When Can We Stop Using Oral Poliovirus Vaccine?

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(See the articles by Laassri et al. and Hennessey et al., on pages 2092–8 and 2124–8, respectively.)

In the years before the introduction of live, attenuated oral poliovirus vaccine (OPV), there was a vigorous debate between advocates of killed and live vaccines. Proponents of live vaccine took the position that OPV would produce immunity more similar to that produced by wild viruses, providing superior individual and population protection. Proponents of inactivated poliovirus vaccine (IPV) felt that there was a risk that attenuated viruses would regain their virulence and that person-to-person spread could permit continuous circulation of vaccine virus.

On the basis of 50 years of experience with Salk’s killed poliovirus vaccine and >40 years of experience with Sabin’s live, attenuated OPV, who was right? As is so often the case, both sides were. The first killed vaccine significantly reduced, but did not eliminate, polio. Mass campaigns with 3 monovalent OPVs brought the number of polio cases close to 0 in the United States. Although monovalent OPVs proved impractical for routine use, high coverage with trivalent OPV eliminated the disease from the United States; the last case caused by wild virus occurred in 1978, more than a generation ago. In 2004, 1255 confirmed polio cases were reported worldwide, a >99.5% reduction from the estimated 350,000 cases that occurred in 1988. This reduction was achieved by using mass OPV campaigns, as originally envisioned by Sabin. As the global polio eradication initiative nears its ultimate goal of stopping circulation of all wild polioviruses, the questions of if and how OPV vaccination can be stopped have become increasingly important.

Why must OPV vaccination be stopped? Vaccine-associated paralytic poliomyelitis was recognized shortly after the introduction of OPV, with cases occurring in both vaccinees and their contacts. The time is coming when the only cause of polio is likely to be the vaccine used to prevent it. Ample molecular data are now available to demonstrate that vaccine viruses can revert to full neurovirulence [1]. Outbreaks of polio in China, Egypt, Haiti, Madagascar, and the Philippines caused by circulating, neurovirulent vaccine-derived polioviruses (VDPVs) demonstrate that these revertant strains are fully transmissible and pose significant population risks. VDPV outbreaks are associated with incomplete vaccine coverage over a period of years, allowing a large population of susceptible children to accumulate [2]. Worldwide, only 70–80% of children receive 3 routine doses of diphtheria-tetanus-pertussis and OPV in their first year of life. Many of the poorest countries in the world are unable to vaccinate even 50% of their children. Under these circumstances, continuing to use OPV after eradication is very risky.

Some have proposed the global replacement of OPV with IPV. For example, in this issue of the Journal, Laassri et al. [3] demonstrate that enhanced-potency inactivated vaccine reduces both the titer of poliovirus excreted in stools and the duration of excretion. These findings suggest that currently available IPV will inhibit circulation of VDPVs and, consequently, should provide a greater degree of herd immunity than the original Salk vaccine. Because the reductions in virus excretion are smaller than those produced by OPV, Laassri et al. propose further enhancement of IPV to improve the population protection afforded by that vaccine. However, the effectiveness of such an improved vaccine in inhibiting poliovirus transmission would have to be verified experimentally, particularly in high-risk tropical developing countries where the immune response to both IPV and OPV is suboptimal [4]. The time and expense of developing, testing, and securing regulatory approval for a new IPV makes it unlikely that such a vaccine could be available on a timely basis.

Apart from the public health and ethical issues associated with continued vaccination against a nonexistent disease, OPV cannot simply be supplanted by IPV. Production capacity for the currently available enhanced-potency IPV is insufficient for global use. Expanding production capacity...
by building new facilities is both time consuming and extremely costly. Even with a massive, global financial commitment, sufficient quantities of IPV could not be available for the rapidly approaching date when the changeover would be necessary. Furthermore, low rates of immunization achieved in routine vaccination programs in the least-developed countries would mean that a high proportion of their populations would still remain unprotected, despite adequate vaccine supply [5].

A final reason for stopping vaccination with OPV—a reason that would also apply to IPV—is that the economic benefits of eradication will not be achieved if vaccination continues. The global savings in direct vaccination costs are estimated to be at least US $1.5 billion each year. The public-sector funding used to pay for polio vaccination will then, hopefully, be transferred to other important domestic and international public health programs.

There are, however, risks associated with stopping vaccination. For example, despite intensive virological surveillance for 3 years before eradication being certified, wild polioviruses might still be circulating at undetectably low levels when vaccination is stopped. Polio could also reemerge though inadvertent release of viruses used in vaccine production or the laboratory, similar to the last case of smallpox in Birmingham, England. The World Health Organization has recently developed a plan for stopping the use of OPV worldwide after the certification of global polio eradication [6]. The principal components of the plan are as follows: (1) biocontainment of all polioviruses, including wild, Sabin, and vaccine-derived strains, to reduce the risk that a laboratory accident will reintroduce poliovirus into a susceptible population; (2) maintenance of highly sensitive surveillance for circulating polioviruses, so that outbreaks are detected quickly; (3) stockpiling of monovalent OPV strains, to control any outbreak that might occur; and (4) simultaneous global OPV cessation, so that population immunity is at the highest possible level when the last dose of OPV is administered, to minimize the chances of circulating VDPV emerging.

A remaining risk is the long-term excretion of polioviruses by certain classes of immunodeficient individuals, a phenomenon recognized >30 years ago. Hypogammaglobulinemic patients are particularly susceptible to vaccine-associated paralytic poliomyelitis and have been most commonly found to be long-term excreters after developing paralysis. Some, however, have remained asymptomatic for many years. Stopping OPV use will prevent additional immunodeficient persons from becoming chronically infected through vaccination. Studies of cohorts of immunodeficient persons have shown that chronic infection is, fortunately, rare. So far, only 28 persons with primary immune deficiency disorders and chronic poliovirus infection have been identified in the 40 years that OPV has been used [6]. Presumably, countries with identified chronic excreters of poliovirus will continue to use inactivated vaccine until these persons die or until it is clear that they no longer pose a threat. Because 1 person has been excreting VDPV for at least 20 years and remains healthy [7], IPV may still be needed for decades.

In developing countries, the full scope of chronic poliovirus infection still needs to be better defined. Most of the population will not have access to sophisticated care that will prolong the life of an immunodeficient person. There is particular anxiety, though, about the large number of HIV-infected persons, especially in Africa, who might become chronically infected and transmit VDPV to others. This concern persists despite the qualitative differences between the immunodeficiency associated with HIV and the B cell defects associated with vaccine-associated paralytic poliomyelitis. Chronic infections would be likely to occur only during the advanced stages of immunodeficiency, when life expectancy would be short because treatment is, essentially, unavailable. The article by Hennessey et al. [8] in this issue of the Journal is an attempt to address that concern. They cultured stool samples from 325 HIV-infected persons in Cote d’Ivoire during the months after a mass OPV campaign. No polioviruses were found, leaving them 95% confident that the rate of chronic poliovirus infection is <1%.

Does Hennessey et al.’s study answer the question definitively? No. In fact, no healthy long-term excreter has been found by the kind of rational approach employed by Hennessey et al., even in hypogammaglobulinemic patients who are apparently at the highest level of risk [9]. All long-term excreters have been found by serendipity, though negative studies simply cannot demonstrate that an event never occurs. Could cohort selection in their study have been better? Yes. It would have been better if all study subjects had young children in their household and all were severely immunocompromised. However, the difficulty of conducting research in developing countries should not be underestimated. With the crowding and poor sanitation existing in African slums, it is likely that subjects would have been in contact with recently vaccinated children and/or exposed to vaccine viruses from environmental sources. Is the study reassuring? Yes, but additional studies should be performed, and with some urgency.

Although we can better define the extent and duration of chronic excretion of VDPV, the biggest threats to polio eradication now come from politics and complacency—threats that have the potential to keep eradication from ever being achieved. The eradication initiative has been ongoing for 17 years. There is a risk that donor fatigue may set in and financial support may dry up. A mixture of politics and religion led to a cessation of vaccination campaigns in northern Nigeria. The consequent outbreaks there not only have paralyzed >1000 children but also have seeded wild polioviruses across Africa and beyond. Polio-free countries were complacent about routine immu-
organization, allowing pockets of low coverage to develop. Wild poliovirus reached Mecca from North Africa and then spread to Yemen and Indonesia, where it found fertile soil. As of 28 October 2005, 473 cases of polio caused by wild poliovirus have been identified in Yemen, and 278 have been identified in Indonesia. Mass campaigns have been conducted to control these outbreaks and other smaller ones that followed importation into additional countries that had been previously free of polio. These expensive campaigns add a further stress to a program short of funding.

As scientists, it is easy for us to look for technical solutions to problems, but the mundane issues of having the fortitude and mobilizing the resources needed to complete the daunting tasks before us are the biggest challenges that we face. We are fortunate that the ranks of polio eradication workers are staffed with optimists who know it can be done and will see the job through to completion.

References