POLICY

OPV Cessation—the Final Step To a "Polio-Free" World

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The World Health Assembly voted in 1988 to eradicate poliomyelitis, on the basis of a large body of evidence indicating the efficacy of a combination of routine immunization, supplementary polio immunization campaigns, and highly sensitive surveillance (*1*). By early 2003, indigenous wild polioviruses were limited to discrete areas of just 6 of the more than 125 countries that were considered infected in 1988. Disease burden declined from an estimated 350,000 cases in 1988 to 784 reported cases in 2003. In that year, however, the initiative faced two potentially fatal challenges. The 12-month suspension of all immunization with oral polio vaccine (OPV) in a number of northern states of Nigeria (*2*) led to reinfection, by mid-2005, in 18 previously polio-free countries, from Mali to Indonesia. The second, and more threatening, development was the failure of very high coverage with trivalent OPV to interrupt polio in some densely populated areas in India and Egypt (*3*). By mid-2005, however, political advocacy had led to the restart of OPV immunization in Nigeria and the "reinterruption" of polio in many reinfected countries, while technical advances [monovalent oral poliovirus type 1 vaccine (mOPV1)] (*4*) had already eliminated some of the polio reservoirs in India and Egypt.

With the interruption of wild polioviruses globally increasingly on track, attention has returned to the challenges posed by the "post-eradication" era. Planning for that era is now driven by the recognition that even with eventual interruption of all wild-type poliovirus, paralytic polio will continue until routine use of live vaccines is stopped (*3*, *5*, *6*).

The Rationale for Stopping OPV

OPV has been one of the most effective tools for disease prevention in public health. Soon after licensure, however, it was recognized that OPV use resulted in rare cases of vaccine-associated paralytic poliomyelitis (VAPP) (*7*). Consequently, after eliminating indigenous wild poliovirus and because of the progress toward global eradication, some countries with very high immunization coverage have moved to inactivated poliovirus vaccine (IPV) for routine childhood immunization (*8*). Although the public health benefits of OPV continue to outweigh the VAPP risk (*9*), this balance can be expected to change with the interruption of wild-poliovirus transmission in all countries. An estimated 250 to 500 VAPP cases would continue to occur each year in OPV-using countries on the basis of current vaccine utilization patterns. (*10*).

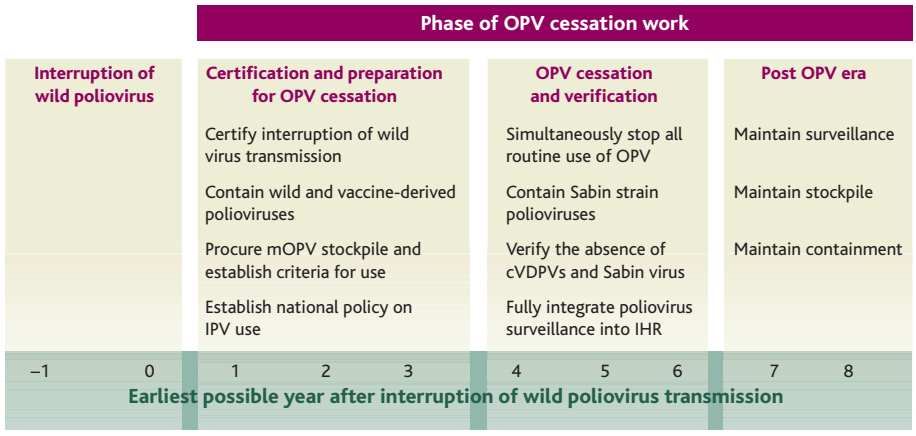
Of even greater significance is the recent documentation that OPV viruses under some circumstances regain both neurovirulence and the capacity to circulate and cause outbreaks (*11*). By mid-2005, such circulating vaccine-derived polioviruses (cVDPVs) had been established as the source of polio outbreaks that paralyzed more than 50 people total in Hispaniola (2000–2001) (*12*), the Philippines (2001) (*13*), Madagascar [2002 (*14*), 2005], China (2004) (*15*), and Indonesia (2005). A seventh such outbreak, in Egypt, has been described retrospectively (*16*). All recent cVDPVs have been rapidly interrupted with an OPV campaign. After global eradication of wild-type polioviruses, however, the continued use of OPV would continually generate cVDPVs. The spread of just a limited number of these cVDPVs would eventually negate the elimination of wild-type polioviruses from human populations.

Finally, the use of OPV in individuals with some primary immunodeficiency syndromes has been shown to result, rarely, in prolonged excretion (>6 months) of vaccine-derived polioviruses; these individuals are called iVDPVs (*17*). Although none of the 28 iVDPVs detected to date are known to have generated secondary cases, and 25 spontaneously stopped excreting or died, "chronic" excretion (>36 months) did occur from four iVDPVs (*18*), all of whom lived in high-income countries that plan to continue IPV use. Acquired immunodeficiency syndromes, such as that associated with HIV infection, have not been associated with prolonged poliovirus excretion (*19, 20*).

Risks Associated with Stopping OPV

Mathematical modeling suggests that there is a 65 to 90% chance of at least one outbreak of cVDPV occurring somewhere in the world during the 12 months immediately after cessation of OPV use globally, with that risk declining to 1 to 5% at 36 months (*21*). Countries with low routine immunization coverage at the time of OPV cessation are expected to be at greatest risk. The overall probability of substantial international spread of such a virus is remote, especially as monovalent OPVs are available for rapid response.

There is a longer-term risk of reintroducing a wild, vaccine-derived or Sabin poliovirus strain from a vaccine production site, a laboratory, or an iVDPV. The magnitude of the facility-associated risks is largely contingent on the extent of poliovirus destruction before OPV cessation and largely contingent on the quality of high-level biocontainment (*22*). Before OPV cessation, the magnitude of the iVDPV risk must be more accurately defined, and



Major phases for OPV cessation.

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Published by AAAS

strategies for clearing chronic iVDPVs must be pursued, including evaluation of potential antiviral drugs.

The final risks derive from intentional use of polioviruses. The risk of an effective bioterrorist incident using poliovirus is remote (*23*), because of high population immunity at OPV cessation, continued access to a polio vaccine stockpile thereafter, and the inherent difficulties in targeting polioviruses. The decision by several countries, including those generally thought to be at highest risk for intentional use of biologic agents, to maintain high population immunity through continued IPV use should further deter intentional use of polioviruses.

Managing Cessation of Routine OPV Use

In a polio-free world, no vaccination strategy is without risk (*24*). Six major "prerequisites" have been defined to reduce and to manage the risks of paralytic poliomyelitis that would be associated with OPV cessation (for additional details, see table S1).

First, there must be confirmation of interruption of wild-poliovirus transmission globally. In 1995, mainly on the basis of the experience in the Americas (*25, 26*), 3 years was established as the minimum period between the last circulating wild poliovirus in a geographic block of countries and its certification as polio-free (*27*). Quantifiable performance targets were set for polio surveillance based primarily on identification and investigation of children less than 15 years of age with acute flaccid paralysis (AFP) (*28–30*).

Second, biocontainment of all polioviruses must be ensured (*31*). To date, 158 countries have initiated a survey for wild poliovirus materials, covering over 210,000 facilities. As of May 2005, ~800 facilities had been identified with relevant materials, which will either be destroyed or placed under biocontainment. OPV cessation will also require international consensus on, and verification of, biosafety measures for Sabin viruses. The World Health Organization (WHO) is promoting development of IPV from Sabin strains to reduce the risks associated with large-scale wild-poliovirus amplification in the post-OPV era, while facilitating maintenance of a "warm base" for restart of OPV production should that ever prove necessary (*4*).

Third, an international stockpile of monovalent OPV vaccines (mOPV) is being established so that type-specific immunity could be rapidly established if poliovirus were reintroduced (*32*). Bulk vaccine could also be used to resume routine immunization quickly in the "post-OPV" era, while production from seed virus is restarted if required. Criteria for the use of mOPVs must be internationally agreed upon given the implications of reintroducing attenuated poliovirus strains in a post-OPV era. The enhanced efficacy of mOPV and elimination of unnecessary serotypes will further reduce the risk of inadvertently generating a cVDPV during an outbreak response. Strategies for minimizing the risk of a cVDPV after an mOPV response must also be further elaborated, including the potential use of antivirals or a combination of mOPV and IPV in the initial response (*33*).

Fourth, sensitive surveillance for polioviruses must be sustained, particularly during the 3 years immediately after OPV cessation. The existing global AFP surveillance capacity will require continued financial support, with supplementary activities such as systematic screening for iVDPVs. Poliovirus surveillance is being incorporated into the *International Health Regulations* (IHR) to sustain detection and response activities (*34*). Rapid diagnostic tools, particularly Immunoglobulin M (IgM) assays and direct molecular detection techniques, are being evaluated for integration into the global polio laboratory network.

Fifth, extensive work (such as international agreements on timelines) is needed to prepare for simultaneous OPV cessation worldwide. Eliminating the risk of a Sabin strain reintroduction will require rapidly collecting and destroying OPV stocks everywhere.

Finally, each country must decide whether to maintain immunity against polio in the post-OPV era. The risks of intentional or inadvertent poliovirus reintroduction into increasingly naïve populations must be measured against the financial, opportunity, and programmatic costs associated with IPV use (*35*). Such decisions are particularly important in resource-poor settings (*36*). IPV currently costs at least 4 or 5 times the estimated "break-even" price for replacing OPV in routine immunization programmes (*37*), and existing IPV producers have predicted there will not be substantial volume discounts because of high fixed production costs. WHO will continue to review the role of IPV as additional data are collected on both the vaccine and the risks associated with OPV cessation.

The most important lesson for long-term polio immunization policy comes from the smallpox eradication effort—the capacity to conduct research on polio vaccines and control strategies must be maintained to ensure that appropriate tools are always available.

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10.1126/science.1115813