What Role for Inactivated Poliovirus Vaccine in the Eradication Endgame?

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(See the article by Laassri et al., on pages 1344–9.)

The 5-decade drive to control and eradicate polio through immunization [1] has benefited from the availability of 2 excellent vaccines, the inactivated poliovirus vaccine (IPV) of Salk and colleagues, licensed in 1955, and the live attenuated oral poliovirus vaccine (OPV) of Sabin, licensed in 1961. The 2 vaccines have complementary advantages, and both have played—and continue to play—important roles in polio control. IPV has been used primarily in developed countries with good sanitation and temperate climates, whereas OPV has been the primary weapon in the World Health Organization (WHO) initiative to eradicate polio from the developing world [2, 3]. The introduction of IPV in the United States and other high-income developed countries was followed by a sharp decline in polio incidence, but IPV was gradually replaced by OPV in the early 1960s, with only The Netherlands, Nordic countries, and some Canadian provinces continuing exclusive use of IPV. OPV offers the promise of global polio eradication because of its efficient induction of intestinal immunity, ease of administration, suitability for mass immunization campaigns, and lower cost.

Great strides have been made toward the goal of global polio eradication, with the apparent eradication of wild poliovirus type 2 in 1999 [4]; the highly localized endemic circulation of wild poliovirus type 3 to pockets in southern Afghanistan, northern India, and northern Nigeria; and the dramatic progress in the control of wild poliovirus type 1 in Egypt and southern Asia (updates are posted on the WHO Web site, http://www.polioeradication.org/). The incidence of polio has declined from an estimated 350,000 cases in 1988 to 1948 cases in 2005. However, wild poliovirus type 1 from reservoirs in northern Nigeria, where polio immunization had been interrupted in 2003 and 2004, spread to 18 previously polio-free countries in 2003–2005, from Guinea in the west, to Yemen and Somalia in the Horn of Africa, to Indonesia at the southeastern edge of Asia, resulting in a steep increase in the number of cases last year [5]. Nationwide mass immunization campaigns with OPV have rolled back polio in most of these countries, but outbreaks continue in Indonesia, Somalia, and Ethiopia, while northern Nigeria remains an active reservoir for poliovirus types 1 and 3.

These recent events underscore the urgency of completing the task of eradicating all wild polioviruses. The success of the WHO initiative has fundamentally altered poliovirus ecology, to the point at which the only source of immunity to poliovirus in all but a few parts of the world is immunization. When immunization rates fall, as they have in many polio-free, low-income developing countries, risks for large outbreaks increase rapidly among the growing cohorts of nonimmune children. The outbreak virus may be an imported wild poliovirus, or it may be a circulating (c) vaccine-derived poliovirus (VDPV) that has recovered the capacity to cause paralytic polio in humans and to spread by efficient person-to-person transmission [6]. Indeed, both type 1 imported wild poliovirus and type 1 cVDPV cocirculated in Indonesia in 2005 (for updates, see http://w3.whosea.org/en/Section1226/showfiles.asp). cVDPVs have most frequently emerged in areas with low rates of vaccine coverage and where the other biological risks for poliovirus circulation converge. However, in 2005, 5 years after the cessation of OPV use in the United States and Canada [7], a VDPV was found in rural Minnesota, among members of a community who refuse immunization [8]. The initiating OPV dose was estimated, on the basis of the extent of sequence divergence from the type 1 OPV strain, to have been given 1–2 years before VDPV detection, reinforcing the point that continued OPV use presents an ongoing risk for VDPV emergence and spread in all unimmunized populations, even in coun-
tries using IPV. In addition, in very rare instances, persons with hypogammaglobulinemia may be chronically infected with VDPVs for up to 10 years or more [6]. Most of the known immunodeficient VDPVs have been reported from high-income developed countries, but an increasing number of recent reports are coming from middle-income developing countries [9].

The potentially growing risks of VDPV emergence highlight the need for well-coordinated, synchronous cessation of OPV use worldwide as soon as is safely possible. OPV cessation will be immediately followed by the recall of all remaining OPV stocks from the field and preceded by the establishment of large stockpiles of monovalent OPV strategically placed for rapid deployment in the event of an emergency [10, 11]. The need to stop OPV use is driven not only by the risks of VDPV emergence and spread but also by the continued global occurrence of 250–500 cases of vaccine-associated paralytic poliomyelitis (VAPP) annually [10]. Soon, the annual incidence of VAPP will likely exceed that of polio caused by wild poliovirus infections, making continued OPV use increasingly unsustainable for a disease that has otherwise disappeared. Both VAPP and VDPV risks are the consequences of the intrinsic genetic instability of the Sabin OPV strains and of the strong negative selection against key genetic determinants of attenuation when OPV replicates in the human intestine [12–14]. In view of the continued VAPP risk at a time of sharply decreased risk for importation of wild poliovirus, the United States adopted, from 1997 to 1999, a sequential IPV/OPV immunization schedule, to reduce the risk of VAPP in primary OPV recipients by combining the complementary advantages of the 2 poliovirus vaccines and as a transition to an all-IPV schedule beginning in 2000 [15].

Among the concerns attending this change in immunization schedule were reports that prior immunization of infants with IPV increased the rate of accumulation and excretion of potentially neurovirulent OPV revertants on subsequent administration of OPV [16, 17]. Although later studies did not entirely confirm the original observations [18, 19], the initial reports raised the prospect that the sequential IPV/OPV schedule might actually elevate the risk of VAPP among nonimmune contacts of primary OPV recipients. In this issue of the *Journal of Infectious Diseases*, Laassri et al. provide definitive evidence that the use of a sequential IPV/OPV schedule does not increase excretion of neurovirulent OPV revertants. In a well-designed study, 527 healthy infants were immunized with OPV alone, IPV alone, or IPV followed by OPV. Stool samples collected from the study groups were screened for poliovirus by polymerase chain reaction (PCR) amplification of the full-length viral RNA, and the cDNAs were analyzed for the proportion of revertants at key attenuating sites in the 5′ untranslated region by use of oligonucleotide microarray hybridization analysis. The direct PCR method eliminates any potential biological selection that might occur during cell culture isolation. The sites studied (nt 480 and 525 for Sabin type 1, nt 481 for Sabin type 2, and nt 472 for Sabin type 3), the same as those investigated in the earlier studies [16, 17], are known to revert rapidly during replication in the human intestine [12]. The reversion rates, highest for Sabin type 2 and lowest for Sabin type 1, were found not to be significantly altered by prior exposure to IPV. These virologic findings are consistent with those of epidemiologic studies in the United States, where no cases of VAPP were associated with the sequential IPV/OPV schedule during the 1997–1999 transition to the IPV-only schedule [7, 20].

In their discussion, Laassri et al. build a case for wider use of IPV for global polio immunization, either alone or in a sequential IPV/OPV schedule. Indeed, many high-income countries have already shifted to an IPV-only schedule, and a sequential IPV/OPV schedule is now used in several eastern European countries. It is likely that these trends will continue among countries able to maintain high rates of routine immunization. A transitional IPV/OPV schedule could lower global VAPP rates among OPV recipients, but, in areas with low routine immunization rates, such a strategy could prolong the risk of VAPP among unimmunized contacts of OPV recipients and extend the potentially large risks of VDPV emergence. Accordingly, such a transition phase should necessarily be short, and many countries have shifted directly from OPV to IPV. However, implementation of a global IPV-only policy, even for a limited period after synchronous OPV cessation, will confront several major challenges [11, 21]. The most important of these is the unknown efficacy of IPV in preventing poliovirus transmission in tropical developing countries. IPV induces good pharyngeal immunity but substantially lower intestinal immunity than that induced by OPV [22], which probably accounts for its inefficacy in developed countries where respiratory transmission of poliovirus is particularly important [18]. By contrast, IPV appears to have reduced efficacy in countries with poor sanitation, where fecal-oral transmission predominates [23]. Moreover, the optimal schedule for routine immunization with IPV differs from the WHO/Expanded Program on Immunization routine schedule [21, 23]. Increasing the potency of IPV may help to improve population immunity in tropical zones, but the fundamental differences between the immune response to the live OPV and that to any nonreplicating poliovirus vaccine [24] may be difficult to overcome. These biological challenges are compounded by social and logistical challenges, as the rates of routine immunization remain stubbornly low in most low-income countries at highest risk for poliovirus transmission. In these areas, the immunity gaps have been closed by periodic mass campaigns with OPV. The injectable IPV is less suitable than OPV for mass campaigns, thus requiring increased reliance on high rates of routine immunization coverage. Finally,
IPV costs substantially more to produce than OPV, and global use of IPV would require major new financial commitments. Local IPV production to reduce costs in developing countries is not a viable option, because of the large facility investments required to assure complete containment of live virus during IPV production and the need for the surrounding community to maintain very high rates of IPV coverage. Whatever endgame strategies are adopted globally, they will be implemented in the context of declining public awareness of polio as a health threat, a result of the very success of the WHO initiative.

We inherited from the early pioneers in polio immunization a clear vision on how to begin the journey to polio eradication [1, 25]. Less clear is how we should best complete the journey. Safe navigation of this final, potentially difficult, phase of the journey will require judicious implementation of the most effective tools at our disposal (including various OPV formulations, IPV, and new antiviral drugs) and the best efforts of the public health and research communities.

References