Countering the Posteradication Threat of Smallpox and Polio

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After eradication, there is a small but finite risk that smallpox and/or poliomyelitis viruses could accidentally escape from a laboratory or be released intentionally. The reintroduction of either virus into a highly susceptible population could develop into a serious catastrophe. To counter such an occurrence will require the use of vaccine, perhaps in substantial quantities. In the United States, new stocks of smallpox vaccine are being procured and arrangements are being made for a standby production facility. Similar provisions need to be considered for polio. To counter an epidemic of polio will require the use of the oral vaccine, which is presently the World Health Organization–recommended vaccine of choice for countries throughout the developing world. In these countries, its continued use is advised because of its ability to induce intestinal immunity, its ability to spread to other susceptible household members and to protect them, its ease of administration, and its low cost.

After the interruption of transmission of smallpox and polio viruses, it had been expected that vaccination against these diseases would cease and that the respective vaccines would no longer need to be produced or stored. A significant component of the anticipated savings to be realized through eradication was related to cessation of vaccination [1, 2]. However, expectations with regard to vaccine use and storage have changed because of concerns about a possible future catastrophe, were either virus to escape accidentally from a laboratory or to be released intentionally into a population with minimal immunity to the disease. In the case of polio, unexpected findings regarding the persistence and natural behavior of the polio vaccine viruses have provided another compelling reason for reconsidering a longer-term vaccination policy. Because of these factors, it has now become clear that stockpiles of both smallpox vaccine and oral polio vaccine (OPV) must be maintained for many years, perhaps indefinitely, and that polio vaccination must be continued for the indefinite future. This article summarizes the events and factors that have forced a reconsideration of expected vaccine use and storage in the posteradication era, highlighting in particular the complex issues associated with polio vaccine policy.

SMALLPOX

Smallpox was declared by the World Health Assembly to have been eradicated in 1980. On its recommendation, all countries stopped vaccination, the last in 1984 [3]. Stocks of variola (smallpox) virus were destroyed or transferred to 1 of 2 World Health Organization (WHO) reference laboratories (in Russia and the United States); vaccine production ceased; and manufacturing facilities were dismantled. A reserve of some 200 million doses of vaccine was retained by the WHO, in storage at −20°C near Geneva. Titers of these stocks were determined periodically to assure that they retained full potency. In 1990, however, 12 years after the last case of smallpox, the WHO faced difficult budget problems and decided to retain only 500,000 doses of vaccine. The balance of the vaccine was offered for return to countries that had donated it, but none asked to have it returned.

Two years after WHO had reduced its vaccine stocks, a former Soviet scientist revealed that in Soviet laboratories, beginning in the 1980s, successful efforts had been made to produce smallpox virus as a biological weapon and to grow and store the virus in multiple-ton quantities. This occurred despite the

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fact that this activity was forbidden by international agreements to which the Soviet Union was signatory [4]. It was a startling revelation. Of special concern was the fact that after the end of the cold war, many Russian scientists with expertise in production of biological weapons left for employment in other countries. It is unknown whether any took smallpox strains with them or whether any of the 12 or more countries that are believed to be working on biological weapons are working with smallpox virus. Whatever the case, it is now clear that the threat of smallpox virus being used as a weapon or escaping from a laboratory is substantially greater than had been realized as recently as a decade ago.

Coping with epidemic smallpox would be difficult or impossible with limited supplies of vaccine, no available therapy, and populations of whom perhaps ⩾80% are fully susceptible to the disease. Given a smallpox case-fatality rate of 30%, an international catastrophe can be foreseen unless there are reserves of vaccine available for emergency use. Accordingly, the United States has now contracted for delivery of 40 million doses of a tissue cell culture–grown smallpox vaccine and for maintenance of a standby production facility. Fortunately, the smallpox vaccine is highly stable, and with proper storage its full potency can be maintained for decades. It is hoped that these stocks, together with those in other countries, would provide a sufficient reserve to stop a smallpox outbreak wherever it might occur. However, at this time there is no intention to reinstitute routine vaccination, because the risk of vaccine-associated complications is sufficiently high to discourage it except under emergency circumstances.

POLIOMYELITIS

Poliomyelitis presents a very different set of problems, and the options for posteradication policies are currently under discussion. A number of possible approaches are described in detail in a recent WHO publication, under the designation "end game strategies" [5]. Primarily, they focus on vaccination policies. Also discussed is the relevant question of what should be done to ensure, to the extent possible, that poliovirus does not escape from laboratories, either as a result of mishandling of known or possibly infectious material or a deliberate release. Vaccination options being considered range from continuing to use OPV or inactivated polio vaccine (IPV) for an indefinite period, to stopping vaccination altogether on some sort of phased schedule, to perhaps developing a new OPV.

Three recent events, however, indicate that at this time there is no tenable option but to continue polio vaccination with OPV (in most countries) for the foreseeable future. First, an outbreak of paralytic disease caused by a revertant type I vaccine strain has recently been discovered; second, it has been documented that some persons with immune deficiency disorders can excrete the vaccine virus for at least 10 years; and third, it is now evident that there are problems with eradicating polio and documenting its eradication in strife-torn areas.

Recent Events of Significance

Outbreaks due to revertant Sabin vaccine strains. The discovery in October 2000 of a paralytic disease outbreak due to a revertant Sabin vaccine strain is a watershed event with regard to longer-term policies for polio control. Analysis of an outbreak of >16 cases of paralytic disease on Hispaniola (the island shared by the Dominican Republic and Haiti) has revealed that the virus responsible was a vaccine-derived type 1 strain of poliovirus, whose genetic divergence from the original vaccine strain indicates that it had been circulating for ~24 months before causing illness [6]. A recent retrospective study of poliovirus isolates from Egypt has also revealed that ~32 cases of paralytic disease occurred from 1988 through 1992 were associated with type 2 vaccine–derived isolates [7]. Each of these strains is readily distinguished from naturally occurring ("wild") strains of poliovirus. Therefore, their occurrence does not call into question WHO's primary goal of eradicating polio; that is, interrupting the transmission of wild polioviruses.

The findings in Hispaniola and Egypt were unexpected. During the >40 years that OPV has been in use—during which time billions of vaccinations have been given—it had never before been documented that a Sabin polio vaccine strain reverted and assumed the transmissibility characteristics of a wild-type strain [8]. It was known since before licensure of the vaccine that the different polio vaccine strains regularly showed some reversion to virulence (as demonstrated in tests in monkeys) when they passed through the intestinal tract [9]. Soon after licensure in 1962, it was discovered that paralytic disease could occasionally occur in vaccine recipients and their close contacts [10]. All cases were believed to be isolated occurrences, however. It is possible that outbreaks due to vaccine-derived strains of poliovirus may have occurred, but in the absence of techniques for nucleotide sequence analysis, they were not differentiated from naturally occurring outbreaks of wild poliovirus infection. Because the occurrence of cases attributable to OPV was sufficiently rare and the characteristics of the vaccine were sufficiently superior to those of IPV, OPV continued to be recommended as the vaccine of choice in most countries.

Paul Fine, in commenting on the strategy option described by Wood et al. [5] before the most recent revelations from Hispaniola and Egypt, expressed concern about the reversion of OPV to virulence: "Even with much more information than is now available, we are unlikely to be fully confident that OPV viruses cannot persist where there are high numbers of susceptible [persons] living in poor hygienic conditions" ([11], p. 358). If the virus can circulate undetected for 24 months in Hispaniola, where surveillance, although not ideal, is generally

better than in many developing countries, it is plausible that, in some countries, the virus could persist undetected for even longer periods before causing an outbreak of paralytic disease. However, many questions about these revertant strains remain to be defined: specifically, the frequency and conditions under which such strains might arise, as well as their contagiousness and propensity to cause paralytic illness.

Long-term carriage and excretion of polio vaccine viruses. Possible additional troublesome sources for revertant vaccine viruses are persons with certain hereditary immune deficiency disorders. Nine persons have been found to excrete vaccine viruses for periods of time ranging from a few months to nearly 10 years [5]. Few studies have provided indications about the frequency of this phenomenon but, because the hereditary risk factors may occur in as many as 1 of every 10,000 persons [8], it is probable that there have been and are a number of other persons who can and have carried and excreted the virus.

Problems in strife-torn areas. For countries to entertain the possibility of stopping vaccination, they must first have full confidence that virus transmission has been interrupted worldwide. Understandably, a special concern at this time are strife-torn areas where government authority does not extend throughout the country, as is the case in Liberia, Somalia, Sudan, Angola, Afghanistan, and the Democratic Republic of the Congo. Although polio control programs are in place in each of these countries, there are large areas in each country that are inaccessible or difficult for health personnel to access. The conflicts in most of these countries are long-standing and severe; it seems unlikely that they will be settled sufficiently any time soon to permit the field work necessary to interrupt polio virus transmission and to conduct careful surveillance for 3 years to ensure that transmission has ceased.

Such problems were also encountered during the smallpox vaccination program, but usually the program could be executed during periods of as little as 3–6 months of comparative tranquility in an area. However, there are 2 major differences in dealing with the control of smallpox and polio in insecure areas that are difficult to access. First, surveillance to determine whether and where the smallpox virus was present was comparatively simpler than polio surveillance and could be accomplished rapidly. The vast majority of patients had a distinctive rash; there were no asymptomatic patients and no long-term carriers. Thus, a team could rapidly search an area and determine whether the virus was present and, if it was, determine its extent and distribution without consulting a laboratory. Contrast this with the surveillance problems presented by poliomyelitis, in which there are $\geqslant$200 asymptomatic infections for every paralyzed patient. The only way one can ascertain whether the virus continues to circulate in an area is by an extended period of surveillance, during which a great number of stool specimens are examined. Time and access to a laboratory are critical requirements.

The second difference has to do with the efficacy of vaccination. One inoculation of smallpox vaccine protects nearly 100% of those vaccinated. However, in areas where polio is endemic, at least 3 doses of OPV, and often 5 or 6 doses, are required to achieve protective levels of 90% against types I and III poliovirus, which are the predominant paralytic strains [9]. Therefore, although vaccination immunity against smallpox could be increased rapidly in areas of conflict where access was possible for only a few weeks or months, this is not possible for polio.

Vaccination. Given the practical problems of achieving and confirming eradication in strife-torn areas and the recent findings that demonstrate the potential for polio vaccine strains to cause outbreaks of paralytic disease, there would appear to be no option at this time but to plan to continue vaccination programs for the foreseeable future and perhaps indefinitely. By sustaining reasonably high levels of population immunity, protection would also be provided against the possibility of catastrophic epidemics, should poliovirus accidentally escape from a laboratory or be disseminated deliberately.

At present, most industrialized countries are using IPV and most developing countries are using OPV. There are cogent reasons for this difference. Soon after licensure of OPV in 1962, it became the vaccine of choice for almost all countries. This was primarily because it was much easier to administer, it provided substantial intestinal immunity against infection with wild poliovirus, and it spread to close contacts, thereby protecting a number of people who were not themselves vaccinated. The only drawback to the use of OPV was the occasional occurrence of a case of paralytic illness among vaccine recipients and, sometimes, their close contacts. This occurred with a frequency of about 1 case per 1 million recipients of first doses of vaccine and, overall, about 1 case per 3 million doses of vaccine distributed [9].

Over time, many industrialized countries opted to use IPV to avert this risk, despite several attributes that continued to favor the use of OPV. Specifically, IPV was substantially more costly and had to be given by injection, instead of orally. Because it is an inactivated product, it does not spread to household contacts as did OPV, and although it confers pharyngeal immunity (as does OPV), it provides little intestinal immunity. For industrialized countries with ample health care resources, such factors as cost of vaccine, ease of administration, and spread of the vaccine were marginal considerations. Moreover, because virus transmission in industrialized countries is believed to occur primarily through droplet infection from the pharynx, the lack of intestinal immunity was not considered important. For developing countries, however, each of the special characteristics of OPV is of special relevance. This is es-

pecially true for intestinal immunity, because transmission of polio in these countries is believed to occur primarily by the fecal-oral route.

Under epidemic conditions, OPV is, by far, the preferred vaccine in all countries. Within days after community-wide application, OPV provides immunity and blocks circulation of wild virus strains. IPV, by contrast, requires 6–8 weeks for a satisfactory antibody response and would appear to have little inhibitory effect, at least in developing countries, on the spread of wild polio viruses.

Given present realities, there is no practical option other than continuing polio vaccination for the foreseeable future. One proposed alternative to using IPV in some countries and OPV in others would be to use IPV in all countries, perhaps combined with diphtheria-tetanus-pertussis vaccine [5]. Although an apparently simple solution, this approach is far more problematic than it might seem. Combining antigens into a single product while retaining the antigenicity of each of the products has proved difficult [12]. This problem is illustrated by the fact that, even today, there is no vaccine product available in the United States that combines IPV with any other antigen, although such a product is available in Canada and some European countries. Because diphtheria-tetanus-pertussis vaccine is produced in many different national laboratories, each of which uses different methods and materials, the task of converting all or even most of these laboratories into effective producers of a combined product would be a daunting challenge.

A more serious problem for developing countries is the questionable effectiveness of IPV. A carefully conducted WHO collaborative study in Thailand, Oman, and The Gambia revealed that after receiving 3 doses of IPV at 6, 10, and 14 weeks of age, as many as one-third of children were unprotected against type I polio, the most common type of wild virus [13]. Why IPV performed so poorly in this study, even though it consistently provides satisfactory serological responses in industrialized countries, is under study.

A third problem would be production of IPV after eradication was achieved. The three polio strains used in the inactivated vaccine are known to be highly virulent; all 3 were recovered from patients with severe paralytic polio, 1 of whom died [9]. To ensure that, during the posteradication period, these virulent polio virus strains did not escape the vaccine production facility, the facilities would be required to be more secure than any now producing this or any other biological product. The feasibility and costs of doing so are unclear.

Finally, if OPV use were to be stopped, it is unclear what provisions could be made to ensure both vaccine-production capability and the availability of large emergency reserves of vaccine. Unlike smallpox vaccine, which remains potent almost indefinitely at −20°C, OPV has a storage life of only a few years. The costs of sustaining a large standby production facility would not be inconsequential, even if the project were feasible.

Laboratory Containment of Poliovirus

The risk of poliovirus escaping from a laboratory bears significantly on vaccination policy. The risks are reviewed by Wood et al. [5], who identify 12 instances between 1941 and 1976 when laboratory-associated cases occurred. As they point out, the risk of an escape is low but cannot be ignored. Accordingly, they propose "the formidable task of locating the many laboratories that have stocks of infectious and potentially infectious wild poliovirus and ensuring that such stocks are destroyed or adequately contained." They add that "the bigger challenge will be to identify *all* laboratories with potentially infectious clinical, epidemiological, research, or environmental specimens collected for other purposes, in a geographical area and at a time of wild poliovirus endemicity." The plan calls for all such specimens to be dealt with under biosafety laboratory level–3 security as soon as polio virus transmission is thought to have been interrupted (a point once identified as December 2002). They propose that, after eradication is confirmed, materials containing poliovirus be handled under biosafety laboratory level–4 conditions (a point once expected to be December 2005).

The magnitude of the projected plan for dealing with laboratory specimens is formidable, and the likelihood of meeting its objectives is questionable. Racaniello, a research scientist, in commenting on the WHO's proposed program, characterizes the task as "mind-boggling, particularly in light of the absence of an enforcement authority," "simplistic," and "unsolvable" ([14], p. 360). In the course of the smallpox eradication program, a similar plan for laboratory containment was instituted, but the magnitude of the task was far less because there were very few diagnostic laboratories for smallpox and only a handful of investigators, and the search was specifically for known specimens of smallpox only. Nevertheless, the task was difficult; a number of investigators and national authorities resisted destroying specimens or transferring specimens to 1 of 2 designated WHO reference laboratories. The proposed plan for poliovirus is many orders of magnitude more complicated.

Efforts need to be made to minimize the risk that poliovirus will escape from a laboratory after transmission of wild poliovirus is interrupted. However, if vaccination is an ongoing process, the problems of virus escape are significantly diminished. With diminished risk, use of less draconian (although still onerous) measures for control of virus specimens would be possible, and there would be a greater likelihood of cooperation of laboratories and investigators. Efforts could be focused on those laboratories engaged in diagnostic or research studies of the poliovirus itself, rather than on all laboratories with fecal or other specimens in which poliovirus was an incidental and unknown contaminant.

Polio Program Goals

The ultimate goal of polio eradication has been to stop transmission of the naturally occurring ("wild") polioviruses. As in the smallpox program, eradication of the virus itself would be desirable. However, given the many laboratories that have materials believed to contain poliovirus and the practical impossibility of verifying the destruction of all materials that might contain poliovirus, the definition of the goal has been stated in measurable terms (as was the case for smallpox eradication): stopping virus transmission in humans.

Paralytic illnesses caused by OPV have been considered to be in a special category, on the basis of the fact that viruses isolated in such cases can be clearly differentiated from the naturally occurring wild virus strains. The occurrence of a few cases of vaccine-associated paralysis each year has been properly considered to have no bearing on a country's polio-free status. For example, the region of the Americas is still considered to be polio-free, despite the outbreak of paralytic disease caused by a revertant type I vaccine strain. For the present, at least, it makes sense to consider these viruses (both the strains and the diseases they cause) in a separate category and to investigate all suspected outbreaks carefully.

CONCLUSION

It is clear that there are finite risks (albeit small) of smallpox and polio outbreaks after eradication is achieved. For either virus, the epidemic that might ensue in a susceptible population could be catastrophic. Therefore, provisions must be made to ensure that ample supplies of both OPV and smallpox vaccines are readily available to counter such a threat. This is less problematic for smallpox, because the vaccine can be safely stored for decades and vaccination can be quickly instituted, since the virus can be detected rapidly in a population. For poliomyelitis, the situation is entirely different. Long-term storage of OPV is not possible, and detection of strains of virus capable of causing paralysis is likely to be difficult and delayed; for example, such strains circulated in Hispaniola for fully 2 years before they caused disease and were detected.

The arguments for continuing polio vaccination for the foreseeable future, with use of OPV or IPV, according to epidemiological circumstances, are compelling. Although it had been expected that vaccination could be terminated with the cessation of poliovirus transmission, our understanding of polio and the polio vaccines has changed. The premises upon which strategies were originally based were that OPV strains would not be responsible for generating outbreaks of paralytic disease and that, after vaccination, individuals would stop shedding the virus within a 2–3 months. Both of these assumptions have proved wrong. Although the task of achieving polio eradication is more complicated than had been foreseen, the objective of stopping transmission of the wild poliovirus remains the proper goal of the program. It is hoped that there will be few revertant outbreaks of paralysis associated with the polio vaccine and that the virus will be both less contagious and less pathogenic than wild virus strains. More information about these strains is needed; therefore, surveillance and the investigation of all cases and outbreaks are of special importance.

There is a cost associated with a continuing vaccination program, but compared with the costs for all other vaccines, it is not that large, and it should be manageable for most countries. It would be reasonable to expect that a substantially less intensive effort than has been required for interruption of wild poliovirus transmission would suffice.

To manage polio over the long term, the best solution would be an oral vaccine that offers all the advantages of current vaccines but does not revert to virulence and is more heat-stable and antigenic. This should command priority on an international research agenda.

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