Recent Events and Observations Pertaining to Smallpox Virus Destruction in 2002

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To destroy all remaining stocks of variola virus on or before 31 December 2002 seems an even more compelling goal today than it did in 1999, when the 52d World Health Assembly authorized temporary retention of remaining stocks to facilitate the possible development of (1) a more attenuated, less reactogenic smallpox vaccine and (2) an antiviral drug that could be used in treatment of patients with smallpox. We believe the deadline established in 1999 should be adhered to, given the potential outcomes of present research. Although verification that every country will have destroyed its stock of virus is impossible, it is reasonable to assume that the risk of a smallpox virus release would be diminished were the World Health Assembly to call on each country to destroy its stocks of smallpox virus and to state that any person, laboratory, or country found to have virus after date x would be guilty of a crime against humanity.

More than 18 months have passed since the 52d World Health Assembly reaffirmed the decision of previous assemblies that the remaining stocks of variola virus should be destroyed [1]. However, it authorized “temporary retention up to [but] not later than 2002 and subject to annual review by the World Health Assembly.” It provided for the creation of an expert group to oversee an interim research program and to assure the adequacy of containment measures taken by the laboratories. Since that time, important progress has been made, and other considerations have emerged as scientists and policy makers have given further thought to the potential outcomes of present research as they pertain to considerations of public health and national security.

This summary communication addresses the most pertinent of these considerations and indicates why we continue to believe that it is most important to adhere to the provisions and deadline established by the 1999 Assembly.

At the first meeting of the expert group (in December 1999), two research objectives were identified as the primary reasons for retaining variola virus: (1) the possible development of a more attenuated, less reactogenic smallpox vaccine, and (2) the possible development of an antiviral drug that could be used in treatment of patients with smallpox. An ancillary but important initiative was to evaluate again the possibility of establishing a functional variola virus/monkey model to facilitate the two research objectives.

A MORE ATTENUATED VACCINE

In the United States, a vaccine strain that would be as effective as the New York Board of Health (NYBOH) strain but that would be less prone to induce complications was originally seen as a desirable objective. In June 2000, an interagency meeting of government scientists was convened at the Centers for Disease Control and Prevention to determine the possibility of further evaluating currently available attenuated strains of vaccinia. Two candidates that had been extensively evaluated in the 1970s were the German MVA and the Japanese LC16m8 strains [2]. Both were propagated by tissue culture. They produced less marked cutaneous and febrile reactions in humans but satisfactory antibody levels. Animal studies indicated that they might be less neurotropic than the NYBOH strain. Neither had ever been used in an area in which smallpox was endemic, however.
The group recognized that if smallpox were to be released, the threat of its spreading widely was of paramount concern. Existing vaccine strains (NYBOH and Lister, for example) have been shown, in the circumstances of a natural challenge, to provide solid protection to almost all who received them, even when administered 2–3 days after exposure. Such an assurance of efficacy would be impossible to provide for any experimental vaccine simply because challenge in natural circumstances is no longer possible. Thus, a decision was made to procure additional NYBOH vaccine for the US national reserve. This conclusion effectively forecloses the rationale for further research on modified vaccines. Thus, it would seem appropriate that future research efforts pertaining to vaccination be directed toward mitigating the possible effects of adverse reactions to vaccinia through use of such as antivaccinial drugs or monoclonal antibodies.

AN ANTIVIRAL DRUG

As further mature consideration has been given to the possibility of developing an antiviral drug, several difficult and practical considerations have arisen that, taken together, question both the feasibility and wisdom of pursuing this strategy.

First is the question of cost for development and licensure of a new antiviral entity. Pharmaceutical manufacturers estimate that it costs in excess of $500 million and some 8–10 years of research and development to bring to market a new antimicrobial product. No government has yet signaled its willingness to make an investment of this magnitude for development of a new antiviral agent and quite possibly to expend substantially more than that amount of money again in providing a reasonably sized stockpile for possible use. Further funds would need to be set aside for replenishment of supplies as they deteriorated over time.

Second is the question of how much confidence either clinicians or public health professionals could have in using, under emergency conditions, an experimental drug either to treat patients after rash has emerged or to prevent disease among those who might have been exposed and possibly infected. However effective such a product might appear to be in tissue culture or in experiments with monkeys (a surrogate host) infected with monkeypox virus (a surrogate virus), no one could be confident that it would be effective in humans. The only reliable test would be the successful treatment of humans infected with variola virus, and that would be impossible except under epidemic circumstances. Perhaps somewhat more confidence in a new drug would accrue were there a variola/monkey model, but efforts to identify a satisfactory model have continued to meet with no success.

Third are the practical limitations, from a clinical and public health perspective, for use of an antiviral agent even if one were available. A therapeutic drug would be useful for treatment of some patients during the first and possibly second wave of cases. By then, the more certain and practicable strategy of prevention through vaccination would take precedence over treatment and would certainly be given preference in use of resources.

To use an antiviral agent as a prophylactic—that is, to prevent development of smallpox among those potentially exposed—would pose a staggering task to the most sophisticated and well-staffed public health system. Even assuming the need for only one dose of a drug daily, the practical logistics of distributing sufficient drugs to cover the large numbers of persons potentially exposed, to provide sufficient supervision to assure that such drugs were actually taken daily, and to pursue such a regimen throughout the weeks, if not months, that cases might be expected to occur would tax all resources. Clearly, vaccination has to be the primary defense. It is inexpensive; large-scale programs can be organized rapidly; and, with a single inoculation, it provides a level of protection that would be unlikely to be achieved with a drug, whenever or however administered.

An antiviral drug might be useful in preventing disease in immune-compromised persons who would be at risk of occurrence of progressive vaccinia, if vaccinated. However, it would seem to us to make more sense to focus research efforts on the development of an anti-vaccinial drug that could be used to treat cases of progressive vaccinia should they occur. Such a drug could be much more fully evaluated in animal studies, thus providing a high level of confidence that it would be effective when circumstances called for its use. Such research would not require retention of variola virus.

THE THREAT OF POSSIBLE RECOMBINANT STRAINS OF VARIOLA

Concern about the possible development of more-virulent recombinant strains of variola has arisen, stemming from Australian studies showing that an ectromelia-IL4 recombinant kills mice that are naturally resistant to the virus and also kills those mice who have been vaccinated [3, 4]. All manner of other hypothetical scenarios can be and have been imagined. Some have argued that the recombinant threat alone should be reason enough for retaining variola virus strains. Superficially, this might seem prudent, but the implications to us suggest otherwise. There might be logic in a broad-based research program to explore the range of possible alterations in the genome that might be induced and so better define the nature of the threat. However, not only would such experiments be in direct violation of the Biologic and Toxin Weapons Convention, but they might, at the same time, define a whole new array of bio-weapons, more awesome than any now known. And, predictably, these would not be kept secret for very long.
seems to us that there is a stronger argument than ever for bringing to bear all possible political and moral suasion to persuade countries and laboratories to destroy existing stocks of smallpox virus and to cease all research on variola virus itself. Nothing can guarantee that this will prevent an international catastrophe, but it would serve to mitigate the likelihood of its occurrence.

**SMALLPOX VIRUS IN OTHER LABORATORIES**

Finally, notice should be taken of the press’s frequent allusions to the fact that destruction of the virus is being postponed because of recent reports that laboratories other than those in Atlanta, the United States, and Novosibirsk, Russian Federation, might have retained smallpox virus. The question of whether other laboratories might or might not have surreptitiously retained strains of smallpox has not been nor should it now be a consideration in deciding whether or not the Assembly asks all countries to destroy their stocks of smallpox virus. The World Health Organization Expert Committee on Orthopoxvirus Infections recognized from its earliest meetings that there was no way that anyone could ever verify that each and every country had destroyed its stock of virus. To think otherwise would be naïve. To the Committee, it seemed reasonable then, and seems as reasonable now, to assume that the risk of a smallpox virus release would be diminished were the World Health Assembly to call on each country to destroy its stocks of smallpox virus and to state that any person, laboratory, or country found to have virus after date x would be guilty of a crime against humanity. This approach would be entirely consonant with activities now contemplated under the broader Biological Weapons Convention to abolish research on and production of offensive biological weapons.

**SUMMARY**

The logic and importance of actions to destroy all remaining stocks of variola virus on or before 31 December 2002 seem to us to be even more compelling than they did a year ago.

**References**

1. Fifty-Second World Health Assembly. Smallpox eradication: destruction of variola virus stocks. 1999; Resolution 52.10.