

Report for Congress

Received through the CRS Web

Smallpox Vaccine Stockpile and Vaccination Policy

January 9, 2003

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Summary

On December 13, 2002, President George W. Bush announced the administration's long-awaited policy for vaccinating U.S. citizens against smallpox. That same day, the government began vaccinating an estimated 500,000 troops and other personnel who serve in high risk parts of the world. Voluntary vaccination of up to 500,000 civilian healthcare and public health workers probably would not begin until after January 24, 2003, a date set by Section 4 of the Homeland Security Act of 2002 (P.L. 107-296). The Bush Administration plan for civilian healthcare workers follows the October 17, 2002, recommendations made by an advisory panel to the Centers for Disease Control and Prevention (CDC) on several smallpox vaccination implementation issues. The panel advised immunizing two groups of civilians: (1) public health response teams who would investigate initial smallpox cases and implement control measures; and (2) healthcare teams composed of 50-100 individuals at each of the 5,100 acute care hospitals in the United States who would care for smallpox patients.

Smallpox vaccine has a higher rate of serious complications than any other vaccine in current use. When this vaccine was routinely given more than 30 years ago, about 1,000 persons per million vaccinated for the first time experienced reactions that were serious but not life threatening, such as accidental inoculation, in which the rash occurs elsewhere on the body (from the vaccination site) due to direct contact with vaccinia. Blindness may result if the rash develops near the eye. About 14 to 52 people per million vaccinated for the first time developed potentially life threatening reactions; one or two per million died as a result of vaccination. These more serious complications include: (1) encephalitis which may be fatal or leave survivors with paralysis or other central nervous system symptoms; (2) growth of the vaccination lesion without healing, which occurs in immunocompromised individuals and is often fatal; (3) passage of vaccinia to a fetus, which may lead to stillbirth; and (4) development of vaccinia lesions over sites where there is or has been eczema, which may be fatal. Because live vaccinia virus is used in the smallpox vaccine, complications may occur in individuals who don't even receive the vaccine but are only exposed to someone who has recently been vaccinated. The federal government is encouraging both academic scientists and companies to develop a safer vaccine and antiviral treatments.

In the Homeland Security Act of 2002 (P.L. 107-296), Congress addresses the smallpox vaccine liability concerns of vaccine manufacturers and health care workers by designating them to be federal employees for the purpose of administering smallpox vaccine. The federal government would assume liability for smallpox vaccine-related injuries and deaths under the Federal Tort Claims Act which does not permit jury trials or punitive damages. If an individual injured by the smallpox vaccine were to file suit against the federal government, that individual would be required to provide evidence of negligence. However, most vaccine-related injuries are not the result of negligence. It is expected that health care insurance and worker's compensation programs would pay for patient care expenses in the event of a smallpox vaccine-related injury. This report will be updated as needed.

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Smallpox Vaccine Stockpile and Vaccination Policy

The terrorist attacks of the fall of 2001 resulted in increased attention to preparedness for other such possible events, one being the deliberate release of variola virus, the virus which causes smallpox. Although there is little uneasiness over the safety of the only known samples of variola virus, held by the CDC in Atlanta and a laboratory near Novosibirsk in Russia, there is some concern that samples of the virus may have been acquired by terrorists or rogue governments, particularly because of the unrest that occurred during the break up of the Soviet Union.¹

Smallpox disease and smallpox vaccination

Smallpox is transmitted via person-to-person contact or inhalation of saliva droplets from the breath of an infected person. The incubation period of 12-14 days (range 7-17 days) is followed by the sudden onset of flu-like symptoms. After 2-3 days the distinctive rash begins to appear, and it is this stage, which lasts for 7-10 days, that is most infectious. As scabs begin to form infectivity rapidly declines. About 65% to 80% of survivors have deep scars or pockmarks which tend to occur on the face. The last recorded natural case of smallpox occurred in Somalia in 1977; a fatal laboratory-acquired case occurred in England in 1978. The last U.S. case was in 1949. After a worldwide effort of organized vaccination, smallpox was declared eradicated by the World Health Assembly in May 1980.

Smallpox vaccination is achieved via inoculation using live vaccinia virus, a pox virus that is closely related to variola virus. Vaccination is highly effective: 95% of people who receive the vaccine before exposure to smallpox (variola) virus will be protected from developing the disease. Vaccination within 2 to 3 days after exposure to variola will prevent smallpox or significantly lessen the effects of the disease in most people. Vaccination 4 to 7 days after exposure to variola virus may offer some protection from disease or may modify the severity of disease. A successful vaccination provides 3 to 5 years of protection from smallpox. Partial protection is thought to continue for 10 or more years but the length of time and level of protection is uncertain.

Rather than the typical hypodermic needle, smallpox vaccine is given using a 2-pronged (bifurcated) needle that is dipped into the vaccine solution. The prongs

¹ See also: CRS Report RL31059, *Biological Weapons: A Primer*; RL31368; CRS Report RL31368, *Preventing Proliferation of Biological Weapons: U.S. Assistance to Former Soviet States*; and CRS Report RS21288, *Smallpox: Technical Background on the Disease and its Potential Role in Terrorism*.

retain a drop of vaccine and the needle is jabbed into the upper arm several times causing a drop of blood to form. Within 3 to 4 days an itchy bump develops; by the end of a week a pus-filled blister forms and begins to drain. Because live vaccinia virus is used in smallpox vaccine, care must be taken (hand washing, careful bandage disposal) not to spread the virus to other parts of the body or to other people who may be at risk for adverse reaction. During the second week, the blister dries and a scab develops; the scab falls off in the third week, leaving a small scar. A successful reaction, often referred to as a “take,” is often more evident in people who are vaccinated for the first time than in those who are revaccinated.

The side effects associated with use of smallpox vaccine are not insignificant. Less serious complications of vaccination include sore arm, headache, body ache, fatigue, rash, and fever. When this vaccine was routinely given more than 30 years ago, about 1,000 persons per million vaccinated for the first time experienced reactions that were serious but not life threatening, such as accidental inoculation, in which the rash occurs elsewhere on the body (from the vaccination site) due to direct contact with vaccinia. Blindness may result if the rash develops near the eye. About 14 to 52 people per million vaccinated for the first time developed potentially life threatening reactions; 1 or 2 per million died as a result of vaccination. These more serious complications include:

- ! postvaccinial encephalitis, which may be fatal or leave survivors with paralysis or other central nervous system symptoms;
- ! progressive vaccinia, or growth of the vaccination lesion without healing, which occurs in immunocompromised individuals and is often fatal;
- ! fetal vaccinia, passage of vaccinia to a fetus, which may lead to stillbirth;
- ! eczema vaccinatum, or development of vaccinia lesions over sites where there is or has been eczema, which may be fatal.

Because of the serious complications from the vaccine, and since the risk of importation of a smallpox case had been greatly reduced due to vaccination programs and quarantine regulation, the U.S. Public Health Service recommended in 1971 that routine smallpox vaccination be discontinued; the U.S. program stopped in 1972. Smallpox vaccination has not been required for international travel since January 1982 and distribution of the vaccine to the general public stopped in 1983. Routine smallpox vaccination of U.S. health care workers was discontinued in 1976; military recruits stopped receiving the vaccine in 1990.

An unfortunate side effect of the eradication of smallpox, widely acclaimed as a major public health triumph, is that the U.S. population and the rest of the world are vulnerable to biologic weapon attack using variola virus. In past natural outbreaks, smallpox killed 30% of those who had no immunity. Approximately 119 million U.S. residents born after 1972 lack immunity. The immunity of the 157 million U.S. residents born before 1972 has declined and their level of disease protection is uncertain.

U.S. smallpox vaccination policy

Bush Administration policy. On December 13, 2002, President George W. Bush announced the administration's long-awaited policy for vaccinating U.S. citizens against smallpox.² That same day, the government began vaccinating an estimated 500,000 troops and other personnel who serve in or may be sent to high risk parts of the world and who are not medically at high risk of vaccine-related adverse effects. The State Department will also offer the vaccine on a voluntary basis to some overseas personnel.

Under the Bush Administration plan, civilian healthcare and public health workers will also be vaccinated against smallpox, but on a voluntary basis.³ The plan for civilian healthcare workers follows the October 17, 2002, recommendations made by an advisory panel to the Centers for Disease Control and Prevention (CDC) on several smallpox vaccination implementation issues.⁴ The panel advised immunizing two groups of civilians: (1) public health response teams who would investigate initial smallpox cases and implement control measures; and, (2) healthcare teams composed of 50-100 individuals at each of the 5,100 acute care hospitals in the United States that would care for smallpox patients. Each volunteer will be questioned about his or her medical history and educated on the medical risks associated with the vaccine. If there is any indication that the individual may be at risk for complications from the vaccine he or she would be directed to undergo additional medical tests (HIV, pregnancy) before being vaccinated.

On November 22, 2002, CDC asked all 50 states, four cities (New York, Los Angeles, Chicago, Washington, D.C.) and the territories to submit by December 9, 2002, a plan for immunizing the above-mentioned healthcare workers and public health smallpox response teams. The plan should provide for immunization of the teams within a 30-day time frame. CDC will review the plans and notify the state or territory whether the plan was complete and met CDC criteria. Smallpox vaccine will not be released until plans are approved by CDC. As of December 19, 2002, CDC had received plans from all 50 states and Los Angeles, Chicago, New York City and Washington D.C. According to CDC, the plans indicate that about 440,000

² Remarks by President Bush on December 13, 2002, regarding smallpox vaccination can be found at: [<http://www.whitehouse.gov/news/releases/2002/12/20021213-7.html>]. See also the White House fact sheet "Protecting Americans: Smallpox Vaccination Program" at: [<http://www.whitehouse.gov/news/releases/2002/12/20021213-1.html>].

³ Because of liability concerns, vaccination of healthcare workers probably will not begin until after January 24, 2003, a date effectively set by Section 4 of H.R. 5005, The Homeland Security Act of 2002 (P.L. 107-296). In addition, Section 304 provides that the United States may be held liable for injuries caused by a smallpox vaccine only if the vaccine was administered during the effective period of a declaration of a public health emergency by the Secretary of Homeland Security.

⁴ The October 17, 2002, ACIP Smallpox Vaccination Recommendations can be found at: [<http://www.bt.cdc.gov/agent/smallpox/vaccination/acip-recs-oct2002.asp>].

healthcare workers may be offered smallpox vaccine and over 3,600 medical facilities that may participate are identified.⁵

Because of the health risk associated with the vaccine, President Bush stated that as commander in chief he also would be vaccinated because he would not ask others to take the risk unless he was willing to do the same. The president reportedly received a smallpox vaccination on December 21, 2002, and has not experienced any side effects.⁶ At the present time, however, smallpox vaccine is not recommended for anyone else in the administration or the general public. The Department of Health and Human Services (HHS) is working to develop a process to make smallpox vaccine available to adults in the general public who insist on being vaccinated and who are not at high risk for any of the complications posed by the vaccine. Such individuals may be eligible to enroll in a clinical trial or may receive unlicensed vaccine in 2003 or licensed vaccine in 2004.⁷ As of January 8, 2003, 5 clinical trials of smallpox vaccine were recruiting patients.⁸

Events leading up to Bush Administration policy. Federal vaccination policy attempts to balance the likelihood of the adverse effects of smallpox vaccine against the likelihood of a biowarfare attack using variola virus. After the terrorist attacks in the fall of 2001, CDC and HHS asked the Advisory Committee on Immunization Practices (ACIP) to consider if changes were needed in the June 2001 recommendations on smallpox vaccination.⁹ Under the June 2001 recommendations, only laboratory workers who directly handle smallpox-related virus were vaccinated. Following public meetings, draft supplemental recommendations on smallpox vaccination were developed by ACIP and the National Vaccine Advisory Committee (NVAC). The draft was approved by ACIP on June 20, 2002.

Under the June 20, 2002, draft ACIP plan, vaccination of the general public prior to a smallpox attack was not recommended because “the risk of an attack was assessed to be low” and, therefore, “the potential benefits of vaccination do not outweigh the risks of vaccine complications.” Instead ACIP recommended voluntary

⁵ CDC Telebriefing Transcript. Updates: Smallpox Educational Activities and West Nile Virus. December 19, 2002. [<http://www.cdc.gov/od/oc/media/transcripts/t021219.htm>]

⁶ Allen, M. Bush Receives Smallpox Vaccination. *Washington Post*, December 22, 2002, p. A11; Associated Press. Bush Fine After Vaccine, *Washington Post*, December 23, 2002, p. A5; and, Associated Press. Bush Has No Ill Effects From Smallpox Vaccine, *Washington Post*, January 7, 2003, p. A6.

⁷ See the White House fact sheet “Protecting Americans: Smallpox Vaccination Program” at: [<http://www.whitehouse.gov/news/releases/2002/12/20021213-1.html>], and the White House “Frequently Asked Questions” document at: [<http://www.whitehouse.gov/news/releases/2002/12/20021213-3.html>].

⁸ Further information on the smallpox vaccine clinical trials can be found at: [<http://www.clinicaltrials.gov>].

⁹ ACIP is a 15 member group of medical and public health experts that provides advice to CDC and the rest of HHS on vaccine use and policy for effective disease control in the civilian population. ACIP recommendations can be found at: [<http://www.bt.cdc.gov/agent/smallpox/vaccination/index.asp>].

smallpox vaccination of two groups. The first group would investigate initial smallpox cases and implement control measures. The second group would consist of healthcare personnel at a limited number of designated hospitals that would be involved in caring for smallpox patients. ACIP estimated that under the June 2002 plan, 10,000 to 20,000 individuals would have received the vaccine. State health officials and hospital administrators expressed concern over designating only certain hospitals for the care of smallpox patients, reasoning that victims would likely go to their nearest hospital.

The ACIP draft recommendations were reviewed by CDC and HHS and a revised plan was sent in early September 2002 to the White House for approval. At an October 4, 2002, news conference federal health officials stated they were considering plans to immunize up to 10 million healthcare workers against smallpox and offer the vaccine to the general public by 2004.¹⁰ In response to these statements, the American Academy of Pediatrics (AAP) and the American Medical Association (AMA) urged caution in expanding voluntary smallpox vaccination beyond front-line healthcare workers citing as concerns the potential health risks of the vaccine, the associated liability problems, and the public's lack of knowledge about dangers of the smallpox vaccine.¹¹ The American Academy of Family Physicians had previously expressed a similar position.¹² The Infectious Disease Society of America has also recommended that smallpox vaccination of the general public should not be employed, not even on a voluntary basis.¹³

On October 17, 2002, ACIP released further recommendations on smallpox vaccination. The recommendations were developed at the request of CDC with input from NVAC and the Healthcare Infection Control Practices Advisory Committee (HICPAC). The expert groups were asked to provide guidance on 8 smallpox vaccination implementation issues. In response to concerns over the June 2002 plan which designated only certain hospitals for the care of smallpox patients, the panel advised voluntary immunization of health care teams (composed of 50-100 individuals) at each of the 5,100 acute care hospitals in the United States. ACIP estimated that about 500,000 hospital workers would receive the smallpox vaccine under the revised plan.

Some are hesitant to recommend vaccination of the general public prior to a smallpox outbreak or attack because smallpox vaccine has a higher complication rate than any other vaccine in current use. An estimated 28 million people with eczema and 10 million people with a compromised immune system (for example, organ

¹⁰ Altman, L.K., and S.G. Stolberg. Smallpox Vaccine Backed for Public. *New York Times*, October 5, 2002. p. A1, A12.

¹¹ The AAP statement can be found at: [<http://www.aap.org/advocacy/releases/octsmallpox.htm>]. The AMA statement is at: [<http://www.ama-assn.org/ama/pub/print/article/1617-6824.html>].

¹² The AAFP position can be found at: [<http://www.aafp.org/x10636.xml?printxml>].

¹³ The Infectious Disease Society of America (IDSA) is a professional society representing 7,000 physicians and scientists who specialize in infectious diseases. The IDSA website can be found at: [<http://www.idsociety.org/>].

transplant recipients, HIV/AIDS or cancer patients) – approximately 15% of the population – are at high risk for developing serious complications.¹⁴ Such complications will also occur in the rest of the population, but at a lower rate.

Because live vaccinia virus is used in the smallpox vaccine, complications may occur in individuals who don't even receive the vaccine but are only exposed to someone who has recently been vaccinated. One recent study found that even if high risk individuals and their household contacts (25% of the U.S. population) were excluded from vaccination, an estimated 1,600 serious adverse events and 190 deaths would occur if people aged 1 to 29 years were vaccinated, and 4,600 serious adverse events and 285 deaths would occur if people aged 1 to 65 years were vaccinated.¹⁵

Liability problems associated with the use of smallpox vaccine could be enormous. Section 304 of the Homeland Security Act (P.L. 107-296) addresses liability concerns of manufacturers and distributors of the smallpox vaccine, healthcare entities where the smallpox vaccine is administered, and healthcare workers who are authorized to administer the vaccine.¹⁶

Control of a smallpox outbreak

CDC has been updating the smallpox response plan that was previously developed during the 1970s for responding to the potential importation of smallpox. This document, called the *CDC Smallpox Response Plan and Guidelines*, incorporates and extends many of the concepts and strategies that were successfully used 30 to 40 years ago to control smallpox outbreaks and eradicate the disease.¹⁷ The CDC Plan, much of which has been in place for many years, assists state and local public health departments in developing their own regionally tailored smallpox outbreak response plans. It outlines the public health strategies and approaches that would guide the response to a smallpox emergency and identifies many of the federal, state and local activities that must be undertaken.

On September 23, 2002, the CDC released the “Smallpox Vaccination Clinic Guide,” which provides operational and logistical considerations for mass voluntary vaccinations in the event of a confirmed attack involving smallpox virus. The “Clinic Guide” is a small part of the much larger *CDC Smallpox Response Plan and Guidelines*. CDC is also working with state and local public health departments to improve preparedness for responding to other potential bioterrorist weapons.

¹⁴ Kemper, A.M., et al. Expected Adverse Events in a Mass Smallpox Vaccination Campaign. *Effective Clinical Practice*, v. 5, March/April 2002. p. 84-90.

¹⁵ *Ibid.*, p. 84.

¹⁶ For further information on Section 304 of P.L. 107-296 see: CRS Report RL31649, *Homeland Security Act of 2002: Tort Liability Provisions*, by (name redacted); and, Smallpox Questions and Answers: Section 304 of the Homeland Security Act on the CDC website at: [<http://www.bt.cdc.gov/agent/smallpox/vaccination/section-304-qa.asp>].

¹⁷ The CDC Smallpox Response Plan and Guidelines can be found at: [<http://http://www.bt.cdc.gov/agent/smallpox/response-plan/index.asp>].

In the past, naturally occurring outbreaks of smallpox have been controlled using ring vaccination: all the patient's contacts are tracked down, vaccinated and quarantined until the disease spread is stopped. Such a strategy is logical if there is limited vaccine, or a significant level of smallpox immunity in the population, or if a society wishes to limit the number of adverse events and fatalities caused by mass smallpox vaccination. However, in a modern society with low levels of smallpox immunity, mass transit and rapid forms of long distance travel, ring vaccination may not be feasible especially if the attack occurs in many sites and infects a large number of people at each site. Moreover, our social and economic system may be greatly stressed by the necessary implementation of quarantine.¹⁸ Some experts also question whether the existing public health system can actually implement a nation-wide smallpox vaccination program quickly enough under a bioterrorist attack situation.¹⁹

Researchers are using mathematical models of disease transmission to determine the outcome of a smallpox attack under a range of different conditions, such as the number of initial infections, the transmission rate (number of secondary cases caused by each initial case), the number of vaccinators, and whether ring or mass vaccination is used to control the outbreak. The models are still under development and provide contradictory results. For example, a model developed by researchers at Emory University found that ring vaccination, even when it's started only after the 25th case of smallpox, can contain an epidemic almost as well as mass vaccination, provided that at least 80% of those exposed can be found and vaccinated.²⁰

In contrast, a model developed at Yale University found that mass vaccination results in far fewer deaths and much faster epidemic eradication.²¹ The Yale model predicts that in a smallpox attack on a large city causing 1,000 initial cases, ring vaccination results in 367,000 cases and 110,000 deaths over 350 days, but mass vaccination following an attack results in 1,830 cases and 560 deaths over 115 days. However, if 40% of the population is vaccinated prior to attack, the number of deaths would be reduced to 40,000 if ring vaccination is used following a 1,000-case attack, but lowered even further to 440 deaths if mass vaccination is used after the attack. The Yale group concludes that unless pre-attack vaccination is used, serious consideration should be given to replacing the existing CDC policy with mass vaccination in the event of a smallpox attack in a large urban center.

Traditional methods, like ring vaccination, are based on the fact that smallpox spreads through person-to-person contact. A controversial report, presented at a June 15, 2002, Institute of Medicine meeting on smallpox vaccination, indicates that

¹⁸ For further information on quarantine issue see CRS Report RL31333, *Federal and State Responses to Biological Attacks: Isolation and Quarantine Authority*, by Angie Welborn.

¹⁹ Foege, William. Can Smallpox Be As Simple As 1-2-3? *Washington Post*, December 29, 2002, p. B5.

²⁰ Enserink, M. How Devastating Would a Smallpox Attack Really Be? *Science*, v. 296, May 31, 2002. p. 1592-1595.

²¹ Kaplan, E.H., et al. Emergency Response to a Smallpox Attack: the Case for Mass Vaccination. *Proceedings of the National Academy of Sciences, Early Edition*, July 8, 2002. [<http://www.pnas.org>]

aerosolized smallpox virus from a Soviet bioweapon test may have accidentally caused 10 cases of smallpox and three deaths in 1971 in what is now Aralsk, Kazakhstan.²² Some scientists criticized the report because they believe that aerosolized smallpox virus would be quickly inactivated by environmental factors, such as UV radiation from the sun. However, the authors of the report believe the best explanation for the outbreak is that the initial case, a technician on a research vessel, acquired smallpox when her boat entered waters 9 miles downwind from a Soviet bioweapons test site located on Vozrozhdeniye Island in the Aral Sea. Because an aerosol of smallpox virus would have the potential to infect a much larger number of people than person-to-person contact, this report is of concern to public health experts.

Although the 119 million unvaccinated people in the U.S. could face a mortality rate of about 30% in a smallpox attack, there is some question over the level of protection remaining in the 157 million individuals who were vaccinated more than 30 years ago. Complete protection from smallpox disease begins to taper off 3 to 5 years after vaccination. However, some historical data indicate that vaccinated individuals may experience milder disease symptoms and a lower mortality rate (5% instead of 30%) even up to 50 years post-vaccination.²³ Additional studies would be needed to confirm this point, but if correct, a smallpox attack might not be as deadly or spread as rapidly as some experts had thought. It might also influence decisions on who in the U.S. population should be the first to receive vaccines if a smallpox attack does take place.

U.S. stockpile of smallpox vaccine

Within the last year, HHS has been successful in greatly increasing the U.S. stockpile of smallpox vaccine via agreements with three separate sources: Wyeth Laboratories, a pharmaceutical company located in Marietta, PA; Acambis, a British drug firm with offices in Cambridge, MA; and Aventis Pasteur, a French vaccine company with a plant in Swiftwater, PA. The policy debate by ACIP and others on how many U.S. residents should be vaccinated has been made possible by HHS efforts to increase the U.S. stockpile of smallpox vaccine.

Wyeth Laboratories. In the fall of 2001, the National Institutes of Health (NIH) funded a study on whether the 15.4 million doses of smallpox vaccine in the U.S. stockpile could be diluted without losing potency. The vaccine, called Dryvax, was manufactured by Wyeth in 1982. Results of the study, released in April 2002,

²² The report, CNS Occasional Paper No. 9, *The 1971 Smallpox Epidemic in Aralsk, Kazakhstan, and the Soviet Biological Warfare Program*, edited by J.B. Tucker and R.A. Zilinskas, was published by the Center for Nonproliferation Studies of the Monterey Institute of International Studies. The report and commentaries on the report are available at: [<http://cns.miis.edu/pubs/opapers/op9/index.htm>]. See also: Enserink, M. Did Bioweapons Test Cause a Deadly Smallpox Outbreak? *Science*, v. 296, June 21, 2002. p. 2116-2117; Broad, W.J. and J. Miller. Report Provides New Details of Soviet Smallpox Accident, *New York Times*, June 15, 2002, p. A1, A15; and Brown, B. Soviets had '71 Smallpox Outbreak. *Washington Post*, June 16, 2002, p. A25.

²³ Cohen, J. Smallpox Vaccinations: How Much Protection Remains? *Science*, v. 294, November 2, 2001. p. 985.

indicate that the Dryvax can be safely diluted by a factor of 5 or 10. In 97% to 99% of study participants the diluted vaccine produced a “take” or skin lesion, a positive indicator of a protective immune response.²⁴ Although none of the 680 study subjects, aged 18 to 32, had a serious adverse reaction, there was a high frequency of pain, swelling and redness at the inoculation site as well as fever, headache, rash, muscle aches, fatigue and chills. More than a third of the subjects missed work, school, sleep, or other activities because of an adverse reaction.

On October 25, 2002, the Food and Drug Administration (FDA) approved a supplement to the license application for Dryvax. Although the original license for Dryvax has been in effect since 1931, a supplemental approval was necessary because a new liquid (diluent) is used to reconstitute the vaccine and a different manufacturer is used to make the bifurcated needles.²⁵ Of the 15.4 million doses of Dryvax held by HHS, only 2 lots – 2.7 million doses – have been released for use; 1 million doses will be set aside for the military and 1.7 will be for civilian use. The license only applies to an undiluted vaccine. Individuals in the military and healthcare workers who will be vaccinated under the initial stages of the Bush Administration plan will be given full strength smallpox vaccine rather than a diluted version. The remaining 12.7 million doses of Dryvax will be released on a lot by lot basis. Availability of the diluted vaccine will be limited to clinical trial settings.

Acambis. On November 28, 2001, HHS announced that Acambis Inc. had been awarded a \$428 million contract to produce an additional 155 million doses of smallpox vaccine by the end of 2002; this amount expands on an initial order of 54 million doses.²⁶ In September 2000 CDC had awarded a contract to Acambis for 40 million doses of smallpox vaccine by 2004. In September 2001 CDC renegotiated an accelerated production schedule under which Acambis agreed to produce 54 million doses by late 2002.

According to Acambis, the terms of the contracts with the federal government limit its ability to provide much detail on the status, quality or timing of delivery of smallpox vaccine.²⁷ Acambis states this is for security reasons, because the vaccine is intended to protect U.S. citizens from a potential bioterrorist attack. However, Acambis indicated that significant progress has been made towards achieving the contractual objectives. The first doses of smallpox vaccine have been produced for the U.S. vaccine stockpile and, according to an Acambis news release, CDC is fully

²⁴ Frey, S.E. et al. Clinical Responses to Undiluted and Diluted Smallpox Vaccine. *New England Journal of Medicine*, v. 346, April 25, 2002. p. 1265-1273.

²⁵ Wyeth Dryvax Smallpox Vaccine Approved for 100-Dose Kit, 30-Day Expiration. *Pink Sheet*, November 11, 2002, p. 22; and Connolly, C. FDA Grants License for Smallpox Vaccine. *Washington Post*, November 2, 2002, p. A13.

²⁶ The November 28, 2001, HHS press release can be found at: [<http://www.hhs.gov/news/press/2001pres/20011128.html>].

²⁷ Interim results for the 6 months ended 30 June 2002. Acambis news release dated September 18, 2002, found at: [<http://www.acambis.com>].

supportive of the progress made to date. CDC expects production of the Acambis vaccine to be completed in May 2003.²⁸

The Acambis vaccine uses a single strain of vaccinia rather than the mixture used in Dryvax. Also, the vaccinia virus used in the Acambis vaccine is produced in cell culture in contrast to the traditional method used to make Dryvax in which vaccinia virus was grown on the skin of live calves. Although animal studies indicate that the Acambis version may have a lower risk of causing encephalitis, the other side effects are expected to be about the same as the traditional vaccine.

Phase I clinical trials²⁹ comparing the Acambis vaccine with Dryvax began in March 2002.³⁰ In September 2002 Acambis announced the results of the Phase I trials and stated that the vaccine was well tolerated and caused an immune system reaction in research subjects.³¹ All 100 previously unvaccinated subjects developed a “take” within 10 days after vaccination with the Acambis vaccine; there were no serious or unexpected adverse events. Acambis is currently conducting Phase II clinical trials and expects to begin Phase III trials in 2003. The company indicates that the work required to obtain FDA approval of the vaccine could continue through early 2005.³²

Aventis Pasteur. At the end of March 2002, Aventis announced that it sought to donate to the U.S. government about 85 million doses of smallpox vaccine that were manufactured in 1958 for the U.S. Department of Defense. Preliminary tests of the Aventis vaccine indicate that it is probably as potent as Dryvax.³³ Both the Aventis vaccine and Dryvax were manufactured using traditional methods involving live calves. Clinical trials of the Aventis vaccine began in the spring of 2002. Dilution tests of the vaccine will also be conducted.

Negotiations with the federal government for the donation began in October 2002. The company estimates the value of its donation at \$150 million. However, according to a company spokesman, prior to September 11, 2001, Aventis was “in

²⁸ CDC, personal communication, January 9, 2003.

²⁹ Most clinical trials are designated as Phase I, II, or III, based on the type of questions the study is trying to answer. In Phase I clinical trials, researchers test a new drug for the first time in a small group of 20-80 people to evaluate safety and identify side effects. In Phase II clinical trials, a larger group (100-300) of people is used to test efficacy and further evaluate safety. In Phase III studies, 1,000 to 3,000 people are given the drug to confirm effectiveness, monitor side effects, and compare it to commonly used treatments. These phases are defined by the FDA in the Code of Federal Regulations.

³⁰ Enserink, M. Smallpox Vaccines: New Cache Eases Shortage Worries. *Science*, v. 296, April 5, 2002. p. 25, 27.

³¹ Interim results for the 6 months ended 30 June 2002. Acambis news release dated September 18, 2002, found at: [<http://www.acambis.com>].

³² *Ibid.*

³³ Enserink, Smallpox Vaccines: New Cache Eases Shortage Worries, p. 25.

the process of developing protocols for disposing of [the vaccine].”³⁴ Because the vaccine consists of a live virus and is infectious, disposal of the vaccine would have required FDA approval as well as additional expense to the company. When HHS indicated its possible interest in acquiring the vaccine, Aventis completed the viability testing that it had begun earlier when the company planned to dispose of the vaccine. Aventis is requesting reimbursement for testing and packaging expenses and presumably will be able use the value of the donation as a tax deduction.³⁵

Development of new smallpox vaccines and treatments

In the summer of 2002, CDC was negotiating a contract to increase the U.S. stockpile of intravenous vaccinia immune globulin (IV-VIG), a product used to treat some, but not all, serious adverse reactions to smallpox vaccine.³⁶ CDC was seeking to increase the stockpile by 30,000 doses, the amount needed if a mass U.S. smallpox vaccination did not include pregnant women. If pregnant women were included, an additional 40,600 doses would be needed. The product was expected to be available in 2003.³⁷ CDC also has a similar product manufactured in 1994, intramuscular vaccinia immune globulin (IM-VIG), that could be used to treat 600-800 adverse events, the number expected when vaccinating 4 to 6 million people.³⁸

If a smallpox vaccine could be used without the high rate of serious complications, the threat of a bioterrorism weapon using smallpox virus would be reduced. The federal government is encouraging both academic scientists and companies to develop a safer vaccine. Aventis Pasteur plans to begin testing a smallpox vaccine using a greatly weakened strain of vaccinia called NYVAC.³⁹

A combination of the traditional vaccine Dryvax with a primer vaccine called modified vaccinia Ankara (MVA) is also being studied. MVA is given several months before Dryvax to diminish serious side effects in healthy and high risk individuals. MVA was used in German studies in the 1970s and recent studies by Bavarian Nordic of Copenhagen. However, because MVA was never tested where

³⁴ Dove, Alan and Karen Birmingham. Smallpox Vaccination Becomes a Social, Financial and Political Issue. *Nature Medicine*, v. 8, no. 5, May 2002, p. 428.

³⁵ Ibid.

³⁶ Smallpox Vaccine Adverse Event Treatment Will Be Made Under CDC Contract. *The Pink Sheet*, July 1, 2002. p. 17-18.

³⁷ However, the White House “Frequently Asked Questions” document indicates that as of the end of December 2002, the United States “will have more than 2,700 treatment doses of VIG (enough for predicted reactions with more than 27 million people.” The FAQ document is available at:
[<http://www.whitehouse.gov/news/releases/2002/12/20021213-3.html>].

³⁸ Smallpox Vaccine Adverse Event Treatment Will Be Made Under CDC Contract. *The Pink Sheet*, July 1, 2002. p. 17-18; and, The CDC Smallpox Vaccination and Adverse Events Training Module—Vaccinia Immune Globulin: Current VIG Information, at:
[http://www.bt.cdc.gov/training/smallpoxvaccine/reactions/vig_current.html]

³⁹ Enserink, M. In Search of a Kinder, Gentler Vaccine. *Science*, v. 296, May 31, 2002. p. 1594.

smallpox virus was actively causing disease (such as Afghanistan in the 1970s), and MVA with Dryvax does not produce a typical smallpox vaccine scar, there are concerns that it may not provide adequate disease protection.

A monkey model of smallpox, developed by CDC and the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), will be used to test the efficacy of newly developed smallpox vaccines. FDA amended its new drug and biological product regulations so that products intended to prevent serious or fatal conditions may be approved for use based on effectiveness data from animal studies when human *efficacy* studies are not ethical or feasible. The new regulations took effect on June 30, 2002.⁴⁰ Human *safety* tests are still required for licensing.

In addition to work on improved vaccine products against smallpox, scientists at CDC and USAMRIID are working on antiviral treatments for smallpox. One drug, cidofovir, has demonstrated activity against variola virus in preliminary tests. In 2001, an Investigational New Drug (IND) application was filed with FDA for the “use of cidofovir in both the treatment of acute smallpox infection and the management of adverse events associated with vaccinia immunization.”⁴¹ A White House “Frequently Asked Questions” document on smallpox states that by the end of December 2002, the United States “will have more than 3,500 treatment doses of cidofovir (enough for predicted reactions with 15 million people).”⁴² Other compounds 25 to 150 times more active than cidofovir have been identified and are under investigation.⁴³

Legislation

During the 107th Congress, legislation involving smallpox primarily addressed concerns over availability of the smallpox vaccine and liability concerns over the use of the vaccine. The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (P.L. 107-188), signed by the President on June 12, 2002, directs the Secretary of HHS to ensure that there is enough smallpox vaccine in the Strategic National Stockpile to meet health security needs and authorizes \$509 million for FY2002 and such sums as may be necessary through FY2006 for this purpose. An emergency supplemental appropriation (P.L. 107-117), signed by the President on January 10, 2002, provided \$512 million for the purchase of smallpox vaccine by HHS.

P.L. 107-296 (H.R. 5005, H.R. 5710), the Homeland Security Act of 2002, addresses liability concerns of vaccine manufacturers and healthcare workers by designating them to be federal employees for the purpose of administering smallpox

⁴⁰ *FDA News*, May 30, 2002, available at: [http://www.fda.gov/bbs/topics/news/2002/new00811.html].

⁴¹ LeDuc, J.W., et al. Smallpox Research Activities: U.S. Interagency Collaboration, 2001. *Emerging Infectious Diseases*, v. 8, July 2002. p. 743-745.

⁴² The White House “Frequently Asked Questions” document is available at: [http://www.whitehouse.gov/news/releases/2002/12/20021213-3.html].

⁴³ LeDuc, Smallpox Research Activities: U.S. Interagency Collaboration, 2001, p. 744.

vaccine. The federal government would assume liability for smallpox vaccine related injuries and deaths under the Federal Tort Claims Act which does not permit jury trials or punitive damages. If an individual injured by the smallpox vaccine were to file suit against the federal government, that individual would be required to provide evidence of negligence. However, most vaccine-related injuries are not the result of negligence. While it is expected that health care insurance and worker's compensation would pay for patient care expenses in the event of a smallpox vaccine-related injury, it is unclear how such expenses of the uninsured would be handled. P.L. 107-296 also amends P.L. 107-188 by moving authority for the stockpile to the Department of Homeland Security (DHS); HHS would continue to manage the stockpile and determine its contents.

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