

# Risk Management in a Polio-Free World

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Inherent in the decision to launch the Global Polio Eradication Initiative in 1988 was the expectation for many people that immunization against poliomyelitis would eventually simply stop, as had been the case with smallpox following its eradication in 1977. However, the strategies for managing the risks associated with a “polio-free” world must be continuously refined to reflect new developments, particularly in our understanding of the live polioviruses in the oral poliovirus vaccine (OPV) and in the international approach to managing potential biohazards. The most important of these developments has been the confirmation in 2000 that vaccine-derived polioviruses (VDPVs) can circulate and cause polio outbreaks, making the use of OPV after interruption of wild poliovirus transmission incompatible with a polio-free world. A comprehensive strategy has been developed to minimize the risks associated with eventual OPV cessation, centered on appropriate long-term biocontainment of poliovirus stocks (whether for vaccine production, diagnosis, or research), the controlled reintroduction of any live poliovirus vaccine (i.e., from an OPV stockpile), and appropriate use of the inactivated poliovirus vaccine (IPV). Although some aspects of this risk management strategy are still debated, there is wide agreement that no strategy would entirely eliminate the potential risks to a polio-free world. The current strategy for risk management in a polio-free world will continue to evolve with better characterization of these risks and the development of more effective approaches both to reduce those risks and to limit their consequences should they occur.

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## 1. INTRODUCTION

In addition to abolishing the morbidity and mortality caused by a specific pathogen, eradication offers the possibility of eventually stopping all control measures once the infectious agent has been eliminated globally.<sup>(1,2)</sup> This characteristic uniquely separates eradication from the concept of national,

regional, or even global elimination of a disease. Ultimately, however, the decision whether to stop control measures depends on the associated risks and the risk management strategies available to mitigate their consequences.

This article provides historical context on the Global Polio Eradication Initiative (GPEI) and outlines the rationale for eventually stopping immunization against polio with the oral poliovirus vaccine (OPV), the associated risks, and the ongoing program of work to ensure optimal management of those risks. The increasing importance and relevance of this work to the overall feasibility of the GPEI has been highlighted repeatedly in recent commentaries on the reinfection of countries that previously eliminated poliovirus.<sup>(3,4)</sup>

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## 2. THE GLOBAL POLIO ERADICATION INITIATIVE

In 1988 the World Health Organization's governing body, the World Health Assembly (WHA), comprised of the Ministers of Health from its 192 Member States, resolved to eradicate polio.<sup>(5)</sup> The WHA's decision reflected a combination of humanitarian and economic arguments. At that time it was estimated that the three wild polioviruses (types 1, 2, and 3) were still paralyzing over 350,000 children every year in more than 125 countries, despite the availability of a cheap and effective vaccine since 1961. Furthermore, the systematic application of a four-pronged strategy by the Pan American Health Organization (PAHO), the WHO Regional Office for the Americas, had clearly demonstrated the feasibility of interrupting wild poliovirus transmission in large geographic areas.<sup>(6)</sup> From an economic perspective, eventually foregoing polio treatment and immunization costs, subsequently estimated at up to US\$ 1.5 billion per year, promised to rapidly recoup the costs of eradication.<sup>(7)</sup> Finally, substantial political and societal will existed to support embarking on this ambitious undertaking, led and galvanized by Rotary International, the volunteer service organization whose 1.2 million members in 140 countries donated over US\$ 600 million of the US\$ 4.0 billion in external financing expended on the initiative as of the end of 2005.<sup>(8)</sup> Indeed, one of the most striking aspects of the GPEI has been the tremendous international goodwill and political commitment it has enjoyed; by the end of 2000 every country in the world, including those with the scarcest of resources and greatest burden of disease, had introduced the necessary strategies and 60 countries, foundations, nongovernmental organizations, and companies had provided external financing for eradication activities.<sup>(8)</sup>

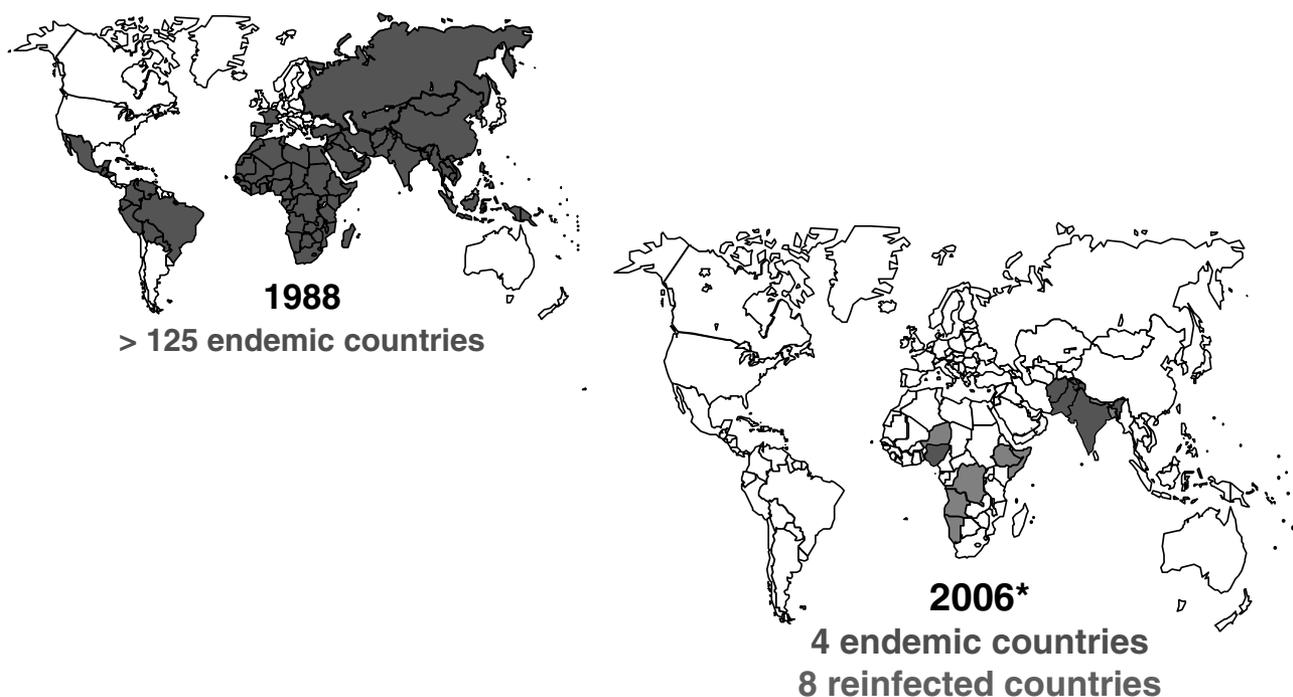
The PAHO strategy for regional polio elimination formed the basis for the global eradication effort.<sup>(9)</sup> The first element of this strategy sought to strengthen routine immunization services to optimize population immunity against polioviruses by ensuring as high a proportion of children as possible received three (subsequently increased to four) OPV doses early in life. Second, annual National Immunization Days (NIDs) were used to interrupt major widespread chains of poliovirus transmission by conducting two rounds of OPV immunization, 4–6 weeks apart, targeting all children aged less than 5 years for additional OPV doses regardless of their immunization history. Third, reporting and virologic investigation were instituted

for all cases of acute flaccid paralysis (AFP) in children aged less than 15 years, and for all "suspect polio" cases in persons of any age, to increase the sensitivity of surveillance for circulating polioviruses. Finally, PAHO introduced large-scale house-to-house OPV mop-up vaccination campaigns to interrupt any remaining localized poliovirus transmission in a country or area.

Although two excellent polio vaccines had been licensed by 1961, the GPEI followed PAHO in choosing OPV over the inactivated poliovirus vaccine (IPV) for both routine and supplementary immunization activities.<sup>(10)</sup> The oral administration of OPV allowed the program to employ vast numbers of volunteers to implement NIDs, in contrast to IPV, which would require injection by trained health workers. The substantially lower cost of OPV (<5% of the costs of IPV) facilitated financing of the eradication initiative. Most importantly, the enhanced mucosal immunity conferred by OPV proved essential to the interruption of community transmission of wild polioviruses, especially in the tropical developing country setting. The secondary spread of the live OPV viruses to protect nonimmunized individuals and increase population immunity was another important advantage of OPV. The major drawback to OPV was the rare side effect of vaccine-associated paralytic poliomyelitis (VAPP).<sup>(11)</sup>

By September 2006, through the systematic application and refinement of the eradication strategies, the number of polio cases occurring each year dropped by more than 99% and only 4 countries still harbored indigenous wild polioviruses (Fig. 1).<sup>(12)</sup> The GPEI had also succeeded in eradicating one of the three poliovirus serotypes (type 2), with the last case of polio in the world due to an indigenous type 2 wild virus occurring in India in late 1999.<sup>(13)</sup> Furthermore, type 3 poliovirus was by September 2006 restricted to just northern Nigeria in Africa, 1 state of India, and a border area of Pakistan and southern Afghanistan in Asia.

While the outlook for global eradication is positive, substantial challenges remain. Of particular note in the context of risk management planning for the posteradication era is the chronic financing gap that has required that the GPEI regularly incur very high risks by scaling back planned immunization campaigns and surveillance activities, particularly in polio-free areas. Such risk taking has not been without consequences; in 2003–2005 alone, the international community eventually had to spend over US\$ 400 million to stop outbreaks that occurred following



**Fig. 1.** Comparison of countries with active poliovirus transmission in 1988 and as of 1 September 2006.

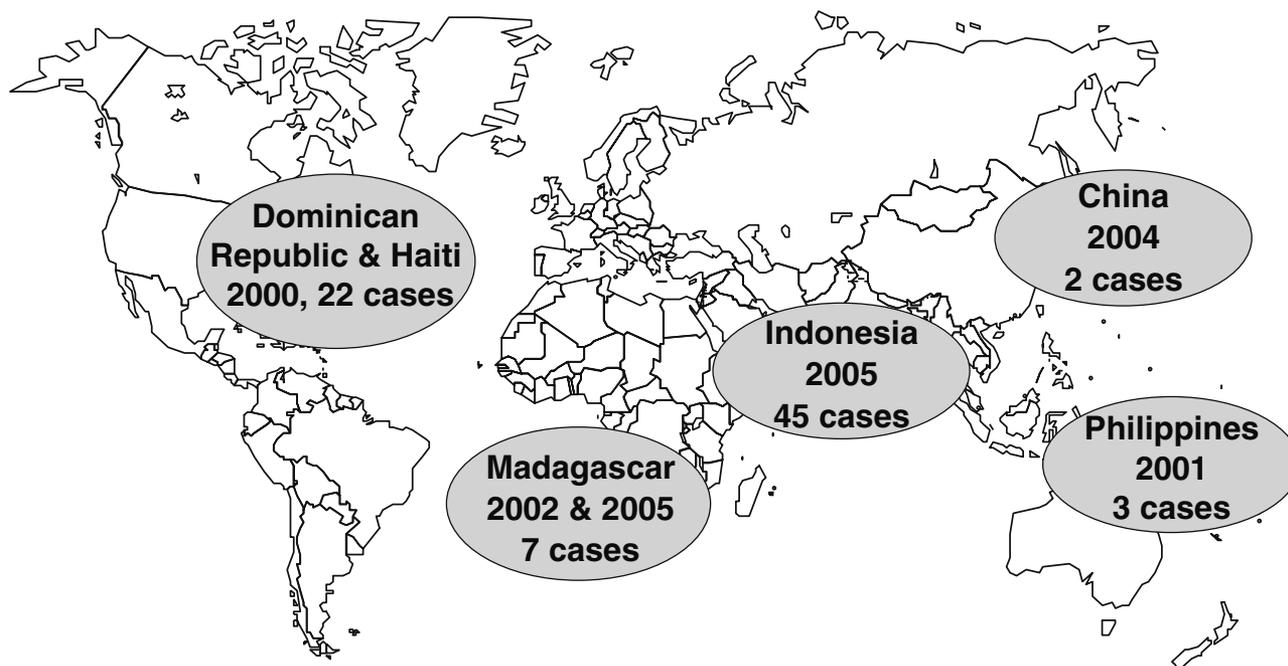
poliovirus importations into previously polio-free areas where OPV campaigns had been prematurely curtailed due to insufficient financing for the GPEI. As eradication has drawn closer, the debate over the eventual cessation of polio immunization has raised many other important considerations.

### 3. THE RATIONALE FOR EVENTUAL OPV CESSATION

The global cessation of smallpox immunization soon after the eradication of its causative pathogen in 1977 contributed greatly to the widespread expectation that polio immunization would stop soon after eradication of wild polioviruses.<sup>(14)</sup> However, there are important differences in the vaccines used to eradicate each of these diseases, as well as the political circumstances of the periods in which each initiative was conducted. The smallpox vaccine was made from the vaccinia virus rather than the smallpox virus itself and caused a very high rate of severe side effects (i.e., up to 1 severe adverse event per 25,000 doses administered).<sup>(15)</sup> Furthermore, the disease was eliminated at a time when concerns about its potential deliberate use to cause harm were much less than they are today.

Until the year 2000, discussions on long-term polio immunization policy were primarily driven by the humanitarian and economic benefits of OPV cessation. In particular, it was widely felt that once wild poliovirus had been interrupted globally the public health benefits of OPV would no longer outweigh the estimated 250–500 cases of VAPP that would continue to occur each year based on current vaccine utilization patterns.<sup>(16)</sup> In fact, as progress toward global polio eradication advanced in the late 1990s and the risk of wild poliovirus importations declined, industrialized countries began switching from OPV to IPV for routine childhood immunization to avoid VAPP,<sup>(17)</sup> despite a high cost-benefit effectiveness ratio for IPV.<sup>(18)</sup>

More recently, however, evidence emerged of a new OPV-associated risk that is of even greater significance than VAPP for long-term polio immunization policy. Specifically, it has been shown that the Sabin strain polioviruses in OPV can regain both neurovirulence and the capacity to circulate and cause outbreaks (Fig. 2).<sup>(19)</sup> Between 2000 and 2005 alone, such circulating vaccine-derived polioviruses (cVDPVs) caused a total of six polio outbreaks—in Haiti and the Dominican Republic (2000–2001), the Philippines (2001), Madagascar (2002, 2005), China (2004), and Indonesia (2005). Other probable cVDPV-associated



**Fig. 2.** Distribution of six polio outbreaks caused by circulating vaccine-derived polioviruses (cVDPVs) between 2000 and 2005.

polio outbreaks have been described retrospectively. Such episodes demonstrate that after wild poliovirus eradication the use of OPV would continually generate cVDPVs, the spread of which could eventually reverse the eradication achievement.

A further risk associated with continued OPV use after global eradication is the generation of new long-term excretors of vaccine-derived polioviruses (VDPVs) that might subsequently reinfect an increasingly susceptible human population.<sup>(20)</sup> Prolonged VDPV excretion (>6 months) occurs only rarely and almost always in individuals with certain primary B-cell-related immunodeficiency syndromes (iVDPVs). None of the 28 iVDPVs confirmed by January 2006 led to any known secondary cases of paralytic polio, although there has been at least one documented case of asymptomatic infection of contacts.<sup>(21)</sup> Twenty-one of the individuals with iVDPVs have spontaneously stopped excreting, died, or were lost to follow-up; five iVDPVs were documented to have excreted chronically (WHO working definition >60 months), two of whom are known to have still been excreting as recently as 2005. Acquired immunodeficiency syndromes involving T-cells, such as that associated with human immunodeficiency virus (HIV) infection, do not appear to be associated with prolonged poliovirus excretion.<sup>(22)</sup>

Recognizing that paralytic poliomyelitis cases and outbreaks would continue as long as there is routine OPV use, expert committees since 1998 recommended the eventual, simultaneous cessation of all routine OPV immunization as soon as possible after confirmation of wild poliovirus eradication.<sup>(23–25)</sup>

#### 4. THE MAJOR RISKS ASSOCIATED WITH OPV CESSATION

While there are clear benefits to eventually stopping OPV, these must be weighed against the associated risks. These can be considered in three categories: the live attenuated poliovirus strains used for OPV production (e.g., Sabin strains), VDPVs, and wild polioviruses. In each case the risk is of human infection, and subsequent transmission, following ingestion of the virus. Poliovirus survival in the environment is finite; infectivity is lost over a period of days, under hot dry conditions, to weeks or several months under cool, moist conditions.<sup>(26)</sup> Long-term storage typically requires temperatures of less than 20°C to maintain high virus titres for periods longer than 6 months.

Strictly speaking, the term “Sabin strain” poliovirus denotes one of the three live attenuated viruses that Dr. Albert Sabin developed for his

OPV. The term is also commonly (though incorrectly) used to refer more generally to any OPV seed virus. Sabin strain polioviruses are ubiquitous due to routine immunization programs that currently use approximately 2 billion doses of OPV each year to vaccinate children in over 150 countries. Such live attenuated polioviruses are present in a variety of other settings due to their use as seed viruses for OPV production, reference standards in vaccine quality assurance and control testing, controls for some polio diagnostic tests, for basic research in a number laboratories, and for teaching purposes in some academic centers. While the vast majority of OPV recipients will experience time-limited (i.e., 3–4 weeks) intestinal replication and shedding of the virus, Sabin viruses can give rise to cVDPVs or generate an iVDPV as described above. Of particular importance for risk management planning is the danger posed by the emergence of one or more cVDPVs immediately after countries stop using OPV, when population immunity will already have started to decline. Mathematical modeling suggests that even with simultaneous cessation of OPV use worldwide a 60–95% chance exists of at least one such outbreak occurring somewhere in the world during the 12 months immediately after cessation, with that risk declining to 1–6% at 36 months and much lower thereafter.<sup>(27)</sup> Without simultaneous OPV cessation worldwide, the risk of cVDPV emergence and spread would increase substantially and possibly prevent the eventual cessation of OPV globally.

As their name suggests, VDPVs arise from the use of live poliovirus vaccines and denote those viruses that have drifted genetically by at least 1% from the

parent, usually Sabin, strain. VDPVs can arise from either prolonged replication of a vaccine strain in an individual or as the result of circulation through numerous individuals in a population. Although VDPVs are rare, after OPV cessation a research or diagnostic facility could inadvertently release a VDPV, a VDPV could be excreted by one of a handful of iVDPVs, and/or a cVDPV could circulate, at least transiently, in a community. While there would be relatively few VDPVs following OPV cessation, they would be of special importance and represent an ongoing concern due to the current lack of an effective antiviral therapy or other proven strategy to eliminate chronic infections.

Wild polioviruses represent the final category. These polioviruses are currently used as seed viruses for the production of IPV, in vaccine quality control and assurance testing, as controls for some diagnostic tests, and in research laboratories. Although wild polioviruses are no longer nearly as ubiquitous as Sabin polioviruses, and no evidence exists of their long-term carriage like iVDPVs, the consequences of an inadvertent or intentional release in the post-OPV era pose a potentially far greater threat. A recent consequence assessment suggests that whereas transmission of a Sabin strain virus may or may not be self-limiting if released into an unvaccinated population in the post-OPV era (depending on the virus type and circumstances), a wild poliovirus could result in a large-scale outbreak with a real risk of eventually reestablishing endemic transmission globally.<sup>(28)</sup>

Figure 3 summarizes, based on current knowledge, the expected evolution of these risks in low- and high-income countries over a probable 3–5 year

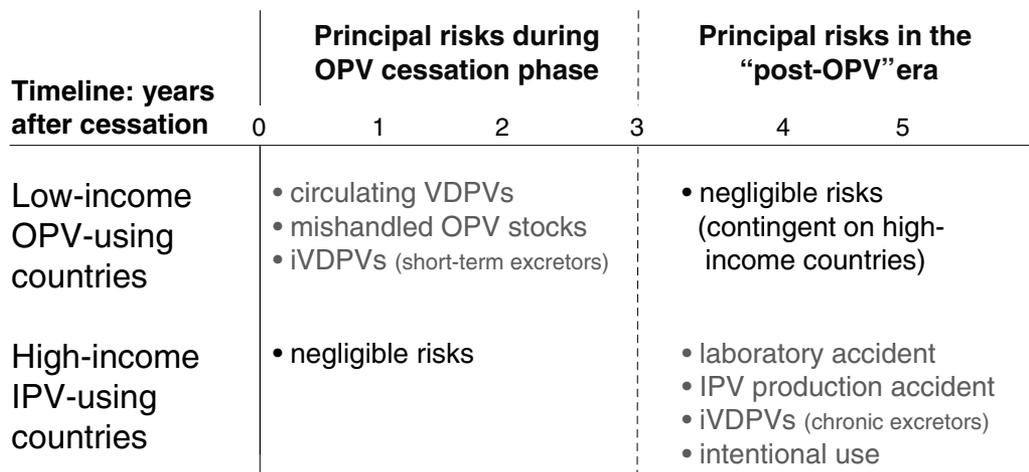


Fig. 3. Risks associated with eventual cessation of routine childhood immunization with oral polio vaccine (OPV), by income bracket.\*

\*In upper-middle-income countries, risks and policies often reflect high-income countries; in low-middle-income countries, risks and policies often reflect low income countries.

“OPV cessation” phase following confirmation of wild poliovirus interruption and appropriate biocontainment of all poliovirus stocks globally.

## 5. RISK REDUCTION AND MANAGEMENT

A comprehensive approach must be taken to optimize the management of the risks associated with OPV cessation. The core principles forming such an approach must be to: (a) stop simultaneously the routine use of OPV worldwide, while population immunity is high, with the subsequent recall and destruction of remaining stocks, (b) reduce the number of procedures performed with polioviruses to those that are essential in the post-OPV era, (c) replace, where possible, wild polioviruses with Sabin strain viruses for any procedure that must continue to be conducted in the post-OPV era, (d) minimize the number of sites handling or storing *any* polioviruses or potentially poliovirus-infectious materials (wild viruses prior to OPV cessation; Sabin strains immediately thereafter) and limiting these sites to areas where the consequences of an inadvertent release could be minimized, (e) institute processes to ensure residual poliovirus-containing sites fully implement appropriate biocontainment and biosafety procedures, (f) maintain high-level surveillance to identify and monitor iVDPVs and to detect an inadvertent or intentional release of any poliovirus into the human population, and (h) establish a stockpile of monovalent OPVs with internationally agreed criteria for their use in mounting type-specific outbreak responses to circulating polioviruses in the post-OPV era.

Minimizing the risks associated with OPV cessation would require establishing international concurrence, through a body such as the WHA, to apply these core principles in all areas of all countries in the world. Additional risk reduction or risk management strategies may be required in areas that pose particular risks during or after OPV cessation. For example, OPV-using areas with large, high-density populations and low routine immunization coverage may be at high risk for generating cVDPVs and need special attention. Countries or communities with facilities that continue to store or handle polioviruses in the post-OPV era for IPV production and quality assurance purposes, to provide international diagnostic services, or to conduct specialized research may constitute an international biohazard and require rather extraordinary measures to prevent, or minimize the consequences of, inadvertent virus release.

These principles have been incorporated into a set of “prerequisites” for eventually stopping the routine

use of OPV for childhood immunization globally.<sup>(29)</sup> Conspicuously absent from the core principles outlined above is the use of IPV for universal childhood immunization. Although universal IPV childhood immunization has been proposed as a potential solution to the risk of cVDPV emergence at the time of OPV cessation, mathematical modeling suggests that IPV would only partially reduce the already small risk of a cVDPV in most countries.<sup>(27)</sup> Furthermore, routine infant immunization with IPV would not substantially mitigate the consequences of poliovirus reintroduction in countries with low routine coverage, such as much of sub-Saharan Africa.<sup>(30)</sup> Consequently, countries must decide at the national level whether to stop all polio vaccination or switch to IPV based on whether there is a real or perceived need to maintain population immunity against polioviruses indefinitely.

Policymakers in each country must balance their national willingness to pay to maintain population immunity to polioviruses against the financial, programmatic, and opportunity costs of introducing IPV, the true costs of which may not be immediately apparent, particularly for resource-poor areas.<sup>(31)</sup> In financial terms alone, UNICEF currently procures IPV at five times the estimated “break even” price for replacing OPV.<sup>(32)</sup> Despite anticipated reductions in the unit price of IPV for low-income countries, the substantial opportunity costs associated with the use of scarce health resources for that vaccine (e.g., rather than to combat HIV, malaria, tuberculosis, measles, pneumococcal, and rotavirus infections) will strongly influence decision making at the national level. Based on their review of the implications, costs, and benefits of IPV introduction for routine immunization, some low-income countries have already decided that the advantages of stopping all polio immunization currently outweigh both the short-term risk of cVDPV emergence and the longer-term risks of poliovirus reintroduction. In contrast, some middle-income, OPV-using countries are considering the introduction of routine infant immunization with IPV as a transition strategy to maintain population immunity against polio during the 3- to 5-year period of OPV cessation and verification of the absence of cVDPVs worldwide.

## 6. NEXT STEPS—THE UNFINISHED RESEARCH AGENDA

Optimizing the tools and strategies for eventual OPV cessation requires continued work to rapidly address ongoing gaps in knowledge about the associated

risks and the opportunities to manage them. First, the risks associated with OPV cessation must be better quantified in terms of their frequency, magnitude, and consequences. For example, the prevalence, natural history, and community spread of iVDPVs must be better understood, particularly in middle-income OPV-using countries where therapy for immunodeficiency syndromes may be available and chronic excretors could survive well into adulthood. Further investigation is needed into the origins and implications of “ambiguous” VDPVs (aVDPVs), for which typically a single representative virus is isolated from a clinical or environmental source, to determine whether additional measures or strategies are needed to manage such viruses.<sup>(19)</sup>

Second, further evaluation of the effectiveness, costs, and benefits of a range of proposed risk reduction strategies should be conducted to assist decisions by national and international policymakers. These include the potential value of targeted OPV pulse immunization campaigns, or a switch to IPV for routine immunization at the time of OPV cessation to boost or maintain population immunity in high-risk areas and reduce, at least theoretically, the probability of subsequent cVDPV emergence. The technical and economic feasibility of producing IPV from Sabin poliovirus strains should continue to be evaluated as a potential strategy for reducing the risk of harmful consequences due to an inadvertent poliovirus release from a vaccine manufacturer into increasingly immunologically naïve populations in the post-OPV era.<sup>(33)</sup>

Finally, the risk management tools and strategies themselves must be reviewed and if possible improved. New, rapid diagnostic tools should be pursued to increase substantially the speed of poliovirus detection and response in the post-OPV era. Assessing the efficacy and cost-benefit ratios of alternative IPV immunization strategies, such as 2-dose schedules and/or fractional dosing, will help determine whether more affordable options might exist for OPV-using countries that choose to introduce IPV, either indefinitely or as a transition step to stopping all polio immunization. Of particular importance is the need to fast track the full evaluation of compounds with promising antiviral properties that could potentially clear or substantially reduce the titre of excreted iVDPVs. The current use of mOPVs in low coverage areas for responding to outbreaks caused by imported polioviruses should be carefully evaluated to explore whether mOPV use in the post-OPV era could inadvertently give rise to new cVDPVs. An understand-

ing of the feasibility of stopping cVDPVs with an IPV response would also help significantly to inform outbreak response strategies for the OPV cessation period and the post-OPV era.

In a polio-free world, no vaccination strategy will be without risk. As knowledge of the risks associated with OPV cessation increases though, so do the prospects for developing more effective strategies to reduce those risks and to limit their consequences should they occur. The experience of the GPEI in eradicating wild polioviruses provides a sobering reminder, however, that the success of these risk management strategies will ultimately depend on the degree to which the international community is willing to finance their development and implementation.

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