 2007.[44]

New Antiviral Drugs. HHS plans to spend $200 million of its 2006 funds on the development of additional antiviral drugs and has recently issued a presolicitation notice describing its intent to award one or more contracts to support the advanced-stage development of new antiviral compounds for the treatment and

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some strains of the H5N1 virus. See Nicholas Zamiska, "Bird Flu Options Expand," *Wall Street Journal Online*, May 11, 2006.

39. Anne Moscona, "Oseltamivir Resistance—Disabling Our Defenses," *New England Journal of Medicine*, vol. 353, no. 25 (2006), pp. 2663-2636.

40. Roche, "Tamiflu in Brief" (fact sheet, April 10, 2006), pp. 4-5, available at www.roche.com/med_mbtamiflu05e.pdf.

41. Martin Enserink, "Oseltamivir Becomes Plentiful—But Still Not Cheap," *Science* (April 21, 2006).

42. Phone conversation with Evan Morris, Executive Director, Roche AAG, Washington, D.C., May 19, 2006.

43. GlaxoSmithKline, "Flu Information Resource" (press release, April 27, 2006), available at http://us.gsk.com/news/flu_overview.htm.

44. E-mail correspondence with GlaxoSmithKline, May 21, 2006.

prevention of pandemic and seasonal influenza.[45] HHS anticipates awarding the contract(s) in the fall of 2006, with a period of performance of up to five years.

Other Medicines to Treat the Sick. Public health officials are looking to other existing medicines that might be effective in treating people who are sick with the flu. Recent studies suggest that an exaggerated immune response (referred to as a "cytokine storm") to the influenza virus infection may have been the cause of the high lethality seen in the 1918 pandemic. Some scientists have suggested testing the use of statins (cholesterol-lowering drugs) for treating the cytokine storm.[46] Statins are more widely available and cheaper than the newer antiviral agents and vaccines which would make them particularly useful during a pandemic if they were found to reduce flu symptoms from the H5N1 virus.

State and Local Governments' and Public Health Systems' Readiness

The preparedness of state and local governments and public health systems will be important in minimizing the human and economic cost of a pandemic outbreak even if the goal of providing vaccine for the entire U.S. population within six months is met by 2011. In the interim, when only a small percentage of the population could be vaccinated, controlling the spread of the disease and treating sick people would be essential before the combination of vaccination and survivors' immunity could limit its damage.

In December 2005, HHS held a planning summit on pandemic influenza with state and local leaders from across the United States. During that summit, HHS announced its plan to hold individual planning summits in every state.[47] To date, summits have been held in over 45 states.[48] Through those meetings, HHS has emphasized that although the federal government will provide support during a pandemic, the ultimate responsibility for pandemic preparedness lies with the states. To help states with their preparations, HHS released a checklist.[49]

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45. See Department of Health and Human Services, "Advanced Development of New Antiviral Agents for Influenza" (presolicitation notice, May 15, 2006), available at www.fbo.gov/spg/HHS/OOS/OASPHEP/DHHS-ORDC-VB-06-01/SynopsisP.html.

46. Institute of Medicine, *The Threat of Pandemic Influenza Are We Ready?* Workshop Summary (Washington D.C.: The National Academies Press, 2005), pp. 194-196.

47. See Department of Health and Human Services, "Federal Government Begins Pandemic Planning with States" (press release, December 5, 2005), available at www.hhs.gov/news/press/2005pres/20051205.html.

48. See Department of Health and Human Services, "State Pandemic Planning Summits," available at www.pandemicflu.gov/plan/summits.html.

49. See Department of Health and Human Services, "State and Local Pandemic Influenza Planning Checklist," (December 2, 2005), available at www.pandemicflu.gov/plan/statelocalchecklist.html.

Additionally, all 50 states have submitted plans to the Centers for Disease Control, which are to be updated as states' preparations advance.[50]

The Administration's implementation plan delegates more than 300 critical actions to various federal agencies. Yet the critical tasks still focus primarily on assisting states to prepare for a pandemic. In the event of a pandemic, states would rely in part on HHS for public health and medical response, the Department of Homeland Security for domestic incident management and federal coordination, and several other agencies for various types of support.[51]

Of the $3.3 billion appropriated to HHS in 2006 for preparedness, $100 million has been allocated to states and U.S. territories, with another $250 million to be disbursed as states meet specific preparedness milestones.[52] That money is in addition to more than $6 billion that has been invested since 2002 in state and local health and medical preparedness for events involving mass casualties such as a natural disaster or act of bioterrorism.[53] However, such events are more likely to be geographically concentrated than is pandemic influenza, which could affect almost all communities in the United States. The extent to which money disbursed for mass casualty events would also help prepare for pandemic influenza is not known.

The Health Care System

Were an influenza pandemic to occur, local health care systems would not have a sufficient number of beds or enough staff or supplies to meet the demand (and observe routine standards of care). In the event of even a mild pandemic, local health care systems would need to rapidly expand operations and deploy infection-control measures and treatments. Public health officials have expressed concern that the system's capacity would be inadequate.[54] FluSurge, a simulation tool developed by the Centers for Disease Control, has produced estimates that a severe pandemic in an urban area would increase the overall demand for hospital

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50. See Department of Health and Human Services, "State Pandemic Plans," available at www.pandemicflu.gov/plan/stateplans.html.

51. See the statements of John O. Agwunobi (cited earlier) and Jeffrey W. Runge, Acting Under Secretary for Science and Technology and Chief Medical Officer, Department of Homeland Security, *Working Through an Outbreak: Pandemic Flu Planning and Continuity of Operations*, before the House Committee on Government Reform (May 11, 2006).

52. See Department of Health and Human Services, "HHS Announces $100 Million to Accelerate State and Local Pandemic Influenza Preparedness Efforts" (press release, January 12, 2006), available at www.hhs.gov/news/press/2006pres/20060112.html.

53. Homeland Security Council, *National Strategy*, p. 22.

54. See the statement of Marcia Crosse, Director, Health Care, Government Accountability Office, before the Subcommittee on Health, House Committee on Energy and Commerce, published as Government Accountability Office, *Influenza Pandemic: Challenges Remain in Preparedness*, GAO-05-760T (May 26, 2005).

beds and staff three times beyond the current capacity and the demand for intensive care beds seven times beyond the current capacity.[55]

Along with the surge in hospitalized people would come a need for supplies and medical equipment. Hospitals would need more protective equipment such as surgical masks, gloves, and gowns, and they would need to have the capacity for increased decontamination and waste management. As occurred during the SARS outbreak in Canada, hospitals would especially need N95 particulate respirators to protect medical staff against infection.[56] Widely adopted just-in-time practices for supplies may help to control costs in normal circumstances but leave too small an inventory margin to accommodate the increased demand for supplies that would accompany an influenza pandemic.

Certain essential equipment would also be needed. Ventilators would be of particular importance because sick patients with inflamed and fluid-filled lungs would need assistance with breathing. CBO's December assessment noted that the United States has approximately 100,000 ventilators, with three-quarters of them in use on any given day.[57] According to HHS, a severe influenza pandemic like the one in 1918 would require 750,000 ventilators to treat victims.[58]

Current appropriations for 2006 provide $162 million to increase the supplies that would be needed in a pandemic. Those purchases would be added to the Strategic National Stockpile. Among the supplies stockpiled are 1.2 million N95 respirator masks (with 103.7 million due to be delivered by September 2007), 5,000 hospital beds, and 4,000 ventilators (with an additional 486 expected by July 2006).

Even with those additions to the national stockpile, the available supplies would be less than what would be necessary to meet the demands of a severe pandemic. Closing the gap would be costly. According to the Center for Biosecurity, a severe pandemic would require about $5 billion in hospital spending—which translates into a $1 million investment for an average hospital for activities such as the development of plans and training and for personal protective equipment

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55. See the statement of Tara O'Toole, Director, Center for Biosecurity, University of Pittsburgh Medical Center, *Protecting the Homeland: Fighting Pandemic Flu from the Front Lines*, before the Subcommittee on Emergency Preparedness, Science, and Technology, House Committee on Homeland Security (February 8, 2006).

56. Ibid.

57. See Congressional Budget Office, *A Potential Influenza Pandemic*, p. 29.

58. See Department of Health and Human Services, "Pandemic Planning Assumptions," available at www.pandemicflu.gov/plan/pandplan.html.

and basic supplies, excluding antiviral drugs or high-cost equipment such as ventilators.[59]

Health planners and facilities operators, both public and private, face the issue of paying large up-front costs to prepare for an uncertain event. A simple analytical approach is to balance the cost of current preparedness against the discounted avoidable cost associated with a future influenza pandemic, taking account of its uncertainty. Paying the full costs for complete preparation today may not be a sound investment, but paying some of the costs is prudent, and learning more about pandemic viruses in general and the H5N1 virus in particular will help inform policymakers' decisions.

59. Eric Toner and others, "Hospital Preparedness for Pandemic Influenza," *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science*, vol. 4, no. 2 (2006), available at www.biosecurityjournal.com/ TONER.pdf.