Polio eradication: the OPV paradox

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SUMMARY
Routine and mass administration of oral polio vaccine (OPV) since 1961 has prevented many millions of cases of paralytic poliomyelitis. The public health value of this inexpensive and easily administered product has been extraordinary. Progress of the Global Polio Eradication Initiative has further defined the value of OPV as well as its risk through vaccine-associated paralytic poliomyelitis (VAPP) and vaccine-derived polioviruses (VDPV). Although both are rare, once wild poliovirus transmission has been interrupted by OPV, the only poliomyelitis due to poliovirus will be caused by OPV. Poliovirus will be eradicated only when OPV use is discontinued. This paradox provides a major incentive for eventually stopping polio immunization or replacing OPV, but it also introduces complexity into the process of identifying safe and scientifically sound strategies for doing so. The core post eradication immunization issues include the risk/benefits of continued OPV use, the extent of OPV replacement with IPV, possible strategies for discontinuing OPV, and the potential for development and licensure of a safe and effective replacement for OPV. Formulation of an informed post eradication immunization policy requires careful evaluation of polio epidemiology, surveillance capability, vaccine availability, laboratory containment, and the risks posed by the very tool responsible for successful interruption of wild poliovirus transmission. Copyright © 2003 John Wiley & Sons, Ltd.

INTRODUCTION
In 1988, when the World Health Assembly (WHA) resolved to eradicate polio by the year 2000, paralytic poliomyelitis was endemic in 125 countries on five continents with an estimated 350,000 cases annually [1]. Although the year 2000 goal was not met, tremendous progress has been made toward the interruption of wild poliovirus transmission (see www.polioeradication.org). In 2002, polio was endemic in only seven countries even though India had a considerable increase in cases compared with 2001 [2]. The last indigenous case in the Americas was in 1991 [3]; in the Western Pacific Region, 1997 [4]; and 1998 in the European Region [5]. Naturally occurring wild poliovirus type 2 has not been detected anywhere in the world since the last recorded case in October 1999 in India [6]. Although much remains to be done, the goal of interrupting wild poliovirus transmission worldwide appears to be within reach.

This extraordinary low point in wild poliovirus transmission has been achieved through national and international will and leadership, generous public and private financial support, and unstinting human energies from the highest international levels to the most remote communities. The vital key to interrupting wild poliovirus transmission, however, has been the attenuated live oral polio vaccine (OPV). Routine and mass administration of OPV since 1961 has prevented many millions of cases of paralytic poliomyelitis. Mass OPV immunization coupled with effective acute flaccid paralysis surveillance has proven to be an effective strategy to eliminate epidemic poliomyelitis and endemic poliovirus circulation in the developing tropical world. Systematic application of this
strategy worldwide is anticipated to interrupt the remaining chains of wild poliovirus transmission.

The public health value of this inexpensive and easily administered oral polio vaccine has been extraordinary. However, OPV is not without risk. An estimated 250–500 [2] cases of vaccine-associated paralytic poliomyelitis (VAPP) are anticipated to result each year from sustained OPV use in a world free of wild poliovirus transmission. Once wild poliovirus transmission is interrupted by OPV, the only poliomyelitis due to poliovirus will be caused by OPV. At the present time, reducing the numbers of VAPP cases through reducing OPV coverage is not an option. In high-risk populations free of wild poliovirus transmission, sub-optimal immunisation rates increase the risks of poliomyelitis outbreaks caused by both wild polioviruses from the remaining endemic countries and from circulating vaccine-derived polioviruses (cVDPV) with transmission and neurovirulence characteristics of wild polioviruses. Continued high coverage with OPV is necessary to prevent poliomyelitis caused by viruses derived from OPV. Poliovirus will be eradicated only when OPV use is stopped. In this review we discuss the virologic issues that underlie the OPV paradox and describe the programme options under discussion for cessation of OPV immunisation.

THE POLIO VACCINES

In 1949, Enders, Robbins and Weller reported the first successful propagation of poliovirus in human non-nervous system tissues [7]. The relatively simple techniques in cell culture for virus titration, antibody quantification, poliovirus isolation and antigenic characterisation, and large-scale virus production stimulated a number of laboratories to begin work anew on a long-sought polio vaccine. Six years later, massive field trials in the United States, Canada and Finland proved the Salk formalin-inactivated polio vaccine (IPV) to be safe and effective. IPV was licensed for use in the USA in April 1955 [8].

At the same time, other groups were developing live attenuated vaccine candidates derived from virulent or naturally attenuated polioviruses. Methods of attenuation included passages in monkey tissues or monkey, mouse, cotton rats and/or chicken cell substrates. The primary assays for attenuation consisted of monkey neurovirulence tests performed by intracerebral or intraspinal inoculations.

In 1957, a WHO committee reviewed the leading candidate strains and recommended expanded field trials with the attenuated strains developed in the laboratory of Albert Sabin. The selection was based primarily on lower neurovirulence scores. The attenuated ‘Sabin-original’ (SO) strains consist of type 1 LSc 2ab (derived from strain Mahoney through an intermediate strain LSc; Li and Schaefer), type 2 P712 ch 2ab (Fox and Gelfand) and type 3 Leon 12a1b (Kessel and Stimpert) [9,10]. All three Sabin strains are temperature sensitive, producing lower virus yields at supra-optimal temperatures than wild polioviruses [11]. Temperature sensitivity was assumed to contribute to attenuation by reducing virus yields at the early stages of replication in the human intestine.

Because widespread use of IPV precluded OPV field trials in North America, Sabin turned to Professor Mikhail Chumakov and the USSR. By 1960, nearly 100 million people in the USSR and countries in Eastern Europe had received the three monovalent Sabin vaccine strains. There were no reported serious adverse effects. The Sabin vaccine was licensed in the USA in 1961 [9].

When OPV became widely available, IPV had been in use for 6 years, and polio had become a preventable disease. The incidence of paralytic poliomyelitis had been reduced by 90% in the USA and in several other developed countries. Polio might well have been eliminated in many countries by IPV alone, but OPV was seen as more attractive. OPV was the ‘perfect’ vaccine. It was inexpensive, required no needles and syringes, was highly effective, produced mucosal immunity, and had no reported adverse reactions. The characteristic spread of live vaccine viruses to siblings and close contacts was seen as an additional advantage, greatly extending the benefits of immunisation to a much larger population, notwithstanding concerns that this constituted vaccination without consent. Faced with the luxury of two highly effective vaccines for prevention of poliomyelitis, medical providers and the public health community opted for the live vaccine on the grounds that OPV was easy to administer, could be used for mass campaigns, and provided immunity comparable to that of natural infection. By 1964, OPV had become the vaccine adopted throughout most of the world [9]. The Nordic countries and the Netherlands remained the only countries continuing to use IPV [8].
THE HISTORY OF POLIO ERADICATION

The origins of polio eradication begin in the late 1950s. Albert Sabin, Hilary Kaprowski and others concluded that routine immunisation with inactivated polio vaccine (IPV) or oral (live) polio vaccine (OPV), so successful in developed countries, would not interrupt poliovirus transmission where social and environmental conditions favoured continuous wild poliovirus transmission. For such developing countries, Sabin proposed mass OPV immunisation [12,13].

Cuba adopted the strategy and eradicated polio in 1962 [14]. Brazil adopted coordinated national mass OPV immunisation in 1980, after 20 years of using other strategies without success [15]. The dramatic decrease of polio in Brazil, followed by similar successes in Mexico and Costa Rica, led the Pan American Health Organization (PAHO) in 1985 to resolve to eradicate polio in the Americas by 1990 [16]. PAHO, its partners (Rotary International, Canadian Public Health Association, Centers for Disease Control and Prevention (CDC) and USAID), and its member countries established the groundwork for a regional eradication strategy.

Rapid success in the Americas in reducing polio and improving other childhood immunisations led to the 1988 World Health Assembly resolution to eradicate polio worldwide by the year 2000 [17]. Leadership in the WHO Regions was key to advancing global polio eradication and increasing childhood immunisation. Earliest to begin were countries of the Western Pacific Region (WPR), spurred on by the large nationwide epidemics in China in 1989 and 1990, when about 10,000 children were paralysed. China launched its first mass immunisation in December 1993 by immunising 83 million children [18]. Other early events that contributed to advancing the eradication initiative were the 1990 World Summit for Children in New York and the declaration of the Americas as polio-free in 1994 [3].

THE ERADICATION STRATEGY

The global polio eradication initiative is based on strong national and international political will, true public/private partnerships, effective community mobilisation, targeted immunisation strategies, aggressive disease surveillance and timely laboratory science, all dedicated to a common goal. National and international political will was demonstrated by the unanimous support of the World Health Assembly Resolution of 1988. Stories since have been legendary of unprecedented collaboration between nations and groups at political odds, including polio ‘days of tranquility’ between warring factions. National and international support and the dedication of people at all levels have made it possible for polio immunisation to proceed, despite enormous logistical, financial and communication challenges.

Public/private partnerships drive the initiative, spearheaded by the World Health Organization (WHO), CDC, UNICEF and Rotary International. Funding partners include: private foundations, such as the United Nations Foundation, Bill and Melinda Gates Foundation; the World Bank; donor governments, including Australia, Belgium, Canada, Denmark, Finland, Germany, Italy, Japan, The Netherlands, United Kingdom and the United States; and corporate partners, including Aventis Pasteur, De Beers and Wyeth Laboratories. In the year 2000 alone, an estimated 10 million people, mostly volunteers, many from Rotary Clubs, immunised 550 million children in 85 countries.

The basic strategy of polio eradication consists of: (1) high routine immunisation coverage of infants with OPV, (2) supplementary OPV immunisation through National Immunisation Days (NIDs) and Sub-national Immunisation Days (SNIDs), (3) sensitive field and laboratory surveillance for poliovirus, and (4) targeted door-to-door ‘mop-up’ OPV immunisation in areas of focal transmission [1,12].

Immunisation

Very high rates of routine OPV immunisation are required to interrupt poliovirus circulation in areas having high population densities, large birth cohorts, poor hygiene/sanitation and tropical climates [9,19]. High density of susceptible non-immune children, frequent contacts with infected individuals, and the prolonged poliovirus/enterovirus season all favour high efficiency poliovirus transmission. Routine OPV coverage rates even exceeding 90% may not be sufficient to block poliovirus circulation under such conditions [9,19]. Routine immunisation rates are well below 50% in many low-income, developing countries. Supplementary immunisation through high quality NIDs and SNIDs serves to raise population immunity rates.
above the thresholds required to block poliovirus transmission. NIDs are usually conducted through at least two successive rounds spaced about a month apart. Primary NIDs during the low poliovirus transmission season (winter months in temperate countries) synchronously induce high levels of population immunity at a time when the fewest chains of transmission sustain poliovirus endemcity. Continuation of NID or SNID rounds into the spring months in highly endemic areas sustain high levels of population immunity and delay or eliminate the onset of the peak transmission season. Rising population immunity reduces the frequency of productive contacts between infected and susceptible individuals. Wild poliovirus circulation stops when contacts fall below the threshold critical for continued propagation of chains of transmission.

Supplementary immunisation is the mainstay of polio eradication in developing countries because of its biological and logistical advantages. In 2001, approximately 575 million children in 94 countries received over 2 billion doses of OPV through supplementary immunisation [20]. High quality NIDs and SNIDs coupled with high levels of routine immunisation have interrupted indigenous wild polioviruses transmission in less than 3 years, even in areas where environmental conditions favour poliovirus circulation. Immunisation strategies are most effective when driven by poliovirus surveillance. Poliovirus surveillance data serve to focus intensified SNIDs and mop-up campaigns to those reservoir communities where chains of wild poliovirus transmission continue to propagate.

**Surveillance**

Aggressive surveillance is central to successful eradication, with the importance of surveillance increasing at each stage of the initiative. The current key surveillance objectives are: (1) to identify reservoir communities so that they may be targeted for supplementary immunisation activities, (2) determine the virologic links between infections or cases, (3) ensure that wild poliovirus eradication has been achieved, and (4) detect any poliovirus circulation associated with vaccine-derived polioviruses. These objectives are being addressed through the integration of acute flaccid paralysis (AFP) surveillance, standard virologic methods, and detailed molecular and phylogenetic analysis of poliovirus isolates.

**AFP**

All AFP cases in the country should be reported and investigated. AFP is not specific for poliomyelitis or poliovirus. The usual background AFP rate from aetiologies other than wild poliovirus infection in all countries is at least 1 case per 100,000 persons < 15 years of age. Other causes of AFP include Guillain-Barré syndrome, transverse myelitis and transient (rarely permanent) paralyses associated with non-polio enterovirus (NPEV) infections [9,21–23]. Stool specimens for virologic analysis are collected from each patient within 2 weeks of AFP onset.

The sensitivity of AFP surveillance to detect wild poliovirus infections is limited, in that only about 0.1%-0.5% of non-immune children infected with wild poliovirus show signs of AFP [9,19]. In populations with higher levels of immunity, AFP cases may appear in less than 1 of 10,000 wild poliovirus infections [19]. Regardless of these limitations, experience has demonstrated that, over time, all effectively performing AFP surveillance systems are able to detect endemic poliovirus circulation in a population. In situations where effective AFP surveillance is difficult to achieve, supplementary surveillance activities, such as sampling community contacts of AFP cases, stool surveys of healthy children, or environmental sampling, are implemented in suspected high-risk areas to increase sensitivity for detecting wild polioviruses [24–29].

**The laboratory**

The WHO Laboratory Network provides global poliovirus surveillance. The Network consists of 124 National Poliovirus Laboratories, 15 Regional Reference Laboratories, and 7 Specialised Reference Laboratories. In this three-tiered global hierarchical system, over 50,000 stool specimens are tested annually from AFP and poliomyelitis cases occurring in any country of the world. Polioviruses are isolated, differentiated as to wild or vaccine origin, and sequenced when appropriate. Standard methods for poliovirus isolation in cultured cells [30] have been enhanced by the use of recombinant murine cells expressing the poliovirus receptor [31,32]. Polioviruses are distinguished from non-polio enteroviruses (NPEV) either by standard neutralisation typing assays [30] or by polymerase chain reaction (PCR) using
Poliovirus group-specific [33] or serotype-specific [34] primer sets. Intratypic differentiation (ITD) of poliovirus isolates (testing whether they are vaccine-related or wild) is performed throughout the global network using one antigenic and one molecular method. The standard antigenic ITD method uses an ELISA system with preparations of highly specific cross-adsorbed antisera [35]. The molecular ITD methods use genotype-specific nucleic acid probes [36], genotype-specific PCR primers [37] or PCR coupled to analysis of restriction fragment length polymorphism [38].

ITD screens out poliovirus isolates that are closely related (>99% VP1 coding region nucleotide sequence identity) to the Sabin OPV strains, which are unlikely to be of current epidemiological interest. The isolates that remain are either wild polioviruses or atypical VDPVs and require further characterisation. Network laboratories routinely sequence the complete VP1 gene of all such isolates from AFP cases. Analysis of the full ~900-nucleotide VP1 region is required to obtain the necessary phylogenetic resolution to reconstruct individual chains of transmission and to distinguish among local endemic reservoirs. Widening the sequencing window to the complete poliovirus genome increases the ability to discriminate among closely related viruses [39]. Findings are promptly relayed to regional and national immunisation managers for immunisation planning and monitoring eradication progress and surveillance quality.

The characteristic rapid evolution of polioviruses constitutes a ‘molecular clock’ that permits the patterns of poliovirus transmission to be followed with precision. Summarising sequence relationships in the form of phylogenetic trees identifies poliovirus isolates as indigenous or imported wild virus, drifted OPV-derived virus or laboratory contaminants [40].

Factors that combine to determine the overall rates of virus evolution include the replicase error rates, the virus population size and growth rate, the frequency of genetic bottlenecks, the intensity of selective forces, and the existence of mechanisms for genetic exchange [41]. Error rates for poliovirus replicase have been estimated to be $10^{-4}$ to $10^{-5}$ per site per replication [42], very close to the error catastrophe threshold for the poliovirus genome [43]. Nucleotide substitutions (~90% of which in the coding region are to synonymous codons) accumulate at an overall rate of $10^{-2}$ substitutions per site per year, and at ~$3 \times 10^{-2}$ substitutions per year at synonymous sites [44–47]. Evolution rates appear to be similar across serotypes and between wild and vaccine-derived polioviruses. The bottlenecks driving the rapid evolution of polioviruses occur during replication in the human intestine [48] and appear to be largely independent of immune selection. Evolution rates are similar during prolonged replication in immunodeficient patients [44–46] and during widespread circulation [39,47,49,50].

Many poliovirus clinical isolates are recombinants [39,49–52]. Heterotypic recombinants are frequently isolated from vaccinees given trivalent OPV [49,51,53]. All wild polioviruses probably have a recent history of recombination, because frequent genetic exchange with other species C enteroviruses and (vaccine-derived) polioviruses appears to be typical of circulating polioviruses [39,50]. Crossovers appear to be most common in the noncapsid region, less common in the 5'-untranslated region [53] and rare within the capsid region (presumably because of structural constraints) [50,54].

Molecular clock data may be used to estimate the dates of the common ancestors to wild [50,55] and vaccine-derived [39,44,45] poliovirus isolates. The detection of common recombination breakpoints among related viruses provide additional support for phylogenetic relationships inferred from the pattern of nucleotide substitutions [39,50].

The very high mutation rate and recombination frequency of naturally replicating polioviruses provides a powerful tool for epidemiological tracking of circulating wild polioviruses, but it also provides an appreciation for the dynamic character of the poliovirus genome in nature. This genome instability is the source of greatest risk associated with the continued use of OPV and an obstacle for new avenues of control.

**OPV ADVERSE RISKS**

**Vaccine-associated paralytic poliomyelitis (VAPP)**

OPV is remarkably free of adverse effects except for the rare case of VAPP, clinically indistinguishable from naturally occurring poliomyelitis. The current WHO guiding principles for diagnosis of VAPP include paralytic poliomyelitis within 60
days of receipt of OPV or exposure to OPV recipient, stool specimens positive for OPV-related virus, and case evaluation by an expert committee [56]. The first official report of VAPP was issued by the US Surgeon General in 1962 and was associated with Sabin type 3 [57]. Not every one accepted the association, given the absence of reported VAPP during the initial field trials and the subsequent years of use. With additional years of experience, the risk of VAPP has been reasonably well defined for many countries. The estimated risk of VAPP was 1 case per 1.4 million OPV doses administered in England and Wales for the period 1985–1991 [58], 1 case per 2.5 million doses in the US for the period 1980–1989 [59], and 1 case per 1.5–2.2 million doses in Latin America [60]. In general, the first-dose risk is higher than subsequent-dose risk, with children with B-cell immunodeficiency being at greatest risk. More recent data from India report an estimated overall risk of 1 case per 4.1 million OPV doses administered through mass immunisation [61]. However, this risk may not yet be stable in India and the use of additional methods may be important in estimating the burden of VAPP cases [62,63]. The global estimate of VAPP is 250–500 cases annually, although a precise rate worldwide is difficult to determine [2].

In the developed world, Sabin type 3 has been most closely associated with VAPP, followed by type 2, with type 1 a distant third [61]. Conventional wisdom has linked this observation to the degree of attenuation. Five base substitutions appear to be the principal determinants of attenuation in Sabin 1 compared with its neurovirulent parent, Mahoney [64]. In contrast, the attenuation of Sabin 2 is associated with only two base substitutions [65,66], and Sabin 3 differs from its neurovirulent parent by only two major attenuating base substitutions [64,67]. In the developing world, however, studies in India [61] and Latin America [60] have shown type 1 closely followed by type 3 as most commonly associated with VAPP.

Vaccine-derived polioviruses (VDPVs)

Immunologically normal OPV recipients usually excrete viruses for 3 to 4 weeks [68]. The base substitutions that attenuate the vaccine in animal models [69] readily revert during this period of virus replication in human intestines [70,71]. Consequently, the virus excreted by healthy vaccine recipients is less attenuated, when tested in animal models, than the original OPV strains. Studies in vaccinees show that type 3 reverts most rapidly, followed by type 2 then type 1, with recombination between vaccine serotypes a common event [24,69–72]. Short excretion periods and high population immunity levels normally limit revertant virus spread. The majority of isolates from vaccine recipients and their contacts are closely related to the Sabin OPV strains. Such isolates with >99% VP1 nucleotide sequence identities are described as ‘OPV-like’ [73]. Greater divergence of sequence identity is considered indicative of prolonged replication. Isolates with ≤99% VP1 sequence identity to the corresponding Sabin strain are described as ‘vaccine-derived polioviruses’ (VDPVs). The demarcation of 1% VP1 divergence for VDPV isolates implies that replication of vaccine virus had occurred for at least ~1 year. It does not imply that isolates having <1% divergence would lack the capacity for prolonged replication (or person-to-person transmission) under suitable conditions. Two categories of VDPV isolates have been identified: immunodeficient VDPVs (iVDPVs) and circulating VDPVs (cVDPVs).

iVDPVs

The potential for prolonged replication by vaccine strains in patients with B cell immunodeficiencies was recognised many years ago [74]. The first iVDPV isolates to be characterised with modern molecular techniques were from patients with either common variable immunodeficiency or X-linked agammaglobulinemia [44–46,75]. Some iVDPV isolates have ~90% VP1 sequence identity to the parental OPV strain, suggesting persistence of chronic poliovirus infections for 10 years or more. Eighteen chronic iVDPV excretors have been detected worldwide, although this number may be an underestimate in the absence of systematic screening of immunodeficient patients. Nearly all have been found in middle- or high-income industrialised countries [76,77] where OPV coverages are high and where access to quality clinical management can extend the survival times of immunodeficient patients. Because chronic iVDPV infections (and mutations) in different patients are independent events [75], iVDPV isolates trace unique pathways of divergence from the original OPV strains [44,46].
Most of the known chronic poliovirus excretors in developed countries have spontaneously stopped shedding or died of complications from their immunodeficiency [77]. There is no current evidence of spread of iVDPVs from chronically infected persons to the wider community. The chances of new iVDPV infections decrease globally as highly developed countries continue to switch to IPV.

cVDPVs

The first evidence of the public health importance of cVDPVs was the outbreak of 21 confirmed polio cases (including 2 fatal cases) associated with type 1 cVDPV on the Caribbean island of Hispaniola in 2000–2001 [39]. Person-to-person transmission of VDPVs was suspected when the first two outbreak isolates were found to be distinct and 2%–3% divergent in VP1 sequence from the parent Sabin 1 OPV strain, yet related to each other. Phylogenetic analysis of VP1 sequences of all 31 isolates from Haiti and the Dominican Republic was consistent with the Hispaniola outbreak originating from a single OPV dose given in 1998–1999 [39].

A more limited outbreak of polio in the Philippines in 2001 was also found to be associated with type 1 cVDPV [78,79]. A third outbreak was detected in Madagascar in 2002, this time involving type 2 cVDPV [80].

A fourth outbreak is recognised from retrospective evidence that widespread circulation of type 2 cVDPV occurred in Egypt in the 1980s and early 1990s. All 30 of the cVDPV isolates from Egypt were from patients with paralytic poliomyelitis, and had sequence properties consistent with increased neurovirulence [81–83]. Quantitative assays in PVR-Tg21 transgenic mice expressing the human receptor for poliovirus, demonstrated that representative cVDPV isolates had the same order of neurovirulence as the prototype wild type 2 poliovirus strain, MEF-1/EGY42, isolated in 1942 from patients with paralytic polio. This recovery of neurovirulence has been demonstrated in a similar manner for isolates from all the cVDPV outbreaks.

Possibly hundreds of thousands persons were infected with the type 2 cVDPV in Egypt based on the ~10 years duration of cVDPV endemicity, the high nucleotide diversity of the cVDPV isolates, the very low paralytic attack rate for type 2 poliovirus infections [84], and the likelihood that the majority of polio cases during this time in Egypt were not investigated. cVDPV circulation in Egypt apparently ceased after 1993 as the rates of OPV coverage increased.

The most significant difference between the endemic circulation of cVDPV in Egypt and the more recent cVDPV outbreaks in Hispaniola (Dominican Republic and Haiti), the Philippines and Madagascar was the much longer period of cVDPV circulation in the former. Genetic evidence suggests that the type 2 cVDPV in Egypt and the type 1 cVDPV in Haiti spread along multiple independent chains of transmission. Two separate lineages of type 2 cVDPV were found in Madagascar, with the first lineage arising about a year before the second [85]. The type 1 cVDPV outbreak in the Dominican Republic appears to have been more localised, possibly originating from a point source introduction from neighboring Haiti. Type 1 cVDPV spread in the Philippines appeared to be even more limited. Sequence relationships of isolates suggest that transmission occurred along a single, minimally branched chain [79].

A common factor to all cVDPV outbreaks has been low population immunity consistent with low OPV coverage and the apparent absence of circulating indigenous wild poliovirus of the same serotype. Other risk factors appear to be the same as for typical wild virus circulation and include crowding, high birth rates, poor hygiene and sanitation, and tropical climate [19,84]. Partly because of the inherently low paralytic attack rates of poliovirus infections, early virologic events preceding cVDPV outbreaks have not been identified. In addition, prospects for early detection of cVDPV outbreaks are further compromised in high-risk areas when gaps in surveillance accompany gaps in OPV coverage.

All outbreak-associated cVDPV isolates described thus far have been recombinants with other species C enteroviruses [39,79]. This observation, however, does not necessarily indicate that recombination plays an obligatory mechanistic role in the phenotypic reversion of OPV. First, the main determinants of attenuation of all three Sabin strains map to 5′-UTR and capsid region sites [67,69,71,86] and most of the observed recombination sites map to the non-capsid region [39,79,80]. Second, poliovirus recombination with other species C enteroviruses is an outcome of mixed infection, with the frequency of recombination being a function of the enterovirus carriage...
rate and the total number of mixed infections. It is becoming increasingly clear that any poliovirus that is circulating will eventually recombine with another related enterovirus of the same species, and that recombination is an indicator of circulation rather than necessarily a step in the increased ability to transmit from person to person. Therefore, given these correlations and uncertainties, if a vaccine-related isolate has significant divergence in its capsid nucleotide sequences (>1% from the parental OPV strains) and has evidence of recombination with group C non-polio enterovirus, it is a likely cVDPV and the associated case should be investigated further.

How frequently cVDPVs may have occurred in more than 40 years of OPV usage is unknown. The powerful molecular epidemiological tools of nucleotide sequencing [87], referral to the poliovirus molecular clock [40], and rapid determination of global phylogenetic relationships have been a routine component of poliovirus surveillance for less than a decade. It is likely that revertants with increased potential for neurovirulence and transmissibility were regularly selected in communities where OPV was used, but revertant spread was restricted by high population immunity acquired through continued circulation of wild poliovirus and/or immunisation programmes. For example, a retrospective study recently identified a type 1 VDPV virus with an uncertain population circulation history [88]. On the other hand, the retrospective discovery that type 2 cVDPV had circulated widely and caused disease in Egypt for nearly a decade without recognition of the virus origin from OPV [83] demonstrates that other cVDPVs may have been missed prior to their elimination through immunisation.

The potential for cVDPV spread, however, is likely to be greater today than in the past. During the pre-vaccine era in the developing world, almost everyone was immune to polio by natural exposure to circulating wild viruses. Following the global introduction of OPV, prior to the polio eradication initiative, poor quality immunisation programmes in high-risk populations did not stop wild poliovirus outbreaks, most likely suppressing cVDPV by reducing the number of non-immune children. Poor quality immunisation programmes in the same populations free of wild poliovirus now very likely lead to increased risk of cVDPV because wild poliovirus infections no longer contribute to population immunity. The polio eradication initiative is a concerted global application of country-appropriate strategies. Maintaining high quality national immunisation programmes and reducing the risk of cVDPV should be the goal for all nations.

POST CERTIFICATION GLOBAL IMMUNISATION POLICY ISSUES

In its simplest iteration, the early model for polio eradication was smallpox. As with smallpox eradication, wild poliovirus transmission would be interrupted, the virus would be held under containment conditions in the laboratory, and polio immunisation would no longer be necessary. The world would be free of poliomyelitis whether caused by wild virus or OPV and thereafter would save $US1.5 billion annually in immunisation costs [1].

However, unlike live polio vaccine, live smallpox vaccine (vaccinia) is many orders of magnitude more stable genetically, vaccination is not via the natural route of infection, and vaccinia virus is distinct from the smallpox virus (variola). Person-to-person spread of vaccinia to unimmunised persons is through close contact and is usually limited to secondary, rarely tertiary, transmission. Disseminated vaccinia is a serious disease for immunodeficient persons, but there is no vaccine carrier state and silent infections are unknown. Vaccination decline or discontinuation in smallpox-free countries was not a threat to eradication. The primary post eradication incentives for discontinuing vaccination were the cost and high risk of adverse effects in the absence of disease. Countries adopted a variety of interim post eradication vaccination policies before eventually stopping, including continued vaccination, vaccination upon-request, selective vaccination of the military, vaccination of travellers and programme neglect. None of these policies posed any vaccine reversion threats to individuals or to the eventual successful eradication. The smallpox experience provides little guidance for developing post eradication polio immunisation strategies [89].

How to stop OPV immunisation was a personal concern of the late Joseph Melnick, the polio vaccine pioneer who served on several occasions as a consultant to the WHO eradication initiative during the early 1990s. Because there was no firm evidence of Sabin OPV-associated polio outbreaks at the time, his concerns did not generate an
immediate sense of urgency. At its first meeting in April 1996, the WHO Technical Consultative Group (TCG) on the Global Eradication of Poliomyelitis initiated formal discussions on planning interim post-eradication strategies for stopping polio immunisation [90]. At its second meeting in 1997, the TCG reviewed a recent report of poliovirus of vaccine origin replicating in an immunodeficient patient for at least 9 years [44]. The TCG recommended that additional studies be undertaken to assure that vaccine derived viruses would not continue to circulate and cause outbreaks of disease after immunisation had been stopped.

In early 1998, WHO convened a meeting on the scientific basis for stopping polio immunisation [91]. Based on those findings, TCG later that year recommended that OPV immunisation should stop and IPV immunisation may stop when there is sufficient assurance that (1) wild polioviruses have been eradicated, (2) vaccine-derived polioviruses (VDPV) will circulate only for a limited period of time, and (3) the remaining stocks of wild polioviruses and infectious materials have been contained in the laboratory. TCG further recommended key research questions to guide decisions on when and how to stop immunisation after polio eradication. Although TCG was aware of preliminary evidence suggesting that polioviruses derived from Sabin type 2 may have circulated and caused disease in Egypt in the recent past [83], data from the current eradication period were lacking. Proof that cVDPV was more than a theory or an isolated occurrence came 2 years later with the 2000–2001 outbreak on the island of Hispaniola [39].

The emergence of cVDPV is now generally accepted as a risk in polio-free developing tropical countries with less than optimal OPV coverage. By analogy, cVDPV is also a risk in such countries after polio immunisation stops. Because the duration and magnitude of the risk remains uncertain, much more needs to be learned about cVDPV, its frequency and the conditions that favour its emergence. Such information is also important in planning for the near future when wild poliovirus transmission is interrupted. It is fairly certain that the current intense national immunisation efforts will be difficult to sustain in many places. High- and many middle-income countries customarily decide for themselves the immunisation strategies that best suit their needs. Most such countries will have completed the switch from OPV to IPV at the time wild poliovirus transmission is interrupted worldwide and are anticipated to continue IPV immunisation for many years afterwards. For countries with high sanitation standards, the IPV strategy brings no significant adverse risks, protects against poliomyelitis of any origin, reduces the consequences of inadvertent transmission from the laboratory, and renders the potential for bioterrorism a moot issue. The real issues are the post certification immunisation strategies for the remaining middle-income and all low-income countries that will be using OPV at the time of certification. The children of these countries account for over 90% of the world’s immunisations [2].

All countries of the world using OPV during the immediate post-certification period must eventually reach a consensus on whether to continue to do so or stop, and if the latter, how. National post-certification immunisation policies must ensure maximum benefits and minimal risks for all populations of the world. An independent national timetable on OPV usage is not an option. Any country that stops all polio immunisations while a neighbouring country uses OPV is likely to be at high risk for cVDPV. How, when, or if OPV immunisation can be stopped have been subjects of considerable debates [76,77,92–95]. In order to develop a coherent global strategy for the maintenance of a polio-free world after wild poliovirus eradication, some very basic policy issues need to be addressed for middle- and low-income countries. Most of the many different scenarios and options that have been widely discussed include the following issues: (1) duration of OPV use, (2) extent of OPV replacement with IPV, (3) how to stop use of OPV, and (4) develop safe and effective new vaccines to replace OPV.

**Issue 1: Continued use of OPV**

High OPV coverage, with possible mass campaigns every few years, reduces the risk of wild poliovirus reemergence from any source in many countries, but poliomyelitis in the form of VAPP will continue. The global estimate of 250–500 VAPP cases annually is viewed by some as a small risk [93], which indeed it is compared with the greater threat of naturally occurring polio. However small the VAPP risk may be viewed in the immediate aftermath of polio eradication, perceptions of parents and Ministries of Health are likely to change once
naturally occurring polio becomes a fading memory. The number of VAPP cases in 2001 already may have exceeded the number of poliomyelitis cases caused by wild virus that year. As the threat of wild poliovirus importation decreased for the United States, an average of eight VAPP cases each year became increasingly difficult to defend. The United States switched from OPV to IPV in 2000 [96]. Germany had switched 2 years earlier for the same reason. It is unclear whether countries will continue to accept the risks of VAPP (estimated to be 3–15 VAPP cases annually in Brazil, 19–76 in China, or 25–100 in India [2]) as the threat of naturally occurring polio recedes. Maintaining the necessary high OPV acceptance rates is likely to be a growing challenge.

The four cVDPV outbreaks that have occurred to date illustrate the risks of low OPV immunisation rates in populations and polio-free developing countries in tropical areas. So far, the numbers of cVDPV outbreaks have been few and transmission has been interrupted using the same immunisation strategy as for wild polioviruses, that is, restoring OPV coverage to appropriate rates. However, the dynamics of cVDPV emergence are unknown in situations of decreased vaccine coverage in large populations, such as northern India and northern Nigeria, where wild poliovirus transmission has been historically intense and eradication has faced its greatest challenge. Reducing risks of cVDPV emergence requires maintenance of strong poliovirus surveillance and high quality immunisation programmes for an indefinite period. This will be a major challenge in areas currently experiencing difficulties in trying to eradicate the indigenous wild poliovirus. Prolonged efforts to continue OPV use at the high levels needed to avoid outbreaks of cVDPV in the developing world will require renewed commitment of international oversight and support to offset the financial and opportunity costs of a sustained long-term programme. Low OPV coverage in developing countries with the greatest risk of cVDPV may well be worse than no coverage at all. The most important factors to be addressed in discussions of continued use of OPV are the burden of VAPP in a polio-free world and the risk, management and disease burden associated with any future outbreaks of cVDPV. The former is largely predictable and measurable, the latter still has many uncertainties other than that they will occur.

**Issue 2: Extent of OPV replacement with IPV**

Countries will continue to shift from OPV to IPV as immunisation programmes improve, multivalent vaccines become more widely available and affordable, and vaccine delivery systems mature. This approach has many attractive features. In principle, increased use of IPV addresses many of the concerns raised as part of the OPV cessation issues, including reduction of VAPP cases, protection of the population during the transition periods to stopping OPV use, and eliminating polio as a bioterrorism concern. Low-income countries would join the high- and middle-income countries in replacing OPV with IPV for at least an interim period of time. The time required to build-up national routine IPV services to replace OPV will be long in many places, but delivery of routine immunisation services remains a top WHO priority. Maintaining high OPV coverage for this period would be similar to the requirements for Policy Issue 1 for the interim period. Further, a major additional benefit of switching to IPV is the simultaneous strengthening of national capacity to immunise children against all priority vaccine preventable diseases.

However, such policy decisions are hampered greatly by the absence of data on IPV effectiveness in preventing or interrupting poliovirus circulation in high-risk populations in low-income countries. Cost is another major factor. An estimated 3- to 4-fold increase in international funding would be needed to meet the higher vaccine cost of IPV over OPV [2]. Substantial additional funding would be required to build the local public health capacity for sustained high routine coverage with vaccines administered by needle and syringe. Other factors to be considered are competing health priorities and opportunity costs in the developing world and the need to vastly increase global IPV production capacity.

**Issue 3: How to stop use of OPV**

Because of concerns about exposure of unimmunised populations to excreted vaccine virus from within a country or from any neighbouring country that continues to use OPV, an ideal scenario envisions a synchronised global OPV discontinuation strategy at a time of highest global OPV use, which possibly includes a ‘global immunisation day’. Implementation of such a strategy requires
unprecedented logistical coordination and collaboration among countries, regions, and the entire world. For those countries electing not to use IPV, the synchronous cessation could potentially reveal deficiencies in estimating anticipated risks, which include iVDPV, cVDPV and reemergence of wild poliovirus from unexpected sources. It remains to be determined whether adequate global containment levels can be achieved to assure such countries of minimal risks from inadvertent reintroduction of wild poliovirus into the community from a laboratory or a vaccine producer [97–100].

On the other hand, this scenario offers the greatest rewards for low- and some middle-income countries, including reduction in immunisation related costs, decreased dependence on international support, and opportunities for redirection of the health infrastructure to address other health priorities. Further, global immunisation days are not inconceivable. Synchronisation of NIDs across countries and regions is a well-established strategy for polio eradication [2,6]. Representatives from some low-income countries have made known their desire to stop immunisation when it is safe to do so [101]. They were willing to accept the risks of OPV cessation if there was strong assurance that other countries would also stop OPV and that effective global surveillance would continue. Of primary importance was the guarantee of full access to a global vaccine stockpile and assurance of international support in the event of reemerging poliovirus.

Decisions about if, when, and how to stop OPV use are dependent on choices that are made about the first two issues above. There are many combinations and interactions among these decisions that require further careful consideration and projection of resource requirements and development of contingency plans. For example, if widespread IPV use is deemed to be core to any strategy, then the urgency of coordinating OPV cessation becomes less important, but issues related to maintenance of OPV immunisation levels and response to outbreaks during the transition period become vital. Because cVDPV risk will be highest immediately after OPV use stops and for several years following, carefully developed immunisation contingency plans and adequate emergency stockpiles of monovalent or trivalent OPV (and possibly trivalent IPV) are crucial. It is important that in conjunction with addressing all these policy issues, post OPV strategies must be developed to respond to cVDPV outbreaks, short of reinitiating global immunisation.

**Issue 4: Develop a safe and effective new vaccine to replace OPV**

Some view a new live polio vaccine as the only option for discontinuing OPV. In view of the enormous advances in the understanding of poliovirus biology [102] since the development of OPV in the 1950s, it seems very likely that vaccine strains with more favourable properties could be developed in the laboratory. However, even if such candidate strains were to be developed, satisfactory demonstration of their safety, genetic stability, non-transmissibility, and efficacy upon widespread use would face daunting obstacles. Clinical vaccine efficacy can be assumed based on surrogate markers for immunity, but vaccine safety cannot be assumed from animal neurovirulence models alone. Field trials of adequate size to detect a reduction in the current VAPP risk of one case (or less) per million are likely to be difficult to mount. Also at question is the source of research and development funds for a vaccine that might be used only for an interim period or for emergency vaccine stockpiles.

**CONCLUSIONS**

The Global Commission for the Certification of the Eradication of Poliomyelitis (GCC), convened by WHO, will declare the world polio-free when all regions have documented the absence of wild poliovirus transmission for at least three consecutive years and when laboratories with wild poliovirus materials have implemented appropriate containment measures [103]. With that declaration will come serious questions regarding the role of OPV in the post-certification era. The OPV paradox provides a major incentive for eventually stopping or replacing OPV, but it also introduces complexity into the process of identifying safe and scientifically sound strategies for doing so. The developing world looks to WHO for the development of a unified global post certification immunisation policy based on the best available science, the resource demands of other health priorities, and the needs of its key stakeholders [101]. A WHO coordinated research agenda addresses many of the basic technical questions and issues. Data from such studies together with investigations initiated through the worldwide polio...
surveillance system will provide valuable insight into VDPV risks and opportunities for prevention. Formulation of an informed post certification immunisation policy will require careful evaluation of many factors related to polio epidemiology, surveillance capability, vaccine availability, laboratory containment, and the risks posed by the very tool responsible for successful interruption of wild poliovirus transmission. Ultimately, a final decision on the appropriate global post certification immunisation policy will be made by the member states themselves through the World Health Assembly.

ACKNOWLEDGEMENT
The authors gratefully acknowledge the assistance of Ms Kim Koporc in the preparation of this manuscript.

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