COMMENTARY

SMALLPOX VIRUS DESTRUCTION AND THE IMPLICATIONS OF A NEW VACCINE

D. A. Henderson

The World Health Assembly is scheduled to decide in May 2011 whether the 2 known remaining stockpiles of smallpox virus are to be destroyed or retained. In preparation for this, a WHO-appointed committee undertook a comprehensive review of the status of smallpox virus research from 1999 to 2010. It concluded that, considering the nature of the studies already completed with respect to vaccine, drugs, and diagnostics, there was no reason to retain live smallpox virus except to satisfy restrictive regulatory requirements. The committee advised that researchers and regulators define alternative models for testing the vaccines and drugs. Apart from other considerations, the costs of new products are significant and important. These include prospective expenditures required for the development, manufacture, testing, and storage of new products. This commentary provides approximations of these costs and the incremental contribution that a newly developed vaccine might make in terms of public health security.

BACKGROUND: SHOULD THE LIVE VARIOLA VIRUS BE DESTROYED?

The question of variola virus destruction has been under consideration for more than 25 years. The first recommendation that the 2 known stockpiles of smallpox virus should be destroyed was made by a 1994 World Health Organization (WHO) Expert Committee on Smallpox following a decade-long review and multiple consultations. In reaching its conclusions, the committee weighed the possible benefits that might accrue through use of smallpox virus for research purposes against the potential risks of the virus accidentally escaping or being released from known or unknown sources. The recommendation for destruction had the written support of 5 major professional organizations concerned with microbiological research* and the support of prominent scientists such as Nobel Laureate David Baltimore. The WHO recommendation was subsequently discussed in successive World Health Assemblies.

Four separate postponements of virus destruction—each 3 or more years in length—were granted in response to requests from member countries to give investigators added

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time to complete specified research projects. The history of the deliberations as well as the arguments for and against destruction of the virus have recently been summarized by Tucker. A debate and vote on the question is now scheduled to take place at the World Health Assembly in May 2011.

To better inform delegates to the Assembly, as well as other scientists, regarding the relevant issues, the Director General arranged for the preparation of a document titled *Scientific Review of Variola Virus Research 1999-2010.* With this compendium available, a WHO Advisory Group of Independent Experts was asked “to review the results of smallpox research already undertaken” and “to assess whether additional research using live variola virus is necessary from a global public health perspective.” The report of this group was to be provided to the twelfth meeting of the WHO Advisory Committee on Variola Research (November 2010).

The Group of Independent Experts “noted with concern that the only compelling scientific and public health reason to keep live variola stocks is to meet current restrictive regulatory requirements for vaccine and drug development.” The group summarized its views by recommending “that researchers and regulatory authorities meet and jointly define future alternative models for testing vaccine and drugs against variola virus in preparation for destruction of variola virus.”

The Advisory Committee on Variola Virus Research stated in its own report that its members held divergent opinions as to whether live variola virus was a requisite need for further research on vaccines, diagnostics, or antiviral drugs. Both the Advisory Committee and the Group of Independent Experts indicated that, at this time, the primary public health reason for retention of the variola virus stocks was for the development of a new vaccine and possibly another antiviral agent. Emphasis was given to the particular need for a new vaccine that could be used with safety in individuals who were immune-deficient or had atopic dermatitis.

Neither report discusses the costs required to develop, manufacture, acquire, and test such products or the relative priority that these efforts should be given. This commentary endeavors to approximate the costs for development of a new vaccine, the expenditures required to manufacture and stockpile it, and the costs required to develop and sustain production capacity should additional quantities be needed. Finally, we assess the potential added benefits that a new vaccine, as well as a third antiviral agent, might provide in countering a release of smallpox.

**Currently Available Vaccines and Manufacturers**

In 1980, the World Health Assembly announced that smallpox had been eradicated and recommended that all countries stop vaccination. Most countries complied within a very few years. Vaccine production ceased, and laboratories were dismantled and converted to other uses. The only smallpox vaccinations now being given are for scientists working with orthopoxviruses and for some military forces. Until the anthrax attack in the U.S. in October 2001, only limited attention had been given to the threat posed by biological weapons. The anthrax release caused serious problems, but a possible smallpox release poses an even greater threat. Smallpox carries a 30% case-fatality rate, no effective treatment is available, and it spreads by person-to-person contact. This is of special concern because the world’s population is now either unvaccinated or last vaccinated more than 30 years ago. Stopping an epidemic requires vaccine, but as WHO surveys have shown, few countries now have stocks of vaccine.

During the smallpox eradication program, the only vaccines used were first-generation vaccines. They were produced much as they had been since about 1875. The vaccinia virus was grown on a large scarified area on the flank of a calf or sheep and the lymph was scraped off after a week, purified, and freeze-dried in small ampoules. The vaccine was a crude product by contemporary vaccine standards but it was effective. However, only a few countries still have small laboratories that can produce limited quantities of this type vaccine.

After the 2001 anthrax attack, the U.S. decided to greatly augment its reserve supply of smallpox vaccine. A second-generation vaccine was developed using a contemporary tissue-culture methodology. U.S. scientists cloned the virus present in the routinely used DryVax vaccine (New York City Board of Health strain) and the Acambis company in cooperation with Baxter Laboratories produced some 180 million doses of a vaccine called ACAM2000 for the U.S. stockpile.

Meanwhile, in Japan during the 1970s, scientists developed a more attenuated vaccinia virus from a widely used European strain (Lister) and produced large quantities of a vaccine called LC16m8. It was grown in rabbit kidney tissue cell culture. The work was initially performed at the Chiba Serum Institute and, after 2002, at the Chemo-Therapeutic-Research Institute (Kaketsuken) in Japan. Because it derives from an attenuated vaccinia virus, it is referred to as a third-generation vaccine although it replicates in the skin like ACAM2000.

ACAM2000 is licensed in the U.S.; LC16m8 is licensed in Japan. Both vaccines are extremely heat-stable and are packaged in vials of 0.25 ml, an amount that provides 100 vaccinations. Vaccination is accomplished by pricking the virus into the skin. The virus grows and stimulates an immune response that protects against smallpox.

More recently, progress has been made in developing a third-generation vaccine, one that does not replicate after inoculation. It is believed that vaccination with such a vaccine would avoid the occasional complications from the ACAM2000 and LC16m8 vaccine viruses growing more extensively than expected and causing serious illness among those with active atopic dermatitis or immune deficiency.
disorders. The most advanced of the nonreplicating strains is called “Imvamune” or MVA (Modified Vaccinia Ankara).10 The Danish Bavarian-Nordic company has begun manufacture of this vaccine and has delivered 1 million doses to the U.S. government. It is not yet licensed. The vaccine is administered intramuscularly in 2 doses, each dose being packaged in a 0.5-ml vial. Two doses 1 month apart are required for vaccination. Maximum protection, as determined serologically, is attained about 6 weeks after the first dose. Given the need for the vaccinee to receive 2 doses of vaccine and the considerable interval before development of immunity, the possible uses for this vaccine under epidemic circumstances is unclear. In contrast, the replicating vaccines provide immediate immunity and require only a single dose.

Globally, vaccine production capacity has steadily decreased to the point that there is now only 1 large-scale vaccine manufacturer, namely Kaketsukan, which produces LC16m8. Its capacity is 80 million doses per year. A production facility for ACAM2000 with a capacity of about 40 million doses has been built in the U.S. by Acambis (now owned by Sanofi-Pasteur), but it will be several years before production is expected to begin. Other than these 2 facilities, the only known production sites are Bavarian-Nordic, which now has a capacity to produce about 8 million Imvamune doses per year, and plants in a few other countries that can produce small quantities of first-generation vaccines. Russia has indicated that it is producing smallpox vaccine, but there is no further information available.

Costs for Smallpox Vaccine Purchase and Development

Relevant data as to the probable costs for developing, manufacturing, and stockpiling a new vaccine have been derived from discussions with current and former staff of the U.S. Department of Health and Human Services, based on their experience in vaccine acquisition since 2002, and discussions with others knowledgeable about vaccine production in the U.S. and in Japan.

• Development costs for a new vaccine: $250 million to $1 billion

A number of efforts have been made to approximate the total development costs for a new biological agent from discovery, through characterization, human and animal testing, and licensure. The most detailed analyses and estimates are provided by DiMasi et al.11 Those with whom we have talked are inclined to accept a higher estimate within the range shown above, citing the increasing costs for animal and human subject testing and increasing requirements for licensure.

• Construction costs for a new production facility: about $500 to $750 million

Estimated costs would vary with such factors as capacity, product, and country where constructed. The figures shown are approximations based on construction costs for the new U.S. facility for ACAM2000 production and for the Bavarian-Nordic facility.

• Costs of 50 million doses of various vaccines for the stockpile

Replicating vaccines (ACAM2000 and LC16m8) — The costs for purchase of a dose of these vaccines is in the range of $2.50 to 3.50 per dose. This is a substantially lower cost than that for most vaccines. It can be explained, in part, by the fact that vaccination requires only a very small aliquot of vaccine when the bifurcated needle is used. Thus, 1 vial (0.25 ml) contains enough vaccine for 100 vaccinations. The cost for 50 million doses would be about $150 million.

Nonreplicating third-generation vaccine (Imvamune) — To obtain a satisfactory immune response with a nonreplicating vaccine, much larger quantities of virus are required than for a replicating vaccine. The costs for production and packaging are thus greater. In a recent U.S. contract award to Bavarian-Nordic, the cost per dose of Imvamune was $25, but because 2 doses are required for vaccination, the cost per vaccinee would be twice this amount. The company indicates that for large volume purchases (e.g., 50 million doses), the cost would be about half of that quoted. Thus, enough vaccine to fully vaccinate 50 million persons would be about $1.25 billion.

• Size of stockpile

There have been no formal discussions regarding the size of a prospective global vaccine stockpile. The U.S. policy has been to have a dose of smallpox vaccine for every citizen and a standby production facility (“warm-base”) that would produce a moderate amount of vaccine every year in order to assure the ready availability for manufacture of additional vaccine if needed in an emergency.

At the international level, it would be unrealistic and unaffordable to have a dose of vaccine for each citizen. However, even if the plan were to have enough for only 5% of the world’s population, a stockpile of 350 million doses would be required plus several standby production facilities. Were second-generation smallpox vaccines to be obtained, the cost would be about $1 billion. Fortunately, the second-generation vaccines have a shelf-life of at least 5 years when stored at −20°C. Based on experience with first-generation vaccines from which the vaccine strains derive, manufacturers believe that the vaccine shelf-life might extend to several decades. To sustain standby manufacturing capacity, however, several million vaccine doses per year would need to be produced.

A stockpile of 350 million doses of third-generation nonreplicating vaccine would be more than $8 billion, based on listed present prices for large-scale vaccine purchase and taking into account the need for 2 doses of vaccine to provide protection. Substantial resources would also be needed annually to sustain the stockpile, because the current vaccine is believed to have no more than a 3-year shelf-life. However, efforts are now being made to freeze-dry...
the vaccine. This presumably would increase the vaccine cost, but the shelf-life would be longer.

**Maintaining a strategic stockpile**

Annual maintenance costs would include expenditures for maintaining a stockpile such as refrigerated space, periodic testing of the vaccine, utilities, personnel for overall management and security, and so on. No attempt has been made to estimate these.

**What Is the Risk?**

How likely is an emergency that would require using large quantities of vaccine? It is generally agreed that the risk of smallpox being released into the world is small but not zero. If the risk were to increase substantially, community-wide vaccination programs might be indicated and perhaps vaccination of healthcare staff, but no country now contemplates such measures. Experts agree that the likelihood of a virus escape from either of the 2 approved smallpox laboratories is diminishingly small considering the stringent security measures now in place. There is, at present, no evidence that smallpox virus exists outside of the U.S. and Russian laboratories, although there is no way to confirm this. Should terrorists obtain virus from some presently unknown source, special skills and equipment to produce and release quantities of smallpox virus would be needed. Should the effort be successful, it could be catastrophic unless vaccine were available to stop its spread.

Experience has shown that epidemics can be stopped reasonably readily by vaccination of the patients’ contacts and local populations at greatest risk. The replicating vaccines are well adapted to do this because they rapidly provide significant protection against smallpox even when administered 3 to 4 days after an individual has been infected. Thus, the strategy for controlling an epidemic depends on the isolation of patients and vaccination of contacts and others at special risk, such as hospital workers. Mass nationwide vaccination would not be called for and, in fact, could be counterproductive in diverting resources from more productive vaccination, surveillance, and containment activities.

The 2 licensed replicating vaccines (ACAM2000 and LC16m8) are well-suited for a stockpile for reasons other than the high level of protection they provide. They can be produced inexpensively and are directly derived from vaccine strains that were effective in protecting humans from smallpox under natural circumstances. From animal studies and immune responses in humans, there is good reason to believe they would protect against smallpox as well as the original strains from which they derived. Methods for production have been worked out, and the shelf-life of the vaccines is exceptional. First-generation freeze-dried vaccines should be no less effective, but they are difficult to produce in large quantities and often contain extraneous matter resulting from their growth on animal skin.

**Are New Vaccines Needed?**

Would the development of other vaccines or antiviral products be of value? A number of different laboratories have been engaged in developing alternative vaccines, including other attenuated third-generation products and fourth-generation subunit alternatives. Various antiviral drugs are also being tested. However, all face a similar insuperable barrier: There is no test that provides reliable information as to how well humans would be protected by the product. There are no animal models of smallpox available and no information as to what surrogate serological measures equate with protection in humans. How well a new product would protect humans cannot be determined with certainty unless there are human smallpox cases.

In considering vaccine policies and options, it should be recalled that first-generation vaccines were in use throughout the world until the late 1970s. Fever, malaise, and a sore arm were not uncommon among primary vaccinees; severe adverse reactions occurred infrequently. Very few were serious enough to warrant hospitalization. However, the risk of having an adverse reaction had to be balanced against the threat of smallpox and its 30% fatality rate. Certainty that the vaccine would protect was the principal concern. This would obviously be of prime concern for a vaccine in the stockpile.

**Complications of the Replicating Vaccines**

The principal rationale for developing a third-generation vaccine, one in which the virus does not grow, was to prevent the small but finite risk of complications of progressive vaccinia and eczema vaccinatum. In people susceptible to these risks, the vaccinia virus growth is not sufficiently contained and extensive skin lesions can develop. Comprehensive studies of complications following vaccination with DryVax were conducted by CDC in the late 1960s. They showed that among 5.6 million primary vaccinees, there were 6 cases of eczema vaccinatum per 100,000 and 1 case of progressive vaccinia. Some believe that the widespread use today of ACAM2000 would result in more frequent complications, because atopic dermatitis and immune deficiency disorders are more common today than in the 1960s. Others, however, speculate that ACAM2000, being a cloned version of DryVax, might be less likely than DryVax to result in adverse effects. The only substantial experience with ACAM2000 is from vaccination in the military. Among more than 500,000 soldiers who received ACAM2000 between March 2008 and January 2011, there were no cases of eczema vaccinatum and 1 case of progressive vaccinia. The second replicating strain, LC16m8, was administered to more than 100,000 Japanese children during the 1970s during their routine vaccination program. No adverse events were reported, but special measures were not
taken to assure complete reporting. Since that time, a number of special studies have been conducted in military recruits that indicate, so far, that adverse reactions are rare.

For treatment of complications, a now greatly improved Vaccinia Immune Globulin is available (VIG, produced by Cangene). Imminently available also are 2 antiviral drugs that have been developed over the past decade: ST-246, produced by the Siga Company, and a cidofovir derivative CMX001, produced by Chimerix. These 2 antivirals have an acceptably low level of toxicity when orally administered and have proven to be effective in animal studies. Small quantities are now in the process of being added to the stockpile.

In recent years, cases of postvaccination heart inflammation, or myopericarditis, have been reported among soldiers after vaccination with DryVax and, later, after ACAM2000. The incidence was about the same for both vaccines: about 1.3 cases per 1,000 vaccinees. The disease is marked by fever, myalgia, and mild chest pain occurring about a week after vaccination. Recovery is rapid; longer-term effects have been rare. Blood tests and electrocardiograms confirm the diagnosis. This finding was mysterious because, among the tens of millions vaccinated with this same vaccine in the U.S. in the 1960s, there were no reports of this problem. Two factors might account for this. Most U.S. citizens had been vaccinated at a younger age, and so military recruits had some partial immunity when vaccinated as adults. The cases were marked by a brief fever, some malaise, and a dull pain in the upper chest. In the military, all postvaccinal illnesses were being closely followed as a routine. Accordingly, electrocardiographic findings were obtained with any chest pain, and lab tests for blood enzymes were performed. During the 1960s, medical follow-up was far less rigorous. Patients that had as few symptoms as observed in military vaccinees were not likely to have sought medical care, or, if they did, further medical studies would have been unlikely. Medical advice would likely have been to take 2 aspirin and to rest until ready to return to work.

Imvamune is the only other candidate strain for larger-scale vaccination at this time. No complications have occurred, but only 2,800 persons have been given the vaccine in clinical trials. Thus, little can be said about possible adverse events should it be used on a large scale.

INTERNATIONAL INTEREST IN SUPPORTING A STOCKPILE

Developing a new vaccine or antiviral drug is a major challenge and a costly one. Based on the experience of the past 6 years, it is questionable that resources will readily be found even to augment emergency smallpox vaccine reserves with existing vaccines.

A 1998 WHO survey showed that few countries have kept smallpox vaccine in stock. Meanwhile, concerns have grown about the threat of biological weapons and the possible use of smallpox in particular. Accordingly, WHO convened a meeting in 2004 to discuss plans for developing an international emergency stockpile. The group recommended that WHO should endeavor to obtain commitments to have available at least 200 million doses. The quantity was arbitrary. It represented what was thought to be the maximum quantity that might reasonably be donated by member countries. WHO reports that as of 2010, the total strategic stockpile amounted to 57 million doses. Of this amount, 30.5 million doses are stored in Switzerland (30 million doses donated by Acambis and 530,000 doses by 5 countries). A virtual stockpile of 27 million doses is held in 4 countries, ready to be shipped in an emergency (20 million doses in the U.S. and 7 million doses held by 3 other countries).

A LOOK TO THE FUTURE: PRIORITIES AND ALTERNATIVES

Where do we stand with respect to smallpox? It has been 33 years since the last case occurred. No country is routinely vaccinating its citizens and none have indicated a desire to do so. The threat of smallpox remains: a potential catastrophe if smallpox were to be released and there was insufficient vaccine to stop its spread. Smallpox virus is believed to be present in only 2 secure laboratories, but there is no guarantee that there are no others. Thus, there is continuing need to be prepared to stop the spread of smallpox should it appear.

A first priority is to assure that there is adequate vaccine in international and national stockpiles to be dispensed immediately to contain outbreaks wherever they might occur and vaccine manufacturing facilities prepared to produce more vaccine should it be needed. An international commitment and special resources are necessary to meet this requirement, as well as a strategic plan for dealing with an epidemic.

There are 2 smallpox vaccines (ACAM2000 and LC16m8) that are now licensed and sufficiently tested to recommend for international use. Both are produced in tissue cell culture; the methodology for large-scale production has been elaborated; they are highly stable; and, when kept at −20°C, they have a long shelf-life. They are derived from known vaccinia strains that were extensively used in the smallpox eradication program and which proved to be highly protective. Both vaccines are inserted in superficial layers of the skin, where they grow and produce immunity.

The primary drawback in the use of the vaccines is the infrequent occurrence of sometimes serious adverse reactions in people with atopic dermatitis or immune deficiency disorders. The reactions stem from extensive, relatively uncontrolled growth of vaccinia virus. Vaccinia Immune Globulin has been partially effective in treatment. Fortunately, final studies of 2 new antiviral drugs are now
being completed, both of which show high levels of efficacy in stopping vaccinial infection in experimental animals. They should be similarly effective in dealing with human complications of vaccinial infection.

Work is proceeding on a variety of other possible smallpox vaccines that might exhibit fewer adverse reactions than the presently available vaccines that must grow in the skin to produce protection. The most advanced is a vaccine called Imunogen, which, after inoculation, does not grow but does induce good antibody responses and protects monkeys against monkeypox. Its drawbacks are its much greater cost and the fact that 2 doses, 1 month apart, and a period of 6 weeks after the first injection are needed to confer protection. Its use under epidemic circumstances is thus limited.

Securing the resources needed for developing and stockpiling a new vaccine or drug is a major hurdle. An even more formidable hurdle in developing a product to cope with smallpox is the fact that there is no way that one can be certain the product will actually protect a human from developing smallpox or would be effective in treating smallpox illness. There is no animal that can be infected so as to mimic a human exposure or the disease itself. In the past, vaccines and antiviral drugs were evaluated during the course of epidemics, but now there is no smallpox. For a disease so severe, there is understandable apprehension about relying heavily on a product that can’t be fully tested.

With 2 highly protective vaccines available and the near-completion of work on 2 antiviral drugs, is it warranted to continue to invest heavily in new vaccines and additional antiviral drugs that we hope and expect will never have to be deployed? Might it not be better to give priority to assuring that we have an adequate emergency reserve of smallpox vaccine and antiviral drugs that we know will protect against smallpox, and in strengthening the international and national response capabilities for surveillance, containment, and laboratory capabilities? The retention of the existing stocks of smallpox virus are not required for this agenda.

References


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