

Project On Government Oversight

Pandemic Flu: Lack of Leadership and Disclosure Plague Vaccine Program

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EXECUTIVE SUMMARY

An influenza pandemic, when it strikes, may cause hundreds of thousands of deaths in the U.S., economic losses in the billions of dollars, and possibly a climate of fear and a breakdown of public order. At the start of a pandemic, the first and best defense is to quickly immunize as many people as possible.

In July 2007, Health and Human Services (HHS) Secretary Mike Leavitt announced that, over the next five years, vaccine manufacturers will develop the capacity to produce and deliver enough vaccine for the American public within six months of the appearance of a pandemic virus.

It should not take that long. The government should be able to speed up the nation's ability to produce enough vaccine. But problems with the current vaccine program, including inadequate leadership and limited public disclosure of information, may be impeding progress.

Leadership

A new agency, BARDA (Biomedical Advanced Research and Development Authority), facilitates collaboration between government, industry, and academia in the flu vaccine program and other public health emergency programs. BARDA was established by Congress in December 2006. Now, more than twelve months later, it still lacks a permanent director.

The magnitude of the threat to the nation calls for the immediate appointment of an exceptional person of near-cabinet-level stature who commands respect in the business and public health communities—someone willing to blast through financial and bureaucratic roadblocks.

Public Disclosure

The vaccine program suffers from the government's failure to make public disclosure an essential element of the program. Lack of disclosure may seem like a minor weakness, but the consequences could prove to be profound. Without such disclosure, problems and possible improvements to the program may not be discovered until too late.

The HHS Secretary or the director of BARDA should require the prompt disclosure of all relevant documents in the pandemic flu vaccine program. Material that should be disclosed includes government contracts for vaccine production, as well as information about vaccine manufacturing capacity, U.S. dependence on foreign sources of material for vaccine production, intellectual property rights, alternatives to current vaccines, and the vaccine program budget. It is essential that the disclosures include a justification of the current plan for vaccine production, and should spell out the reasons for rejecting or de-emphasizing alternative strategies.

INTRODUCTION

The U.S. is in a grim race to prepare for the mass production of a vaccine before the next influenza pandemic strikes. Experts can't predict how dangerous the pandemic will be or when it will begin¹—it could be a decade or more in the future, or it could be less than a year from now. In a pandemic there could be deaths in the hundreds of thousands in the U.S. and in the tens of millions worldwide.² A vaccine will limit the harm caused by the influenza virus when it appears and spreads.³

Unlike seasonal influenza, which appears once a year, outbreaks of pandemic influenza are rare but far more deadly and widespread, sweeping quickly from person to person, through communities, across countries, and around the world. There were three in the past century—in 1918 (“Spanish flu,” the worst of the pandemics), 1957, and 1968. In each of the three, people lacked immunity to new influenza viruses that arose, in whole or in part, from avian influenza viruses. In the pandemic of 1918-1919, an estimated 50 million people died worldwide,⁴ many more than were killed in the battles of World War I.

The worry is that the next pandemic will be like that of 1918, with incapacitating illness and high mortality. Currently, the H5N1 strain of avian influenza is of special concern. Although it is only rarely transmitted from birds to humans—about 350 people have become infected with the H5N1 strain since 2003—more than half of those infected have died.⁵ Up to now, H5N1 has not shown

¹ (1) Experts agree that “another influenza pandemic is inevitable and possibly imminent.” World Health Organization. “Frequently Asked Questions. Avian Influenza: Responding to the Pandemic Threat.” Undated. www.searo.who.int/LinkFiles/Avian_Flu_FAQs_IL.pdf (Downloaded February 14, 2008). (2) Similarly, a document on the U.S. government’s pandemic flu website (www.pandemicflu.gov), states: “While there is no way to know when, or even if, the H5N1 virus will form a variant capable of widespread human-to-human transmission, we know that pandemics are inevitable and our efforts are designed to advance our preparedness to minimize the impact of the next pandemic when it comes.” U.S. Department of Health and Human Services. “Pandemic Planning Update III.” *A Report from Secretary Michael O. Leavitt*. November 13, 2006. www.pandemicflu.gov/plan/pdf/panflureport3.pdf (Downloaded February 14, 2008). (3) Secretary Leavitt has also stated that a flu pandemic is in some ways “an absolute certainty.” Quoted by MSNBC from an interview by the Associated Press: “U.S. may deploy medicine in emergency. Government looking for new ways to distribute drugs, says HHS secretary.” Associated Press, August 2, 2005. www.msnbc.msn.com/id/8801097/ (Downloaded February 14, 2008).

² (1) Meltzer, Martin I, Nancy J. Cox, and Keiji Fukuda. “The Economic Impact of Pandemic Influenza in the United States: Priorities for Intervention.” *Emerging Infectious Diseases*, Vol. 5 No. 5, Sept.-Oct. 1999. pp. 659-671. (2) Murray, Christopher J.L., Alan D. Lopez, Brian Chin, Dennis Feehan, and Kenneth H. Hill. “Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918-20 pandemic: a quantitative analysis.” *Lancet*, Vol. 368, December 23, 2006. pp. 2211-2218. (3) David Brown. “World Death Toll Of a Flu Pandemic Would Be 62 Million.” *The Washington Post*, December 22, 2006. www.washingtonpost.com/wp-dyn/content/article/2006/12/21/AR2006122101466_pf.html (Downloaded February 14, 2008).

³ This report focuses exclusively on deficiencies in the U.S. government’s vaccine program. Other deficiencies in preparedness for an influenza pandemic—inadequate training of health care workers, for example, or shortages of medical equipment or drugs—are not covered here.

⁴ Johnson, Niall P.A.S, and Juergen Mueller. “Updating the Accounts: Global Mortality of the 1918-1920 ‘Spanish’ Influenza Pandemic.” *Bulletin of the History of Medicine*, Vol. 76, Spring 2002. pp. 105-115.

⁵ World Health Organization. “Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1).” www.who.int/csr/disease/avian_influenza/country/en/ (Downloaded February 14, 2008).

a sign of a genetic change that would allow it to spread easily from human to human. However, previous pandemics have occurred because such a genetic change took place.

Regardless of which virus strain causes the next pandemic, panic and civil disorder may follow, as is depicted in a government document:

An outbreak of severe respiratory illness is identified in a small village in a country known to have experienced recent avian influenza disease. . . .

Overall, about 2 percent of Americans with influenza illness die.... Hospitals are overwhelmed ... and there are shortages of mechanical ventilators for treatment of patients with severe pneumonia.... Riots occur at some vaccination clinics as people are turned away or supplies run out. Several trucks transporting vaccine are hijacked Public anxiety heightens mistrust of government Mortuaries and funeral homes are overwhelmed.... A second influenza disease wave begins The majority of people still have not been vaccinated at the time of the second wave.⁶

These excerpts were taken from a government document, but the document itself has disappeared. In October 2005, a few days before the expected release of the document by the Administration, reporter Gardiner Harris obtained a copy of it and quoted from it at length in a *New York Times* article. But the original document was never released to the public. The press office staff at the White House told POGO they can't find a copy, and there is no copy on the Internet or in the Library of Congress. Although other government publications contain similar ideas,⁷ they are discussed in far less gripping language.

Although the original document has dropped out of sight, its ominous message remains: the country is not ready for a pandemic.

An adequate amount of vaccine is the best hope for limiting the death toll during a pandemic, but the government's current timetable for vaccine production is far from reassuring. In July 2007, Health and Human Services Secretary Mike Leavitt announced that, over the next five years, vaccine manufacturers will develop the capacity to produce and deliver enough vaccine for the American public within six months of the appearance of a pandemic virus.⁸

Secretary Leavitt's prediction may be overly optimistic. But even if we assume his prediction is completely accurate, vaccine will probably be in short supply if a pandemic occurs within the

⁶ Harris, Gardiner. "From Washington, a Story About a Killer Flu." *The New York Times*, October 16, 2005.

⁷ United States Homeland Security Council. "National Strategy for Pandemic Influenza. Implementation Plan." May 2006. www.whitehouse.gov/homeland/nspi_implementation.pdf (Downloaded February 14, 2008).

⁸ Department of Health and Human Services. "Pandemic Planning Update IV." *A Report from Secretary Michael O. Leavitt*. July 18, 2007. See section, "Expanding Capacity." p. 8. "Over the next five years, vaccine manufacturers, spurred by a \$1 billion HHS investment, will develop the capacity to produce and deliver enough pandemic vaccine for every man, woman, and child in the United States within six months of the appearance of a pandemic virus." www.pandemicflu.gov/plan/panflureport4.pdf (Downloaded February 14, 2008).

next few years. It will be 2012 before manufacturers are fully ready for a pandemic, according to Secretary Leavitt, and even then it will be *six months* after the start of a pandemic before they can produce enough vaccine.

It should not take that long. The government should be able to speed up the nation's ability to produce enough vaccine. [See Appendix A for more information on flu vaccine production.] But problems with the current vaccine program, including inadequate leadership and limited public disclosure of information, may be impeding progress.

A national commitment to combat a deadly threat is not unprecedented. On past occasions, an impending disaster has generated an overwhelming sense of urgency and cooperation in government. One such case is the Manhattan Project. An unusual set of circumstances—the life-and-death struggle of World War II, the perceived need to make an atomic bomb before the Germans did, two supremely qualified leaders of the project, and unstinting support at the highest levels of government—created an extraordinary spirit of collaboration in government, industry, and academia.

Similar forces drove the rapid development of vaccines, including the first influenza vaccine, during World War II. As historian Kendall Hoyt has observed:

Why were vaccine development efforts so much more productive during this period than any other period in the 20th century? In part, a sense of national urgency to defend against war-enhanced disease threats fostered unprecedented levels of federal support and a spirit of collaboration between military, industrial, and academic scientists.⁹

An extraordinary collaboration between the government, industry, and academia is needed for the quickest possible development of flu vaccines. This will require stronger leadership of the vaccine program and full disclosure of the details of the program so that experts outside the government can more readily provide comments and criticisms.

LEADERSHIP OF THE VACCINE PROGRAM

The magnitude of the threat to the nation calls for a person of near-cabinet-level stature to lead the vaccine program, a person who commands respect in the business and public health communities—someone willing to blast through financial and bureaucratic roadblocks. But no such person has been appointed.

In December 2006, a new agency, BARDA (Biomedical Advanced Research and Development Authority), was created within the HHS by an act of Congress.¹⁰ BARDA's mission is to facilitate collaboration between government, industry, and academia in the influenza vaccine

⁹ Hoyt, Kendall. "Vaccine Innovation: Lessons from World War II." *Journal of Public Health Policy*, Vol. 27 No.1, 2006. pp. 38-57. www.ingentaconnect.com/content/pal/jphp/2006/00000027/00000001/art00005 (Downloaded February 14, 2008).

¹⁰ United States. "Pandemic and All Hazards Preparedness Act" (Public Law 109-417). www.hhs.gov/aspr/omsph/nbsb/publiclaw109417.pdf (Downloaded February 14, 2008).

program and other programs dealing with public health emergencies. Many senior federal employees in the program are recognized as world-class experts in vaccine research and production, but leadership at the top is missing.

Over twelve months have now passed since BARDA was created, and a permanent director of the new agency has still to be appointed.

Worse, the method of choosing the BARDA director was flawed from the start. The government is following the standard practice used in the civil service—picking one of those who completed a job application and filed it in response to a routine government advertisement on the USAJOBS website (“Your one-stop source for Federal jobs”).¹¹ USAJOBS is the governmental equivalent to the classified ads. This is no way to recruit a leader of the caliber that is needed. An alternative, of course, is for the government to actively seek out highly qualified candidates for the job.

PUBLIC DISCLOSURE

The vaccine program suffers from the government’s failure to make public disclosure an essential element of the program. Lack of disclosure may seem like a minor weakness, but the consequences could prove to be profound.

Much information about the program can be found on the government’s website, www.pandemicflu.gov, which has hundreds of documents with thousands of pages. The sheer quantity of information is impressive. However, some of the most important information is missing—information well known to scientists and administrators inside the government’s vaccine program.

Material that should be disclosed and readily accessible includes government contracts for vaccine production, as well as information about vaccine manufacturing capacity, U.S. dependence on foreign sources of material for vaccine production, intellectual property rights, alternatives to current vaccines, and the vaccine program budget. It is essential that the disclosures include a justification of the current plan for vaccine production, and should spell out the reasons for rejecting or de-emphasizing alternative strategies.

This material, posted on the government’s pandemic flu website, will then be readily available for scrutiny—and possible criticism—by non-government experts in public health, engineering, business, and other fields related to vaccine production; watchdog organizations and other public interest groups; journalists; and Members of Congress. Without such scrutiny, problems and possible improvements to the program may not be discovered until too late. For instance, the government’s current timetable for vaccine production may not be the best that can reasonably be expected, but only through full disclosure of all elements related to production, and through the resultant debate, can we know.

¹¹USAJOBS. “Department of Health and Human Services. Deputy Assistant Secretary and Director, Office of BARDA.” Multi-page document posted on the USAJOBS website from May 1 to June 29, 2007 and then removed. A copy of this document, with explanation, is posted as a PDF file on the website for the Project On Government Oversight at www.pogoarchives.org/m/science/flu-vaccine/barda-director-2007.pdf.

Some of the disclosed material will be unsettling to the public. During the first months of a pandemic, for example, people seeking vaccine may be denied it. Although the risk of a vaccine shortage will presumably lessen over the next five years as manufacturing capacity expands, current information about the risk of a shortage should be prominently disclosed and explained. The government document of October 2005, with its graphic portrayal of a vaccine shortage, disappeared after making a single cameo appearance in the *New York Times*. This document should be posted on the government's website, not suppressed.

When a pandemic strikes, problems with vaccine production will become obvious and the consequences may be dire. Government officials should level with the public about this possibility now if they want to have the public's trust during the throes of a pandemic.

TYPES OF INFORMATION TO DISCLOSE

The following documents and information should be disclosed to the public in a conveniently accessible fashion, such as on the government's pandemic flu website. At present, much of this material is not available or is available only partially on government websites. Some of the documents referenced below are required by law to be provided through Freedom of Information Act requests, but are in fact either unavailable or are provided only after a long delay.

- (1) **Government contracts for vaccine production.** The full text of these multi-million dollar contracts should be published online. There are precedents for this. The U.S. Agency for International Development (USAID), for instance, occasionally posts its contracts online.¹² In contrast, HHS has issued only short summaries and press releases on contracts in the flu vaccine program;¹³ the contracts themselves are not available for examination online. Public scrutiny of the contracts has become more important in light of the failure by one company (in the bioterrorism program) to meet its contract requirements, resulting in the cancellation of an \$877 million contract with that company and a major setback to the government's efforts to obtain anthrax vaccine.¹⁴ In addition to the contracts themselves, there should be online publication of progress reports covering the contracts and evaluations of contractors' performance, updated periodically. It is important that those writing the progress reports and performance evaluations be

¹² USAID. "Assistance for Iraq: Contracts and Grants" www.usaid.gov/iraq/contracts/errsgi.html (Downloaded February 14, 2008).

¹³ Department of Health and Human Services. "HHS Awards Contracts Totaling More Than \$1 Billion to Develop Cell-Based Influenza Vaccine." www.hhs.gov/news/press/2006pres/20060504.html (Downloaded February 14, 2008) and Department of Health and Human Services. "Pandemic Influenza Funding Activities" www.hhs.gov/aspr/barda/procurement/panflu.html (Downloaded February 14, 2008) and Department of Health and Human Services. "Pandemic Planning Update III." *A Report from Secretary Michael O. Leavitt*. November 13, 2006.

¹⁴ Lipton, Eric. "U.S. Cancels Order for 75 Million Doses of Anthrax Vaccine." *The New York Times*, December 20, 2006. www.nytimes.com/2006/12/20/us/20anthrax.html?ex=1182312000&en=4653e6b239536077&ei=5070 (Downloaded February 14, 2008).

identified, particularly their government or non-government affiliations and possible conflicts of interest.

(2) **Manufacturing capacity.** The status of the nation's flu vaccine manufacturing capacity, the plans for expanding this capacity, and estimates of the capacity in the future are obviously important, because expanded capacity before a pandemic translates into speedier production during a pandemic.¹⁵ Much of this information has already been published online at www.pandemicflu.gov. However, the success of the government's vaccine program depends on adequate manufacturing capacity. For this reason, further details should be provided on the federal government's specific plans for the expansion of manufacturing capacity. The government should consider further expansion of manufacturing capacity through government subsidies or price guarantees. It is very costly to create new manufacturing plants purely as standby facilities, idle until the outbreak of a pandemic. An alternative is dual-purpose plants used regularly for the production of seasonal flu vaccine; these plants are profitable for the manufacturer and are also available immediately to produce pandemic flu vaccine when needed. The construction of such manufacturing plants can be encouraged by government subsidy of annual flu shots, and Ontario, Canada, has just such a program. Although the U.S. government is aware of this program, there are apparently no plans to adopt it, a decision that should be justified publicly.¹⁶

(3) **Domestic dependence on foreign production.** After the start of a pandemic, manufacturers in a country will devote their full production capabilities to production of vaccine for the domestic use within that country. Foreign sources of materials for vaccine production (and steps that are part of vaccine production) that were available under non-pandemic conditions may be blocked once a pandemic starts. In the fall of 2004, shortly before the beginning of the flu season, half of the total U.S. supply of vaccine for *seasonal* flu was interrupted.¹⁷ The reason: a manufacturer in England, Chiron Corporation, had discovered a technical problem (bacterial contamination) that rendered its vaccine unusable. Partly as a result of this experience, the manufacturing facilities for *pandemic* flu vaccine are now located in the U.S. However, the manufacturers may

¹⁵ (1) International Federation of Pharmaceutical Manufacturers & Associations (IFPMA). "The Link between Seasonal and Pandemic Influenza Vaccine Production." September 26, 2007. www.ifpma.org/Influenza/content/pdfs/2007_09_26_IFPMA_IVS_BG_paper_on_Link.pdf (Downloaded February 14, 2008). (2) Perrone, Matthew. "Gov't Prepares for Bird-Flu Pandemic." *The Washington Post* (the Associated Press), February 1, 2007. www.washingtonpost.com/wp-dyn/content/article/2007/02/01/AR2007020101438_pf.html (Downloaded February 14, 2008).

¹⁶ Schwartz, Benjamin, et al. "Universal Influenza Vaccination in the United States: Are We Ready? Report of a Meeting." *Journal of Infectious Diseases*, Vol. 194 (Suppl. 2), November 1, 2006. pp. S147-S154. But the effectiveness of the Ontario program is uncertain: (1) Groll, Dianne L. and David J. Thomson. "Incidence of influenza in Ontario following the Universal Immunization Campaign." *Vaccine*, Vol. 24, June 12, 2006. pp. 5245-5250. (2) Branswell, Helen. "Pandemic flu vaccine capacity swells but insiders worry about sustainability." *Canadian Press*, October 23, 2007.

¹⁷ Brown, David. "Half of U.S. Flu Vaccine Withheld: Supply Due From British Firm Tainted." *The Washington Post*, October 6, 2004. <http://www.washingtonpost.com/wp-dyn/articles/A8210-2004Oct5.html> (Downloaded February 14, 2008).

currently be dependent on foreign sources for some materials or steps in the manufacturing process. Any such dependence on foreign sources, as well as the timetable for full self-sufficiency, should be described online.

- (4) **Material transfer agreements.** Statements should be published online about the status of the government's efforts to facilitate transfer of materials (such as virus samples, antibodies, and cell lines) from one research group or company to another, including a discussion of cases in which this process is not working well. For example, when efforts to enter into material transfer agreements related to the vaccine program are hindered or delayed, as much information as possible should be made public. In cases like these, as in others involving the protection of intellectual property, the business practices that are customary in ordinary circumstances may be detrimental to public health and safety in an emergency.
- (5) **Intellectual property.** Guidelines and statements should be published online about access to intellectual property (patents, trade secrets, and know-how), including a description of the government's efforts to broaden access through discussion, negotiation, and subsidies; the initial steps of compulsory licensing; and completion of compulsory licensing. If there are specific cases in which this process is not working well, they should be discussed publicly to the extent possible. In addition, specific plans, if any, should be outlined for head-to-head clinical comparisons of the few most promising vaccines containing patented, proprietary adjuvants and/or aluminum salt adjuvants. More generally, the timetable of plans, if any, to start discussions of compulsory licensing with patent owners (or if necessary, to impose compulsory licensing) should be described and explained online. If, as seems likely, the government's current plan is to postpone any compulsory licensing until the start of a pandemic, reasons should be given for this decision. In that case, it is important to include an assessment of the risks of postponement. [See Appendix B for more information on patent rights.]
- (6) **Foreign governments and the World Health Organization.** The U.S., among all countries, has made the largest monetary contribution to global efforts to prepare for a pandemic.¹⁸ The U.S. government is issuing reports on its plans for coordinating its vaccine program with that of foreign governments and the WHO.¹⁹ These public reports should be expanded to include an explicit statement of what the U.S. government will and will not do for other countries when a pandemic begins.
- (7) **Alternatives to current vaccines.** Major increases in government support for the production of other kinds of vaccines, such as live-attenuated vaccines²⁰ and recombinant

¹⁸ Some details are provided on page 28 of GAO-07-604, report of the Government Accountability Office, "Influenza Pandemic: Efforts to Forestall Onset Are Under Way; Identifying Countries at Greatest Risk Entails Challenges." June 2007. www.gao.gov/new.items/d07604.pdf (Downloaded February 14, 2008).

¹⁹ The role of the U.S. is summarized in, U.S. Department of State. "United States International Engagement on Avian and Pandemic Influenza." July 11, 2007. www.state.gov/r/pa/scp/88620.htm (Downloaded February 14, 2008).

²⁰ Luke, Catherine J. and Kanta Subbarao. "Vaccines for Pandemic Influenza." *Emerging Infectious Diseases*, Vol. 12, January 2006. pp. 66-72.

hemagglutinin vaccines,²¹ should be considered and discussed online. Administrators and scientists in the government's vaccine program are undoubtedly well aware of arguments for and against investing more heavily in the production of these types of vaccine. Live-attenuated and recombinant hemagglutinin vaccines lend themselves to rapid, large-scale production and the immunization of large populations²²—a significant advantage if a pandemic should emerge within the next few years. The expertise and most of the facilities needed to produce these vaccines already exist. With the available resources and with adequate funding, billions of doses of vaccine could be produced significantly faster than six months after the start of a pandemic.²³ In recent congressional testimony, a senior HHS official stated that a contract solicitation was issued in August 2007 for development of recombinant vaccines over the next three to five years.²⁴ There should be a public explanation of the need for this long a period. The U.S. could make a noteworthy and honorable contribution to world health by speeding up the timetable for flu vaccine availability around the world.

- (8) **Size of budget.** Questions about the total federal budget for pandemic flu preparedness were raised in a 2006 *Journal of Infectious Diseases* article entitled, "Seasonal and pandemic influenza: Recommendations for preparedness in the United States."²⁵ The article contains recommendations made by representatives from the federal government, state and local governments, professional societies, academia, and the pharmaceutical industry. The authors of the article propose a several-fold increase in the level of funding—namely, an additional \$30 billion—for pandemic preparedness.²⁶ They propose that part of this amount be used to expedite vaccine development, expand domestic vaccine production sources, and increase seasonal vaccination. The arguments for and against their proposal should be discussed by federal employees on the government's

²¹ Treanor, John J. et al. "Safety and Immunogenicity of a Baculovirus-Expressed Hemagglutinin Influenza Vaccine." *Journal of the American Medical Association*, Vol. 297 No. 14, April 11, 2007. pp. 1577-1582. <http://jama.ama-assn.org/cgi/reprint/297/14/1577> (Downloaded February 14, 2008).

²² (1) Fedson, David S. and Peter Dunnill. "New Approaches to Confronting an Imminent Influenza Pandemic." *Permanente Journal*, Vol. 11 No. 3, Summer 2007. pp. 63-69. <http://xnet.kp.org/permanentejournal/SUM07/influenza-pandemic.pdf> (Downloaded February 14, 2008). (2) Fedson, David S. and Peter Dunnill. "Commentary: From scarcity to abundance: pandemic vaccines and other agents for 'have not' countries." *Journal of Public Health Policy*, Vol. 28, 2007, pp. 322-340. www.palgrave-journals.com/jphp/journal/v28/n3/full/3200147a.html (Downloaded February 14, 2008).

²³ Ibid.

²⁴ Vanderwagen, William C. "Pandemic Influenza: HHS Progress in National Preparedness Efforts." Testimony before Committee on Homeland Security and Governmental Affairs, Subcommittee on State, Local and Private Sector Preparedness and Integration, U.S. Senate. October 3, 2007. www.hhs.gov/asl/testify/2007/10/t20071003a.html (Downloaded February 14, 2008).

²⁵ Whitley, Richard J., et al. "Seasonal and Pandemic Influenza: Recommendations for Preparedness in the United States." *Journal of Infectious Diseases*, Vol. 194 (Suppl. 2), November 1, 2006. pp. S155-S161.

²⁶ The figure of \$30 billion is small compared with the economic impact of a flu pandemic without large-scale immunization, which was estimated to be roughly \$35 to \$250 billion in the U.S., depending on the severity of the pandemic. See Meltzer, Martin I, Nancy J. Cox, and Keiji Fukuda. "The Economic Impact of Pandemic Influenza in the United States: Priorities for Intervention." *Emerging Infectious Diseases*, Vol. 5, Sept.-Oct. 1999. pp. 659-671.

pandemic flu website for consideration by non-government experts and the general public. Changes in current plans for vaccine production may require a significant increase in the total budget of the vaccine program. However, the trend of congressional appropriations may be in the opposite direction.²⁷

CONCLUSION

In his article “Unprepared for a Pandemic” in the March/April 2007 issue of *Foreign Affairs*, public health expert Michael Osterholm deplores the complacency of world leaders. Their inaction “reflects a lack of comprehension about the devastation an influenza pandemic would wreak,” he writes.²⁸

Specifically, inadequacies in the U.S. vaccine program remain unaddressed. Although many senior employees in the program are recognized as world-class experts in vaccine research and production, most of the problems discussed here cannot be corrected by these scientists or administrators, no matter how skillful and experienced they are. Only those in the top levels of the U.S. government have the stature to act now, in the calm period of unknown length before a pandemic begins. That puts the decision squarely in the hands of the president, cabinet members, and the few congressional committees with the power to force change.

One problem is the leadership of the vaccine program. More than twelve months have passed since Congress established BARDA, yet a permanent director still has not been appointed.

Another problem is the failure to make some key information and documents readily and publicly available. Certain details of the vaccine program are shielded from close examination and potentially valuable criticism by experts outside government. The protection of the U.S. population depends in large part on the timing and success of the government’s vaccine program. If there is a shortage, the horrific scenario depicted in the missing document of October 2005 could become a reality. Government leaders can choose a different path, taking steps to ensure the timely success of the program for flu vaccine production. If this happens, the manufacturing facilities and know-how created to fight an influenza pandemic will almost certainly prove invaluable in quelling other contagious diseases that emerge in the decades ahead.

²⁷ Korade, Matt. “HHS Advisory Group Told Budget Cuts Imperil Pandemic Preparedness.” *CQ Homeland Security*, December 18, 2007. <http://public.cq.com/docs/hs/hsnews110-000002645930.html> (Downloaded February 14, 2008).

²⁸ Osterholm, Michael T. “Unprepared for a Pandemic.” *Foreign Affairs*, March/April 2007. pp. 47-57. www.cidrap.umn.edu/cidrap/files/67/foraffosterholm0307.pdf (Downloaded February 14, 2008).

RECOMMENDATIONS

- The Secretary of HHS should immediately recruit as the director of BARDA a person of near-cabinet-level stature who commands respect in the business and public health communities—someone willing to blast through financial and bureaucratic roadblocks.
- The HHS Secretary or the director of BARDA should require the prompt disclosure of all relevant documents in the pandemic flu vaccine program, including government contracts with vaccine manufacturers. In addition, there should be full disclosure of information related to:
 - Manufacturing capacity and plans to increase capacity through government subsidies or price guarantees
 - Dependence of domestic manufacturers on foreign production
 - Material transfer agreements, especially cases in which this process is not working well
 - Intellectual property issues, including a justification of apparent plans to postpone compulsory licensing until the start of a pandemic
 - Foreign governments and the World Health Organization, especially a statement of what the U.S. government will and will not do for other countries when a pandemic begins
 - Alternatives to current vaccines, especially the plans for significant increases in government support for other kinds of vaccines
 - Budget plans, in view of the call by some experts for a significant increase in the budget
- The material should be conveniently accessible, perhaps on the government's pandemic flu website. The disclosures should include a justification of the current plan for vaccine production, and should spell out the reasons for rejecting or deemphasizing alternative strategies.

Appendix A

Comments on Vaccine Production During a Flu Pandemic

COMMENTS ON VACCINE PRODUCTION DURING A FLU PANDEMIC

At present, the mainstay of vaccine production is an old method—growing influenza virus in fertilized chicken eggs, and then purifying the virus and converting it to vaccine. The method, devised in the mid-1940s, is dependable but slow. It can take four months or longer from the first step (large-scale production of eggs) to the finished vaccine. The speed with which eggs can be produced by the hundreds of millions—with roughly one egg needed per individual vaccine dose—imposes a limit on the amount of vaccine that can be made quickly.

In contrast, modern cell-based methods of growing viruses have a faster start-up, and they have a production capacity whose limits are set in part by the number and size of the vats in which the cells and virus are grown. At present, however, the maximum production capacity of both methods together, at top speed, is still far too low.

There are several ways to expand vaccine production. The standard influenza vaccine contains inactivated (killed) virus, but a few vaccines—some in development and some now in use—contain live attenuated (weakened) virus. The latter has several advantages: it creates immunity quickly, and a much smaller amount of material is needed per dose, perhaps as little as one-thirtieth or less, which means that many more people can be protected. Also, some experimental vaccines are composed of virus-related protein or DNA. Vaccines of this type are generally potent in smaller doses and are relatively easy to manufacture quickly on a large scale.

At present most vaccines for H5N1 virus also include added substances—“adjuvants”—that improve the effectiveness of small doses of the inactivated virus in the vaccine. Adjuvants could further enhance the total supply of vaccine.

Most of the new, quicker methods have yet to be approved by the Food and Drug Administration.

The immediate construction of many new manufacturing plants – plants held in readiness for the production of pandemic influenza vaccine – would increase the world’s capacity to make vaccine quickly when needed. However, this is costly and may not be the best use of limited resources. In contrast, some of the methods mentioned above lend themselves to rapid large-scale vaccine production in existing manufacturing facilities.

The leading candidate for the source of the next pandemic is the H5N1 avian influenza virus. For this reason, material to prepare H5N1 vaccines is now being manufactured and stockpiled under contracts with the U.S. Department of Health and Human Services. The efficacy of these “pre-pandemic vaccines” in a pandemic is uncertain. In any case, the amounts in the stockpile are sufficient to immunize only a few percent of the U.S. population.

Whether or not the stockpiled vaccines prove usable, the process of manufacturing them has important indirect benefits. Manufacturers are acquiring experience that will help them get a quicker start on vaccine production in a pandemic.

A universal vaccine

Of the many different vaccines under development, almost all are tailored to only a single strain of virus. A single-strain vaccine generally provides little or no protection against the dozens of influenza strains that differ from the single targeted strain.

In contrast, a “universal vaccine”—one that is effective against most or all influenza strains—could be manufactured in quantity long before the outbreak of a pandemic and would be ideal for protecting this country’s and the world’s population. However, a universal vaccine that serves as a replacement for single-strain vaccines may prove unattainable in the foreseeable future.

The multiplicity of approaches, and the importance of free access to materials and methods

Of the various approaches to vaccine development and manufacture, it is hard to predict which will prove best. It depends on the success of work still in progress, on the capacity of manufacturing facilities, and on how soon a pandemic begins.

The sheer multiplicity of approaches, combined with the urgent need for success in the vaccine program before the start of a pandemic, provides a strong reason for scientists, engineers, and industry executives to have unencumbered access to a full range of materials and methods that may be useful, whether patented or not. This kind of free access should begin now and should continue until the vaccine problem is solved or until the pandemic is behind us.

For more information

Further information about vaccine production can be found in the “Vaccine Development” section of CIDRAP’s (Center for Infectious Disease Research and Policy) “Pandemic Influenza” web page.¹

¹ Center for Infectious Disease Research and Policy. “Pandemic Influenza.” (Updated February 20, 2008.) www.cidrap.umn.edu/cidrap/content/influenza/panflu/biofacts/panflu.html (Downloaded February 25, 2008).

Appendix B

Patent Rights and Other Intellectual Property Rights

PATENT RIGHTS AND OTHER INTELLECTUAL PROPERTY RIGHTS

Although it's not known that patent rights are currently impeding progress in vaccine development, there is a good possibility that they may. Patented methods are often profitable to the company owning the patent.¹ For this very reason, patent rights could create a financial barrier to the easy sharing of methods between companies—for example, sharing the best methods of producing a vaccine or enhancing its potency.²

Biotechnology expert Edward Hammond has noted the possibly enormous value of patented discoveries in the event of a pandemic:

The ultimate value of the currently claimed sequences [of the influenza virus gene and parts of the gene] and technologies is uncertain, but if any prove critical to combat a pandemic, it may be enormous. If a particular sequence, adjuvant or cell culture process is uniquely advantageous to producing an effective pandemic vaccine, then access to that technology may be mandatory for protection of public health. With the dramatic upswing in patent activity, these concerns will steadily increase.³

The government should urge vaccine manufacturers to loosen their grip on their own patented methods, as well as on their trade secrets and know-how. In selected cases, manufacturers should be pressed to give other companies quick access to these methods, free of charge or at low cost, instead of charging their usual licensing fees or royalties or blocking access altogether.

In a previous time of crisis, one company took a decisive step to eliminate questions about its patent rights. During World War II, the DuPont Company insisted on surrendering all patent rights arising from its involvement in the Manhattan Project. “The importance to the nation of

¹ Many patents are never used and of those that are used, only a few prove profitable.

² A limited vaccine supply can be expanded several-fold simply by the addition of adjuvants—substances that enhance the potency of small doses of certain common types of vaccine. Patented proprietary adjuvants are now being tested and used by federal government contractors. To maximize the chances of success of the government's vaccine program, licensing fees and royalties should not be allowed to stand in the way of any company, with or without a government contract, that wants to test and use another company's patented adjuvant. Also, patent rights should not be allowed to hinder direct head-to-head comparisons of the most promising adjuvants.

Several companies presented results of their clinical studies on flu vaccines at a meeting in February 2007 sponsored by the World Health Organization. Three companies included their own proprietary adjuvants in some of the vaccines they tested. None compared their own adjuvants with the proprietary adjuvants controlled by the other companies. The studies are described in the presentation documents for this meeting: World Health Organization. “3rd WHO meeting on evaluation of pandemic influenza prototype vaccines in clinical trials, 15-16 February 2007, WHO, Geneva.” www.who.int/vaccine_research/diseases/influenza/meeting_150207/en/ (Downloaded February 14, 2008).

³ Hammond, Edward. “Some Intellectual Property Issues Related to H5N1 Influenza Viruses, Research and Vaccines.” *The Sunshine Project & Third World Network*, July 2007. www.sunshine-project.org/flu/patent_report.pdf (Downloaded February 14, 2008)

the work on releasing atomic energy was so great that control, including patent rights, should rest with the government,” wrote the president of DuPont.⁴

One vaccine company has already moved in this direction. In December 2003, MedImmune, Inc. relaxed its control over a unique method of crucial importance to the production of influenza vaccine. MedImmune made its patented method (“reverse genetics”) available without charge to any company using the method for non-profit, public health purposes in developing vaccines for pandemic influenza.⁵

Federal government officials should publicly applaud this kind of corporate generosity when it occurs.⁶

Sometimes just the threat of a compulsory license imposed by the U.S. or other countries will induce a company to loosen its patent restrictions or lower its prices. This happened with Tamiflu, a patented drug used to treat influenza, and with patented AIDS drugs sought by developing countries that could not afford the high prices of these drugs.⁷

But voluntary action by companies will probably be uncommon. The federal government can then intervene. Under federal law, the government can issue a “compulsory license” that allows a company to use another company’s patented method under terms set by the government and

⁴ Carpenter, W.S., Jr. “To all employees of E. I. Du Pont de Nemours & Company.” August 24, 1945. <http://pogoarchives.org/m/science/is-dupont-19450824.pdf>. Can also be found on the website of the Manhattan Project Heritage Association. www.mphpa.org/classic/DO/D-012.htm (Downloaded February 14, 2008). The decision by DuPont management to surrender patent rights may also have been, in part, an attempt to improve the company’s public image, which was suffering at that time. Cheape, Charles W. *Strictly Business: Walter Carpenter at Du Pont and General Motors*. Baltimore: Johns Hopkins University Press, 1999. pp. 130-133, 191.

⁵ National Academic Press. “Statement from MedImmune, Inc., Regarding Reverse Genetics Technology.” *The Threat of Pandemic Influenza: Are We Ready? Workshop Summary* (2005). pp. 196-197. http://books.nap.edu/openbook.php?record_id=11150&page=196 (Downloaded February 14, 2008). http://books.nap.edu/openbook.php?record_id=11150&page=197 (Downloaded February 14, 2008).

⁶ There’s a limit to MedImmune’s generosity. Companies that plan to *sell* vaccine may be charged for using MedImmune’s reverse genetics technology. MedImmune “will receive an upfront payment and has the potential to receive royalties on certain stockpiles or sales of other influenza products developed using the reverse genetics technology.” MedImmune press release. September 24, 2007. <http://investor.medimmune.com/phoenix.zhtml?c=83037&p=irol-investornewsArticle&ID=1054747&highlight=> (Downloaded February 14, 2008).

The prospect of payments to MedImmune may discourage some companies from making a commitment to manufacture pandemic flu vaccine that will be sold. This is because their vaccines may be made from reference strains created in WHO-affiliated laboratories using MedImmune’s reverse genetics technology.

⁷ (1) Kaufman, Marc. “Swiss Firm may Cede Bird Flu Drug Rights.” *The Washington Post*, October 19, 2005. www.washingtonpost.com/wp-dyn/content/article/2005/10/18/AR2005101801507.html (Downloaded February 14, 2008). (2) Swarns, Rachel L. “AIDS Drug Battle Deepens in Africa.” *The New York Times*, March 8, 2001. www.nytimes.com/2001/03/08/health/08AIDS.html?ex=1192939200&en=70e0a0c10d7accda&ei=5070 (Downloaded February 14, 2008).

without the consent of the patent owner. Economist James Love has analyzed and provided examples of compulsory licensing.⁸

There is an obvious downside to this peremptory step: it may deter corporate investment and innovation in the future. For this reason the government should ensure that appropriate compensation is promptly paid to any company forced to give up its patent rights.

Government officials should openly consider the option of imposing compulsory licensing for certain key patents. Otherwise, the sudden start of a pandemic may make it clear that the best moment to remove a patent barrier has passed, and that the delay will cost lives.

⁸ Love, James Packard. "Recent examples of the use of compulsory licenses on patents." KEI Research Note 2007: No 2. pp. 1-18. www.keionline.org/misc-docs/recent_cls.pdf (Downloaded February 14, 2008). A report on a related issue ("Patent issues related to influenza viruses and their genes") has been commissioned recently by the World Health Organization. www.who.int/csr/disease/avian_influenza/wipo_ipdoc/en/index.html (Downloaded February 14, 2008).