



APRIL 2003

# Issue Brief

## Smallpox Vaccinations: The Risks and the Benefits

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### Introduction

**H**ealth officials have long feared the use of biological weapons against the U.S. population, but since the September 11 and anthrax attacks, preparation for the possibility of bioterrorism has gained greater urgency. Smallpox is considered one of the most dangerous potential biological weapons because it is easily transmitted, few people carry full immunity to the virus, and there is no effective cure. Worldwide smallpox eradication through vaccination programs was declared by the World Health Organization in 1980, virtually eliminating the possibility of a “natural” outbreak.<sup>1</sup> Officially, small quantities of smallpox virus exist in secure and authorized facilities in the United States and Russia.<sup>2,3</sup> Recent news reports have linked smallpox weapon capability to Iraq and Afghanistan.<sup>4</sup> Currently, the State Department and Centers for Disease Control and Prevention (CDC) consider the possibility of a smallpox attack to be low. However, the credibility of this threat could change with new intelligence and rapidly evolving world events.

Since 2001, American scientists, policymakers, and the public have debated whether smallpox vaccinations should be offered to Americans in preparation for a smallpox attack. On December 13, 2002, the Bush administration announced that it would begin vaccinating approximately one million military personnel and emergency public health professionals in January 2003. Voluntary vaccinations would be offered to the public beginning in 2004, although individuals who wish to be vaccinated earlier may have access to the vaccine.<sup>5</sup> According to a Robert Wood Johnson/Harvard School of Public Health poll on America's Response to Biological Terrorism, conducted in the fall of 2002, public concern

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This *Issue Brief* was prepared for The Commonwealth Fund/John F. Kennedy School of Government Bipartisan Congressional Health Policy Conference, January 16–18, 2003.

about a smallpox threat is relatively high.<sup>6</sup> The majority of respondents (64 percent) said that they believed that an attack by terrorists using smallpox would be likely if the United States took military action against Iraq. Eighty-one percent of the respondents favored voluntary vaccination of doctors and nurses in preparation for an attack. Nearly two-thirds were in favor of offering the smallpox vaccine to the general public now on a voluntary basis. Sixty-one percent said that they would choose vaccination if it were offered as a precaution against a bioterrorist threat. If there were cases of smallpox in the United States, 75 percent of respondents would choose to be vaccinated.

### **Background: Smallpox Infection**

Smallpox is caused by the Variola viruses, members of the orthopox virus family. The virus has two principal forms: Variola major and Variola minor.<sup>7</sup> Historically, Variola major epidemics typically resulted in fatality rates of 30 percent or higher among the unvaccinated, whereas Variola minor fatality rates were 1 percent or less. Smallpox spreads primarily through the air, from the nose and mouth of an infected person, and by direct contact. Contaminated clothing and bed linens also can spread the disease.<sup>8</sup> The virus survives most easily under cool and dry conditions. Consequently, smallpox infection spreads fastest during winter and early spring.

The virus initially infects the immune and respiratory systems, where it multiplies and spreads. A secondary infection begins on about day eight, when the virus concentrates in small blood vessels in the skin and beneath the mouth and throat. At the end of the 12-to-14-day incubation period, the patient typically experiences high fever and malaise. A raised bulbous rash appears at this time, first in the mouth and throat, followed shortly by a rash on the face and forearms, the body, and legs. Within two to four days the rash becomes raised and filled with fluid and deeply embedded in the skin. Lesions in the mouth and throat open quickly, releasing virus into the saliva and expired air—the main source of infection to others. Patients are typically most infectious for the first three to 10 days of the rash. In nonfatal cases, as the patient recovers, scabs from the vesicles form, separate, and develop pitted scarring most evident on the face. As scabs form, the infection wanes rapidly.

### **Ease of Smallpox Diagnosis**

Rapid detection is a key component of response to a smallpox attack. Challenges to quick and effective smallpox diagnosis are due to the etiology of the disease itself and the ease of identification and diagnosis by medical professionals. First, the long incubation period almost ensures that some of those infected in a smallpox attack will travel great distances from the site of the exposure before the disease is recognized or quarantine implemented.<sup>9</sup> Second, two forms of smallpox—hemorrhagic and malignant—are very difficult to diagnose. The former is nearly always fatal.<sup>10</sup> Third, milder forms of the illness, caused by Variola minor infection or as a result of residual immunity from previous vaccination, make smallpox harder to diagnose since key symptoms, including the characteristic rash, may be absent.<sup>11</sup> In particular, the presence of a significant portion of previously vaccinated individuals in the United States (born before 1972 when compulsory vaccinations were halted) may make it more difficult to identify an attack.<sup>12</sup> In addition, many American physicians and medical professionals have never encountered a smallpox case clinically, or did so in the distant past. Some people feel that physicians may be inadequately trained to diagnose even the more common forms of the infection. In addition, identification is complicated by the fact that the illness may not be obvious or classic in presentation until the patient has been infectious for three to four days and possibly longer.<sup>13</sup> Also, conventional laboratories are currently ill-equipped to aid in the rapid identification of an infection.

Physician educational efforts have moved forward on two fronts—specialized training and wide-scale awareness. In November 2001, the CDC began training specialized teams.<sup>14</sup> The teams, consisting of physicians, epidemiologists, and laboratory technicians, were vaccinated against smallpox and underwent training to identify and contain outbreaks. As part of the Bush administration's recently announced policy, other public health professionals would be vaccinated beginning in January 2003. In addition, a number of leading clinical journals have published articles alerting medical professional to smallpox's clinical aspects, diagnosis, and treatment. Free courses on bioterrorism preparedness for clinicians, particularly emergency department professionals, have been available on the Internet since

early 2002, sponsored by a number of public and private groups.<sup>15, 16, 17</sup> Despite these educational efforts, the CDC, American Medical Association, and several state medical societies have reported that physicians remain poorly informed about smallpox diagnosis, the side effects of the smallpox vaccine, and the government's plan to control an outbreak in case of an attack.<sup>18, 19</sup>

### **How Well Do Smallpox Vaccines Work?**

To prevent infection, vaccination is considered to be highly effective. The modern-day vaccinia vaccine contains live cowpox virus, a member of the Variola family that produces a less severe infection. The vaccine is typically administered in the upper arm and successful immunization is noted by the formation of a characteristic scar.<sup>20</sup> In general, smallpox vaccination does not grant lifelong immunity, but instead lasts on average five to seven years. Immunity varies greatly among individuals, however, ranging from four months to 10 years.<sup>21</sup>

Vaccination is also recommended to prevent or ameliorate illness after smallpox exposure. Vaccination administered within four to five days of exposure probably offers considerable protection against death but not against infection and illness.<sup>22</sup> Successful vaccination with vaccinia occurs for first-time recipients in more than 95 percent of vaccinations. For those with failed first-time vaccination, revaccination is recommended.<sup>23</sup>

### **ADVERSE EVENTS**

A major motivating factor in halting vaccination in 1972 was the presence of adverse events associated with vaccination. These reactions range from the common and mild to rare and potentially fatal. The side-effect profile associated with the smallpox vaccine is more severe than any other commonly used vaccine.<sup>24</sup> Historically, one death occurred for every one million people who received a first-time vaccination and about one death for every four million revaccinated. Life-threatening reactions occurred in 15 of every million people vaccinated.<sup>25</sup> The risk of adverse events and death in those who have been vaccinated previously is very small. Primary vaccination in children under the age of 10 appears to be most risky according to the historical record.

These rates may underestimate the side effects today because the U.S. population includes more people considered to be at high

risk for serious side effects.<sup>26</sup> These groups include infants, immuno-compromised patients, including those with HIV/AIDS, pregnant woman, and those with eczema.<sup>27, 28, 29</sup> One argument for offering voluntary vaccinations is to allow for the careful screening and identification of the general population for those who may be high risk.<sup>30</sup>

A recently completed scientific study has highlighted concern that there is a small but significant risk that individuals who receive a vaccination may spread infection to unvaccinated people.<sup>31</sup> The study reanalyzed data from Americans vaccinated for the first time in 1963 and 1968. For every 100,000 people vaccinated for the first time, the study found that vaccinia spread by close contact to two to six others not previously vaccinated. Most unvaccinated people who caught the virus developed "accidental infections" consisting of sores that healed on their own and most likely acted like secondhand vaccinations that gave them immunity. However, one or two individuals infected secondhand became very ill with a condition called eczema vaccinatum, which may cause fever and severe extensive rash, scarring, and, in rare cases, death. Of those infected secondhand, the vast majority occurred in children under age 5, who caught the infection from a household member. Others point out that in 1968, out of 14,168,000 vaccinations there were 114 reported accidental inoculations of others and one death in a young child. In 1963, there were no deaths associated with accidental inoculations.<sup>32</sup>

### **AVAILABILITY OF TREATMENT FOR ADVERSE EVENTS**

Individuals who experience a severe complication from the vaccine are given vaccinia immune globulin (VIG). Supplies of VIG are limited.<sup>33</sup> If one million persons were to be vaccinated, as many as 250 people would experience adverse reactions requiring administration of VIG.<sup>34</sup> How much VIG would be needed for a public vaccination program is uncertain. As of January 2003, the CDC had about 5,000 doses of VIG in hand.<sup>35</sup> In August 2002, the CDC contracted with a Canadian company, Cangene, to produce 100,000 additional VIG doses, scheduled for delivery by mid-2003.<sup>36</sup>

## Vaccine Availability

After the September 11 attacks, one of the first federal actions to prepare for a potential bioterrorist attack was a detailed assessment by the CDC of the adequacy of vaccine and therapeutics supplies housed in the National Pharmaceutical Stockpile (NPS). As of November 2001, 15 million doses of the Dry-vax vaccine were available.<sup>37</sup> The National Institutes of Health has conducted studies that suggest it is possible to dilute the Dry-vax vaccine by a 1:10 ratio, which would produce 150 million doses in the short term.<sup>38</sup> This is not enough to vaccinate the entire population in the event of an emergency or to carry out immediate public vaccinations.<sup>39</sup>

Aventis Pasteur announced in early April 2002 that it planned to donate to the government 85 million additional doses of a vaccine, similar to Dry-vax, which have been stored in freezers for 40 years.<sup>40</sup> Test-tube experiments were completed recently and suggest that the vaccine is about as potent as Dry-vax. The efficacy of diluting the Aventis vaccine is also undergoing testing currently.

In November 2001, the U.S. government placed a rush order with a British-American company, Acambis, for 155 million doses of a new smallpox vaccine, in addition to 54 million doses ordered in 2000. The United States paid \$428 million, or \$2.76 a dose. Clinical trials of the vaccine began in March 2002 and the first order was delivered at the end of 2002.<sup>41</sup> In an emergency, the U.S. government currently has enough Dry-vax vaccine (if diluted) and Acambis vaccine to vaccinate the population.<sup>42</sup> The older Dry-vax vaccine is the vaccine that is currently being administered to military personnel, health workers, and first responders. It is the newer Acambis vaccine that the Bush administration plans to distribute for public voluntary vaccinations.

In the longer term, the frequency of vaccine complications is considered sufficiently great to recommend development of an effective vaccine associated with fewer side effects.<sup>43</sup> Researchers funded by the National Institute of Allergy and Infectious Diseases (NIAID) are developing a new vaccine (Modified Vaccinia Ankara, or MVA), currently in human clinical trials. Some 250 million doses are scheduled to be produced, licensed, and delivered to the fed-

eral government by 2005. The NIAID hopes to demonstrate that MVA will be safe for use in high-risk populations.<sup>44</sup> An alternative vaccine (Japanese LC16m8) may have fewer side effects than the NIAID vaccine and be a safer product for use in the general population, but would probably not be used for immuno-compromised individuals.<sup>45</sup> FDA licensing of this vaccine is considered unlikely before 2005.<sup>46</sup>

## Vaccine Liability

The federal government owns all American stocks of the Dry-vax vaccine. The full-strength vaccine and diluted versions were licensed for use on the general public by the Food and Drug Administration (FDA) in late 2002.<sup>47</sup> Clinical testing to establish the safety and effectiveness of the Aventis Pasteur vaccine are ongoing, with the CDC estimating completion in early 2003. The Acambis vaccine is also currently undergoing clinical testing and is on the fast track for licensing approval by the FDA.<sup>48</sup>

The use of existing and newer smallpox vaccines raises two liability issues. First, offering vaccines to the general public before an attack raises concerns about liability for adverse events for the manufacturing companies, health institutions, and medical personnel who give the vaccines.

Second, in the event of an attack, the benefits and risks of vaccination would need to be weighed for individuals at greater risk of experiencing serious complications associated with vaccination. Currently, there are no absolute contraindications regarding vaccination of a person with a high-risk exposure to smallpox.<sup>49</sup> However, persons at greatest risk of experiencing serious vaccination complications are often those at greatest risk of death from smallpox. In addition to the immuno-compromised and others discussed above, children under the age of 18 are considered to be at higher risk. Although children were previously routinely immunized when smallpox was a naturally occurring disease, the Advisory Committee on Immunization Practices (ACIP) currently advises against use of the smallpox vaccine in children less than 18 years of age except in the event of an emergency.<sup>50</sup> In the event of an attack, the risks of children and other high-risk individuals experiencing serious vaccine complications must be weighed against the increased risk of experiencing a fatal small-

pox infection. The use of smallpox vaccines in the general public and potentially on these high-risk populations after an attack raises concerns about liability for adverse events for the manufacturing companies, health institutions, and medical personnel who give the vaccines. Some policymakers suggest that a compensation fund should be established to remunerate victims of significant adverse events associated with the administration of the vaccine for adults and children under emergency circumstances.

### **Costs of Public Voluntary Smallpox Vaccinations**

As part of the new voluntary vaccination program, the Bush administration announced that voluntary smallpox vaccinations would be available free of charge for individuals wishing to be vaccinated.<sup>51</sup> CDC estimates that a smallpox screening and vaccination effort would cost \$5 to \$10 per patient, totaling \$132 million to \$265 million. Other costs covering medical personnel training, supply storage, distribution, and transport would require more funding.<sup>52</sup> Some believe that emergency mobilization for public vaccinations in the event of a public health emergency may cost even more.<sup>53</sup>

### **Deterrence**

Proponents of voluntary smallpox vaccination for the American public believe widespread voluntary vaccinations would dramatically reduce the value of smallpox as a weapon.<sup>54</sup> In the case of an attack, the number of non-immunized would be greatly reduced, and the outbreak would be much easier to manage and would quell public panic and put less strain on public health resources.

### **Public Education**

According to the most recent public opinion polls, Americans are concerned about the threat of smallpox. However, as a whole the public remains relatively uninformed of the disease's symptoms, the ease of transmission, and the vaccine's risks.<sup>55</sup> Supporters of a voluntary vaccination program suggest that the policy also requires an accompanying education campaign to inform individuals of the risks of the disease and vaccination, potential side effects, appropriate medical professionals to consult, and other important issues. In addition, further efforts must be made

to educate physicians regarding vaccine administration, identification of vaccine side effects, and patient counseling regarding the vaccine's risks and benefits.

### **Implementation Plans**

With the newly released policy to offer vaccinations to the public beginning in 2004, the CDC—the agency under the Department of Health and Human Services (DHHS) that is primarily responsible for detecting and tracking infectious disease—and other federal and state agencies will have to prepare plans for the dispatching of the National Pharmaceutical Stockpile, communications with state and local public health agencies, and other preparations for voluntary public vaccinations to begin in 2004. In particular, the public health infrastructure of state and local health departments will need resources and preparedness plans to administer wide-scale vaccinations.<sup>56</sup> Many state and local public health officials argue that they need more time to educate medical personnel and the public, reduce the risk of complications from the vaccine, ensure that hospital care does not suffer if vaccinated workers feel ill, ensure the availability and payment for medical and public health personnel, and determine who would be responsible for liability claims, lost work, and associated medical supplies.<sup>57</sup> Federal officials said efforts over the past several months to prepare state and local public health facilities for voluntary immunizations and emergency immunizations in the event of a smallpox attack have gone well.<sup>58</sup>

### **Preparations for a Smallpox Attack**

Since September 11, experts on all sides of the voluntary vaccination debate have pointed to the inadequacy of federal, state, and local public health infrastructure to identify an outbreak, coordinate distribution of vaccines, and effectively contain infection in the event of a bioterrorist attack absent or prior to mass public immunity.<sup>59, 60, 61</sup> In particular, federal preparedness efforts are fragmented across many agencies with limited responsibilities. General Accounting Office studies of bioterrorism preparedness efforts find that more than 20 federal departments and agencies are involved in preparation or responses to health-related aspects of a bioterrorist attack, and more than 40 agencies have responsibility for responses to terrorism more

broadly.<sup>62</sup> In addition, state and local public health agencies are relatively unprepared. Most require greater capacity for rapid communication with hospitals and other health agencies.<sup>63</sup> Not all agencies have e-mail access, and those that do often do not have capacity to send confidential information. Staffing does not typically include a person on call for emergencies 24 hours a day.<sup>64</sup> The CDC has developed two communications systems, both in early stages of development, to address shortcomings in information exchange. City and county hospital capacity to handle a rapid influx of patients for vaccinations, infection treatment, and adverse event identification and control has also been a source of concern.<sup>65</sup>

Numerous efforts have been undertaken at the federal, state, and local levels to address these concerns. In November 2001, the Bush administration created the Office of Public Health Preparedness within the DHHS. The purpose of this office is to coordinate federal agencies' responses to public health emergencies, including maintenance of the Metropolitan Medical Response System, the National Disaster Medical System, the National Pharmaceutical Stockpile, CDC Support to Local Response Systems and Vaccine and Drug Research and Development. The Department of Homeland Security was created in November 2002, by the Homeland Security Act (P.L. 107-296). Its primary purpose is to oversee the coordination of antiterrorist activities at the federal, state, and local levels, including preparation for public voluntary vaccinations and a bioterrorist attack. The law established a cabinet-level secretary of homeland security position. The DHHS maintains primary authority over biodefense research and development, while ceding control of certain national emergency-response systems, including administration of the NPS. The Office of Public Health Preparedness is also moved under the jurisdiction of the Department of Homeland Security. The law also provides liability protection to doctors and other health care workers who administer smallpox vaccines in case of an attack or through a coordinated voluntary vaccination effort.

#### CURRENT READINESS

In case of an attack prior to public vaccinations, the CDC's director stated that NPS sites, where smallpox vaccines currently available are stored,

are ready and plans are in place to deliver rapidly the final product to all cities of more than 10,000 residents.<sup>66</sup> Concerns remain for smaller cities and counties. Some state and local public health officials have complained that they have received little guidance on how much vaccine will be made available and what plans will accompany the distribution of these supplies.<sup>67</sup>

In September 2002, the CDC released updated instructions to the states for the vaccination of every American in the event of a confirmed outbreak.<sup>68</sup> The CDC policy dictates that in the event of an attack, vaccination would be voluntary, but anyone who has been exposed and refuses vaccination may be involuntarily quarantined for up to 18 days. The latter rule is part of the "ring vaccination" method by which patients with suspected or confirmed smallpox are isolated and the patients' contacts are traced, vaccinated, and kept under close surveillance.<sup>69</sup> The newly updated CDC smallpox policy also provides specific logistical guidelines for states regarding the distribution of vaccines and handling of adverse events for large-scale post-attack vaccinations.<sup>70</sup> Supporters suggest that the current CDC policy eases the strain on personnel requirements and infrastructure and may quell public panic in the event of an attack. Some have criticized the adequacy of the ring vaccination method to contain an outbreak in the event of an attack.<sup>71</sup> Others note that even with more money, there may not be enough trained epidemiologists, lab technicians, physicians, and other public health experts to implement the current CDC plan efficiently.<sup>72</sup>

#### CIVIL LIBERTIES

To contain smallpox infection following a large-scale attack, federal, state, and local governments, particularly public health authorities, may need to take actions that restrict civil liberties as part of the current ring vaccination policy.

In 2001, the CDC released a Model State Emergency Health Powers Act, developed by the Center for Law and Public Health at Georgetown University and Johns Hopkins University.<sup>73</sup> The model legislation is intended to serve as a potential framework for states to use in updating statutes. Existing state laws, many written before the 1930s, tend to contain little detail on the scope of health department authority in emergency situations.<sup>74</sup> The model legislation

provides broad authority to health officials in the event that a governor declares a public health emergency. In particular, provisions authorize public health authorities to undertake mandatory medical examinations, isolate infected people, and quarantine exposed people “with respect to individual liberties consistent with due process.” Mandatory vaccinations, collection of laboratory tests, and limited disclosure of patient records also are authorized.<sup>75</sup> Such provisions have prompted debate regarding the proper level of power to accord health officials in an emergency. States are expected to consider legislation on state authority in emergency health situations in upcoming legislative sessions.

### Recent Legislation

Legislation enacted in 2001 and 2002 addressed concerns regarding the stockpiling of vaccines, development of new vaccines and other therapeutics, and further preparation of public health infrastructure.

- The 2001 Emergency Supplemental Appropriations Act for Recovery from and Response to Terrorist Attacks on the United States (P.L. 107-38) made emergency supplemental appropriations for antiterrorism initiatives and for assistance in the recovery from the September 11 attacks. The appropriations included \$865 million for CDC grants to improve state and local capacity for preparedness for and response to bioterrorism, including the use of smallpox weapons. The DHHS released 20 percent of these funds to states and localities in February 2002. The remainder is scheduled to be released upon receipt of state and local biopreparedness plans to the DHHS. As of December 2002, the DHHS had distributed \$747 million.<sup>76</sup> In addition, \$512 million for the purchase of smallpox vaccines was appropriated and disbursed. Congress also appropriated \$32 million for the NIH-NIAID to enhance smallpox vaccine stockpiling and research and development.
- The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (P.L. 107-188) requires the provision of effective assistance to the states and local governments to ensure that they have the capacity to detect and respond effectively to a bioterrorist attack. It established in the DHHS an assistant secre-

tary for public health emergency preparedness to coordinate such efforts. The Act directs the secretary of health and human services to ensure that a sufficient amount of smallpox vaccine is available. Appropriations to meet these goals were made by Congress, including \$1.5 billion for the states, to improve defenses against biological attacks, enlarge government stockpiles of vaccines and other medical supplies, expand and maintain hospital equipment, and train medical workers.

### Conclusions

The use of smallpox as a weapon against the U.S. population is a worrisome threat with national and potentially international implications. Offering voluntary smallpox vaccinations to the public presents benefits that must be weighed against associated medical, logistic, and economic risks. Policymakers must navigate complex tensions between scientific and political uncertainty, and between the government’s role in protecting its citizenry while guaranteeing individuals’ rights to self-determination.

A voluntary vaccination program raises a range of challenging issues, including the size of the vulnerable population, use of viral transmission among affected individuals, ease of diagnosis, availability and side effects associated with vaccines, and the adequacy of the public health infrastructure to carry out voluntary public vaccinations while preparing to identify and contain an attack.

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