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Received through the CRS Web

Smallpox Vaccine Stockpile and Vaccination Policy

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Summary

On June 20, 2002, an advisory panel to the U.S. Centers for Disease Control and Prevention (CDC) voted against mass smallpox vaccination and instead recommended that emergency medical personnel receive the vaccine. The plan was reviewed by CDC and the Department of Health and Human Services (HHS); a revised version was sent in early September to the White House for approval. Congress addresses control of the vaccine stockpile in the Homeland Security legislation (H.R. 5005, S. 2452). This report will be updated as needed.

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.

Smallpox is transmitted via person-to-person contact or inhalation of saliva droplets in 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. After a worldwide effort of organized vaccination, smallpox was declared eradicated by the World Health Assembly in May 1980.¹ Smallpox vaccination is achieved via inoculation using live vaccinia virus, a virus closely related to variola. Vaccination is highly effective and can prevent smallpox even when given 2 to 3 days after exposure to variola. The last recorded natural case of smallpox occurred in Somalia in 1977; a fatal laboratory-acquired case occurred

¹ The World Health Assembly determines policy and budget for the World Health Organization.

in England in 1978. The last U.S. case was in 1949. The U.S. Public Health Service recommended in 1971 that routine smallpox vaccination be discontinued and the U.S. program stopped in 1972.

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.

Because of these facts, 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.² Under the June 2001 recommendations, only laboratory workers who directly handle smallpox-related virus are vaccinated. After several public meetings, draft recommendations on smallpox vaccination were approved by ACIP on June 20, 2002.³ ACIP did not recommend smallpox vaccination of the general public because “the risk of an attack was assessed to be low” and “the potential benefits of vaccination do not outweigh the risks of vaccine complications.” Instead ACIP recommended that 10 to 20 thousand first responders receive the vaccine. These individuals would act in teams investigating initial smallpox cases and vaccinating the patient’s contacts. Under the ACIP plan, healthcare personnel at a limited number of hospitals involved in caring for smallpox patients would also be vaccinated. The ACIP draft recommendations were reviewed by CDC and HHS; a revised plan was sent in early September to the White House for approval. Media reports indicate that the federal government may expand the number of individuals vaccinated to more than 250,000 healthcare workers, and possibly over 500,000 if other first responders such as police and firefighters are included.⁴

Increasing the number of healthcare personnel vaccinated may be in response to criticism of the ACIP proposal. The Executive Director of the American Public Health Association, Mohammad Akhter, stated that in the event of a smallpox outbreak, victims would head to the nearest hospital rather than a ACIP designated hospital. He was also concerned that the small number of designated hospitals would become overwhelmed by such patients, and therefore advocated that all emergency room personnel should be vaccinated. The Federation of American Hospitals expressed similar concerns, and supports vaccinating more health care workers than under the ACIP plan.⁵

Federal officials are hesitant to recommend vaccination of the general public because smallpox vaccine has a higher complication rate than any other vaccine in current use.

² ACIP is a 15 member group of medical and public health experts that provides advice to HHS and CDC on vaccine use and policy for effective disease control in the civilian population.

³ The draft recommendations can be found at: [www.cdc.gov/nip/smallpox/supp_recs.htm].

⁴ Connolly, C. Smallpox Vaccination for Medical Workers Proposed. *The Washington Post*, September 4, 2002. p. A1, A10.

⁵ Young, J. Proposal to Designate Smallpox Response Center Hospitals Evokes Concerns. *Washington Fax*, June 26, 2002.

An estimated 28 million people with eczema and 10 million people with a compromised immune system (organ transplant recipients, HIV/AIDS or cancer patients), or 15% of the population, are at high risk for developing serious complications.⁶ Such complications will also occur in the rest of the population, but at a lower rate. Liability problems associated with smallpox vaccine could be enormous. The serious complications include:

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

Complications may occur in individuals who don't even receive the vaccine, but are only exposed to someone who has recently been vaccinated. In fact, eczema vaccinatum is more severe among unvaccinated persons exposed to a vaccine recipient than among recent vaccine recipients. 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 1600 serious adverse events and 190 deaths would occur if people aged 1 to 29 years were vaccinated, and 4600 serious adverse events and 285 deaths would occur if people aged 1 to 65 years were vaccinated.⁷ Less serious complications of vaccination include rash, fever, and 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.

Federal vaccination policy must balance the certainty of the adverse effects of smallpox vaccine against the uncertainty of a biowarfare attack using variola virus. 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 is relatively large. Moreover, our social and economic system may be greatly stressed by the necessary implementation of quarantine.

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

⁶ 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.

⁷ Ibid.

an epidemic almost as well as mass vaccination, provided that at least 80% of those exposed can be found and vaccinated.”⁸ In contrast, a model developed at Yale University found that “mass vaccination results in far fewer deaths and much faster epidemic eradication.”⁹ The Yale model predicts that in a smallpox attack on a large city causing 1000 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 under ring vaccination and mass vaccination are 40,000 and 440 respectively. 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 2002 meeting on smallpox vaccination policy, indicates that 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.¹⁰ Previously, scientists believed that aerosolized smallpox virus would be inactivated by environmental factors, such as UV radiation from the sun. However, the authors believe the best explanation for the outbreak is that the initial case acquired smallpox when her boat entered waters downwind from a Soviet bioweapons test site located on an Aral sea island. Because an aerosol of smallpox virus would have the potential to infect a 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. would 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%) even up to 50 years post-vaccination.¹¹ 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.

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

⁸ Enserink, M. How Devastating Would a Smallpox Attack Really Be? *Science*, May 31, 2002. p. 1592-1595.

⁹ 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. [www.pnas.org]

¹⁰ Enserink, M. Did Bioweapons Test Cause a Deadly Smallpox Outbreak? *Science*, June 21, 2002. p. 2116-2117.

¹¹ Cohen, J. Smallpox Vaccinations: How Much Protection Remains? *Science*, v. 294, November 2, 2001. p. 985.

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.

In the fall of 2001, the National Institute 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 its potency. The vaccine, called Dryvax, was manufactured by Wyeth in 1982. Results of the study, released in April 2002, 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.¹² 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.

In November 2001, HHS placed a rush order for an additional 155 million doses of smallpox vaccine (beyond an initial order of 54 million doses) with Acambis. Clinical trials of the vaccine began in March 2002.¹³ The vaccine is a single strain of vaccinia, in contrast to the mixture in Dryvax, and is produced in a cell culture rather than the traditional method which used cows or 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. Acambis expects to deliver the vaccine order by the end of 2002. At the end of March 2002, Aventis announced that it would 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 vaccine indicate that it is probably as potent as Dryvax.¹⁴ Clinical trials of the Aventis vaccine began in the spring of 2002. Dilution tests of the vaccine will also be conducted.

CDC is negotiating a contract to increase the U.S. stockpile of a product used to treat serious adverse reactions to smallpox vaccine.¹⁵ The product, vaccinia immune globulin intravenous treatment (VIGIV) is expected to be available in 2003. Currently CDC has access to a similar product that could be used to treat adverse reactions in about 675 adults, the number expected when vaccinating 4 to 6 million people. CDC is 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.

If the smallpox vaccine could be used without the high rate of serious complications, the threat of a bioterrorism weapon using smallpox virus would be eliminated. The federal government is encouraging both academic scientists and companies to develop

¹² Frey, S.E. et al. Clinical Responses to Undiluted and Diluted Smallpox Vaccine. *The New England Journal of Medicine*, v. 346, April 25, 2002. p. 1265-1273.

¹³ Enserink, M. Smallpox Vaccines: New Cache Eases Shortage Worries. *Science*, v. 296, April 5, 2002. p. 25, 27.

¹⁴ *Ibid.*, p. 25.

¹⁵ Smallpox Vaccine Adverse Event Treatment Will Be Made Under CDC Contract. *The Pink Sheet*, July 1, 2002. p. 17-18.

a safer vaccine. Aventis Pasteur plans to begin testing a smallpox vaccine using a greatly weakened strain of vaccinia called NYVAC.¹⁶ 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 and was used in German studies in the 1970s and recent studies by Bavarian Nordic of Copenhagen to eliminate serious side effects in healthy and high risk individuals. However, because MVA was never tested where smallpox virus was endemic 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 MVA. The Food and Drug Administration (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, 2002.¹⁷

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.”¹⁸ Other compounds 25 to 150 times more active than cidofovir have been identified and are under investigation.

Legislation

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. H.R. 5005, the Homeland Security Act of 2002 as passed by the House, would amend 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. S. 2452, the National Homeland Security and Combating Terrorism Act of 2002, as reported by the Governmental Affairs Committee on July 25, 2002, directs DHS to consult with CDC in the administration of the stockpile by CDC. 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.

¹⁶ Enserink, M. In Search of a Kinder, Gentler Vaccine. *Science*, v. 296, May 31, 2002. p. 1594.

¹⁷ *FDA News*, May 30, 2002, available at: [www.fda.gov/bbs/topics/news/2002/new00811.html]

¹⁸ LeDuc, J.W. et al. Smallpox Research Activities: U.S. Interagency Collaboration, 2001. *Emerging Infectious Diseases*, v. 8, July 2002. p. 743-745.