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COMMENTARY

The Smallpox Threat: A Time to Reconsider Global Policy

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In May of this year, the 67th World Health Assembly will again debate the question of when the remaining specimens of smallpox virus should be destroyed. Over the past 18 years, this has been on the agenda of 5 previous Assemblies, the last being in 2011. At that time, the delegates "affirmed strongly the decisions of previous Health Assemblies that the remaining stocks of variola virus should be destroyed."[1] They asked that the date be decided by the 2014 Assembly.

Inordinate amounts of time, effort, and resources have been spent in endeavoring to reach consensus on this one component of a smallpox threat strategy: whether to destroy or not destroy smallpox virus strains now being retained in the 2 World Health Organization (WHO) Collaborating Laboratories (in the United States and Russia). In both, the virus is being held under secure conditions. This year, a WHO-appointed group of international scientists concurred that there is no justification for retaining live smallpox virus. In any case, as others have pointed out, advances in genomic biology would now permit strains of virus to be replicated should someone wish to do so.[2] Logic dictates an early date for destruction of the last laboratory strains.

Meanwhile, countries and committees have substantially ignored the far more important initiatives that the global community and individual nations should take in order to be prepared to deal with smallpox outbreaks should they occur. Few have stockpiles of vaccine; not more than 8 to 10 countries have sufficient vaccine to cope with an outbreak. A WHO global emergency reserve, recommended 10 years ago, is steadily shrinking. Strategic plans for outbreak containment have been little discussed. At the same time, 2 initiatives have received special attention and resources: one to develop a vaccine that would protect without adverse reactions, and one to perfect antiviral drugs to treat cases should they occur. Both have failed to meet expectations.

In writing this commentary, we have jointly drawn on our own half-century of experience with smallpox to offer a brief historic context for a better comprehension of current efforts and to critique the contemporary status of preparedness and response in coping with the unlikely return of smallpox, which has played such a dominant role throughout mankind's history.

A Brief History of Deliberations about Virus Destruction

From the time of the occurrence of the last smallpox case in 1978, many countries and scientists have argued for the destruction of all known specimens of variola virus. Many fear, realistically, the increasing potential for a global catastrophe should smallpox be introduced into a now largely unvaccinated world, either accidentally by escape from a laboratory or deliberately by a terrorist. As an initial step to

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diminish that risk, all virus laboratories, beginning in 1975, were asked by WHO to destroy such specimens of variola virus as they might have or to transfer them to 1 of 2 WHO Collaborating Smallpox Laboratories (the US Centers for Disease Control and Prevention, Atlanta, GA, or the State Research Center for Virology, Novosibirsk, Russia).[3] By 1983, all countries had provided written notice of their compliance. Research using live variola virus is now believed to be restricted to these 2 laboratories. Both function under continuing international oversight of approved biological security practices and approved research protocols.

Following the 1980 declaration of eradication, a WHO Committee on Orthopoxvirus Infections was established to deal with issues pertaining to smallpox in the posteradication era.[4] Variola virus destruction was a priority concern for countries that most recently had been infected and for whom memories of the disease were most vivid. They contended that destruction of the 2 known stocks of virus would reduce the risk of an accidental release and emphasized to all that possession of smallpox virus was unconscionable and unacceptable to the international community. Moreover, as they pointed out, the decision to undertake eradication had been by a majority vote of World Health Assembly delegates. Thus, it seemed appropriate for virus destruction to be decided in a similar manner. Favoring retention, however, were a number of scientists who believed that, in principle, it would be wrong to destroy an organism that conceivably might play a role, as yet unforeseen, in contributing to basic scientific insights in virology.

Between 1985 and 1995, the WHO Committee on Orthopoxvirus Infections consulted many virologists and public health leaders about activities that should be undertaken before destruction of the virus.[5] It encouraged special laboratory initiatives intended to characterize the essential nature of the existing virus strains, including their genetic structure. It also sought professional judgments from scientists in many countries.

The final report of the WHO Committee was delivered to the Director General for presentation to the 1996 World Health Assembly. It recommended that all existing stocks of variola virus be destroyed. This decision had the written support of 5 international microbiological organizations. However, a proposed presentation and discussion at the World Health Assembly was deferred pending further deliberations. Subsequent assemblies debated the question but continued to postpone setting a date for virus destruction until specified studies were completed. Two principal goals for research were identified: the development of a new smallpox vaccine that would provide full protection without adverse reactions, and 2 antiviral compounds suitable for treatment of smallpox infections.

Three years ago, Tucker published a detailed history of the deliberations. He characterized the issue of smallpox virus destruction as constituting "one of the longest and most contentious policy debates in the field of international health."[5(p55)] He added: "Unless a compromise formula can be worked out …, the result could be a diplomatic train wreck."[5(p55)]

Expert Advisory Committee Deliberations, 2011, 2014

Continuing interest in reaching a decisive conclusion resulted in the scheduling of a major comprehensive review of the issues and research activities so that final decisions could be reached at the 2011 World Health Assembly. In preparation, special meetings of 2 WHO committees were convened prior to the Assembly to review the smallpox research program and to provide their advice. One committee was the long-standing WHO Advisory Committee on Variola Virus Research (ACVVR),[6] which was composed largely of virologists, many of whom were engaged in smallpox research and policy. The advice of a second committee was also sought: the Advisory Group of Independent Experts (AGIES),[7] a group of distinguished scientists who had not been engaged in smallpox research or the eradication program. Available to both committees was a specially developed comprehensive scientific review of all variola virus research spanning the period 1999 to 2010.[8] After considerable discussion, the 2 committees reached a general agreement on most but not all of the major issues pertaining to the retention of smallpox virus. The Assembly deferred making a specific decision and requested that the subject be addressed again at the 2014 World Health Assembly.

The 2 committees held additional meetings in 2013. The majority in each committee agreed that there was no need to retain live variola virus for the development of further diagnostic tests, sequencing the genomes of additional isolates, use in animal models, or further development of smallpox vaccines. The AGIES also felt there was no need to retain variola virus for further development of antiviral agents; a majority of the ACVVR members, however, concluded that this objective justified its retention.

The Threat of an Outbreak of Smallpox

One question is key in all decisions: What is the likelihood that smallpox outbreaks will ever again recur? There is agreement that outbreaks are highly unlikely but that the probability is not zero. Thirty-five years have elapsed since the last case of smallpox. Over the years, many rumors of cases have been investigated; none has proved to be valid. Efforts have been made to isolate virus from bodies exhumed from various burial sites, including in the frozen tundra, but these have failed. Many pox lesions occurring in animals have been cultured. The viruses found were specific to various animal species. Thus, it is essentially certain that there is no natural reservoir of live smallpox virus.

A concern that cannot be allayed is the possibility of release of virus from unknown specimens in a laboratory. In

the mid-1990s, information became widely available about a long-secret industrial-scale biological weapons program in the former Soviet Union.[9] Variola virus had been the organism preferred above all others. The program is reported to have terminated during the 1990s. After this time, some of its scientists emigrated to other countries, bearing with them relevant knowledge and perhaps specimens. To date, however, there has been no evidence to confirm that clandestine activities with smallpox virus have been resumed in any laboratory or country. So far as is known, the only known specimens of variola virus are in the 2 designated WHO Collaborating Laboratories. However, there is no way to be certain that there are no others. Were the virus to be released, there is every reason to believe that it would be as lethal today as it was prior to the interruption of smallpox virus transmission.

Thus, there are valid reasons to ensure that adequate vaccine is available to counter any smallpox threat. Without vaccine, other procedures, such as isolation measures, quarantines, or supportive therapy, would be of little avail. A catastrophic pandemic could ensue.

Vaccines for an Emergency Response

The potential chaos and disruption of a terrorist event were dramatically emphasized by the September 2001 attack on the World Trade Center in New York City and the subsequent dissemination of anthrax organisms in letters. About that time there were intelligence intercepts that suggested there would be yet another biological attack. Anthrax was a threat, but smallpox was particularly to be feared.

The US was not then well prepared to deal with smallpox. At that time, the US had only 15 million doses of a traditional calf lymph smallpox vaccine; it had been in storage for more than 20 years. It was decided that smallpox vaccine sufficient to vaccinate all citizens should be obtained urgently and stockpiled. However, there were no vaccine producers in the US or in other countries that were capable of producing more than a few million doses per year. A new tissue cell culture production method was needed. Senior US staff, working closely with the Acambis company, in a temporarily available Austrian laboratory, succeeded in producing more than 200 million doses of a new tissue cell culture vaccine called ACAM2000 in 18 months. The strain was a plaque-purified virus derived from the long-used New York City Board of Health strain. The vaccine was freeze-dried and is expected to have a shelf life of 10 years or more. The vaccine is now fully licensed.

Progress in other countries in developing emergency stockpiles of vaccine has been disappointing. In 2004 the WHO Committee on Orthopoxviruses was convened to discuss the global needs for smallpox vaccine.[10] The committee recommended the establishment of a special WHO emergency vaccine reserve, to be activated as needed. Proposed was a 200 million dose emergency stockpile to be donated by member countries. It was recommended that 5 million doses be kept in Geneva for immediate dispatch. It was also recommended that there be a "virtual" stockpile of 195 million doses, donated by individual countries but retained in national stockpiles ready for immediate shipment. In making the recommendation, the committee cautioned that this quantity of vaccine might well be inadequate even for dealing with a few moderate-sized outbreaks. However, they recognized that to propose a larger stockpile was unrealistic given the scarcity of national resources.

The committee recognized that there would be a serious problem in obtaining more vaccine if needed. There were at that time only a few national vaccine manufacturers. Most produced the traditional calf-lymph vaccine and had a production capacity of no more than a few million doses. Each would require at least 4 to 5 months to augment production. To develop new facilities capable of producing a tissue culture vaccine was thought to require at least 3 to 4 years. Thus, the committee recommended that there be at least 2 national laboratories that, in an emergency, would be capable of producing large quantities of vaccine in tissue cell culture.[10] At this time, one is under construction and nearing completion. It is being constructed by Sanofi-Pasteur (which purchased Acambis). This is intended to have an annual production capability of at least 50 million doses. Meanwhile, a Japanese manufacturer (Kaketsukan) has built in Kumamoto, Japan, the only other laboratory capable of large-scale production of tissue cell culture smallpox vaccine (80 million doses per year). This vaccine uses a new, more attenuated strain (called LC16m8) derived from the once widely use Lister Institute vaccine strain and is licensed in Japan.[11] The vaccine, like ACAM2000, is freeze-dried and is administered with a bifurcated needle.

10 Years Later

Ten years have elapsed since the WHO Committee on Vaccines met. The WHO emergency stockpile in Geneva is now 3 million doses rather than the recommended 5 million. WHO's virtual emergency vaccine supply held in national stores is now 30 million doses—not 195 million doses. Moreover, it is believed that there are not more than 7 or 8 countries that have sufficient vaccine to vaccinate as many as 20% of their populations should emergency containment measures be needed.

Which vaccines should be available for emergency use? The WHO Scientific Advisory Group of Experts (SAGE) met in November 2013 to provide advice to member countries as to which smallpox vaccines should be included in a stockpile and how they should be used in case of an outbreak.[12] SAGE recommended that the vaccines should be lyophilized (to maximize shelf-life of stockpiles), they should be capable of being administered by bifurcated needles (to allow reduction of the dose needed for traditional scratch vaccination), and they should

produce a visible major cutaneous reaction as a correlate of protection. Only the 2 licensed vaccines, ACAM2000 and LC16m8, meet these stipulations. SAGE recommended that if neither of these vaccines was available, countries should use locally produced vaccines like those used during eradication, which met WHO standards of potency, purity, and stability.

SAGE observed, in passing, that a recently developed vaccine, Imvamune (known as Imvanex in Europe), is not recommended until more information is available regarding its efficacy and safety and until it is produced as a lyophilized product.

Vaccine Use Policies

Vaccine utilization requirements necessarily must take into account that the occurrence of smallpox anywhere in the world is a global threat in a now largely unprotected population. Smallpox has the potential to spread from person to person in any climate and in any season. With the rapidity and extent of international travel, an outbreak in one country has implications for national responses throughout the world. Thus, following an outbreak anywhere, a number of countries, whether infected or not, will very likely seek vaccine for protection of high-risk staff and officials. Given the limited quantities of vaccine available, response planning must opt for strategies that use the least possible number of vaccine doses. The WHO emergency stockpile itself is so small that it would be of value only in limited circumstances; most countries have no national stocks, and those that do are certain to be cautious in offering vaccine to others. With so few sources of vaccine, there is a potential for serious conflict between countries with vaccine and those without.

The overall quantities of vaccine needed will vary greatly depending on a number of factors. An initial attack could affect a few people or thousands. The rapidity with which cases are discovered and isolated and their contacts vaccinated would govern the extent of spread. Much would depend on the degree of prior planning and training at local, national, and international levels. To date, such activities have been modest to negligible in most countries. In the past, an instinctive reaction of government officials has been simply to recommend obtaining enough vaccine to permit mass vaccination over large areas or perhaps nationwide. Given the limited amounts of vaccine available or able to be produced in an emergency, such policies would rapidly exhaust current stockpiles. SAGE specifically recommended against use of mass vaccination.[12]

It is important for all countries to have action plans and training for a targeted response. What is required is early detection of cases and vaccination of the few people who have been in face-to-face contact with each patient since he or she became ill. Typically, patients have 2 to 3 days of high fever and are so ill that they usually remain bedridden. Contacts are usually few in number. Vaccination is effective even when given 3 to 4 days *after* infection. Diagnosis of smallpox cases is comparatively easy and, in an outbreak, does not require laboratory confirmation for most cases. The disease spreads slowly because of a 10- to 12-day interval between successive generations of cases. Thus, large quantities of vaccine are not required to effect control. However, without adequate education and preparedness of the public and medical community, even small, readily contained outbreaks could result in serious civil disorder and a clamor for mass vaccination campaigns.

A New Vaccine and a New Antiviral Agent

Throughout the debates regarding destruction of smallpox virus, a principal argument for retaining live smallpox virus was to achieve 2 goals. The first was to have a smallpox vaccine that would provide full protection against smallpox without causing adverse reactions; the second was to have 2 antiviral compounds suitable for treatment of smallpox infections.

Creating new vaccines and drugs is well recognized to be difficult, time-consuming, and costly, but funds have been provided for several efforts.[2] Progress has been difficult, however, in part because of a lack of suitable animal models and the fact that there are no human cases. Other mammalian orthopoxviruses have been helpful in research, but all exhibit significantly different responses. None behaves like the natural smallpox virus does in humans. Thus, after more than a decade of research in highly capable laboratories, there is only 1 vaccine and 1 antiviral product that have progressed sufficiently to warrant a limited purchase for the US emergency stockpile. Neither fulfills the objectives originally envisaged. How they might be incorporated into a response plan has not been elaborated.

Several prospective antiviral drugs, intended for treatment of clinical cases, have been in development. One, tecovirimat (Arestvyr, or originally ST-246),[13] has been purchased to date for the US stockpile: 1.3 million courses of treatment at a cost of $175 million. What is needed is a drug that would be effective in treating patients exhibiting the typical pustular rash. It is notable that in human smallpox, the pustular rash does not appear until some 2 weeks after the patient has been infected with the virus. Most animal studies, however, have begun treatment immediately after infecting the animals. What remains to be shown is that monkeys, for example, infected by aerosol can be successfully treated many days later after pustules have begun to develop. Studies to date have not been encouraging. The drug is not licensed for use.

Considerable effort has been invested in developing a safe, protective vaccine for individuals with eczema or immune-deficiency diseases, who are at a greater risk of complications should they receive 1 of the 2 replicating

vaccines (ie, ACAM2000 or LC16m8). For this purpose, a new vaccine, Imvamune (originally modified vaccinia Ankara or MVA), a nonreplicating vaccine, has been developed by the Bavarian Nordic Company. To date, 20 million doses (enough for 10 million people) have been purchased by the United States for its stockpile at a cost of $505 million. In 2013, the European Union granted marketing authorization for this product subject to an annual reassessment.[14] It is not licensed in the United States.

The new vaccine, however, is substantially more expensive and requires the administration of 2 doses of vaccine by syringe and needle. Full protection is not obtained until 14 days after the second dose.[15] The vaccine is stable for only 2 years at –20°C. More concerning is the fact that fewer than 7,000 people have been vaccinated. Reported adverse reactions are few, but, even so, incomplete studies indicate possible risks of myocardial effects.[15] There is no apparent programmatic use for the vaccine at this time.

Summing Up

The perceptible threat of a smallpox release is little different today than it was 35 years ago; the implications of a smallpox outbreak in an increasingly susceptible world are more dire. Regrettably, there are few countries that have been sufficiently concerned so as to possess an emergency vaccine stockpile or to make other preparations to respond to an outbreak should it occur. It makes little sense to continue to invest in new vaccines or antiviral agents when there is so little interest in purchasing well-tested, available vaccines to provide at least minimal protection.

Rather than pursuing dreams of a perfect vaccine or a drug to treat a preventable disease, it would seem more rational to invest available energy and time in the development of smallpox vaccine stockpiles (national, regional, or global) and operational plans for isolation of patients, vaccination of contacts, and protection of high-risk medical and health personnel. There are now available 2 excellent replicating strains of freeze-dried vaccine virus that are highly protective, whose shelf life is 10 years or more, and whose cost is about $3 per dose. We suggest, as a reasonable goal, to have aggregate stockpiles of vaccine amounting to perhaps 10% of the global population, with another 300 million doses in a WHO stockpile. One licensed vaccine production facility is in operation, and a second is due to come on line by the end of the year.

Should the current stocks of live smallpox virus be destroyed? Given our knowledge of recombinant biology, retention of live variola virus is scientifically unnecessary. The virus, after all, could be recreated by a skilled microbiologist. Thus, at this time, we would propose 2 alternatives: (1) an internationally witnessed destruction of virus in each of the 2 Collaborating Laboratories, and (2) creation of an international lockbox for the virus strains to retain the genetic diversity of the isolates should they ever be needed for uses unforeseen.

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