Circulating vaccine-derived polioviruses: current state of knowledge.
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Circulating vaccine-derived polioviruses: current state of knowledge

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Abstract Within the past 4 years, poliomyelitis outbreaks associated with circulating vaccine-derived polioviruses (cVDPVs) have occurred in Hispaniola (2000–01), the Philippines (2001), and Madagascar (2001–02). Retrospective studies have also detected the circulation of endemic cVDPV in Egypt (1988–93) and the likely localized spread of OPV-derived virus in Belarus (1965–66). Gaps in OPV coverage and the previous eradication of the corresponding serotype of indigenous wild poliovirus were the critical risk factors for all cVDPV outbreaks. The cVDPV outbreaks were stopped by mass immunization campaigns using OPV. To increase sensitivity for detecting vaccine-derived polioviruses (VDPVs), in 2001 the Global Polio Laboratory Network implemented additional testing requirements for all poliovirus isolates under investigation. This approach quickly led to the recognition of the Philippines and Madagascar cVDPV outbreaks, but of no other current outbreaks. The potential risk of cVDPV emergence has increased dramatically in recent years as wild poliovirus circulation has ceased in most of the world. The risk appears highest for the type 2 OPV strain because of its greater tendency to spread to contacts. The emergence of cVDPVs underscores the critical importance of eliminating the last pockets of wild poliovirus circulation, maintaining universally high levels of polio vaccine coverage, stopping OPV use as soon as it is safely possible to do so, and continuing sensitive poliovirus surveillance into the foreseeable future. Particular attention must be given to areas where the risks for wild poliovirus circulation have been highest, and where the highest rates of polio vaccine coverage must be maintained to suppress cVDPV emergence.

Keywords Poliovirus/genetics/isolation and purification; Poliovirus vaccine, Oral/adverse effects; Poliomyelitis/etiopathology/chemically induced/prevention and control; Immunization programs; Disease outbreaks/Review literature (source: MeSH, NLM).

Mots clés Poliovirus humain/génétique /croissance et développement; Vaccin antipoliomyélite Sabin/effets indésirables; Poliomyélite antérieure aiguë/étiopathologie/induite chimiquement/prévention et contrôle; Programmes de vaccination; Revue de la littérature (source: MeSH, INSERM).

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Introduction

The oral poliovirus vaccine (OPV) of Albert Sabin is nearly ideal for use in polio eradication (1–3). OPV is easily administered by mouth, facilitating its widespread use; it induces intestinal immunity, making recent OPV recipients resistant to infection by wild polioviruses and effectively blocking wild poliovirus transmission when used in mass campaigns; and it provides long-term protection against polio through durable humoral immunity: OPV virus can spread to and immunize unvaccinated contacts of vaccine recipients, increasing the impact of OPV beyond those actually immunized. Through effective use of this excellent vaccine, the WHO Global Polio Eradication Initiative has nearly achieved its goal of eradicating wild polioviruses (4, 5).

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Despite its many advantages, OPV use carries certain liabilities (3, 6). Genetic stability was a prime concern during OPV development, and a delicate balance was struck between attenuation of neurovirulence, immunogenicity in humans, and genetic stability (7, 8). The first evidence of the clinical consequences of the genetic lability of OPV was the appearance of cases of vaccine-associated paralytic poliomyelitis (VAPP) soon after licensure and widespread use of OPV (1). The much higher incidence of polio from wild poliovirus infections at the time, however, mitigated concern over the rare occurrence of VAPP (1), and it has only been in recent years that VAPP has become an increasingly significant proportion of the global polio burden (1). Occasionally, immunodeficient persons exposed to OPV become chronically infected (9–11), excreting derivatives of the OPV strains for many months or years (1, 12–14). Chronic OPV excretors, however, seem to be very rare, and have so far been found only in upper- and middle-income countries where appropriate clinical management of immunodeficiency is available (15).

In retrospect, it is remarkable that OPV has attained such an outstanding record of safety and efficacy over the four decades of worldwide use (3, 6). It is now known that most RNA viruses have highly mutable genomes that are potentially capable of very rapid evolution, many orders of magnitude faster than the genomes of DNA viruses or cellular organisms (16, 17), and polioviruses are among the most rapidly evolving of all RNA viruses (1, 12, 14, 18, 19). Moreover, the attenuating mutations of the OPV strains are strongly selected against when the vaccine replicates in the intestinal tract of OPV recipients (20–22).

To counter the daunting challenges of delivering a live, attenuated RNA virus vaccine via its natural route of infection, immunization strategies were developed to minimize adverse events (1, 23). In developed countries, OPV was first delivered in mass campaigns to achieve high rates of coverage, and this was followed by a strategy of comprehensive routine immunization. Similar strategies were adopted in developing countries, with mass OPV campaigns often playing a more prominent role than routine immunization. In most instances, OPV was delivered in the context of pre-existing high population immunity to poliovirus, because of recent exposure to circulating wild polioviruses or, as with developed countries in the early 1960s, from the combination of immunity acquired from natural infection and immunity acquired from several years of immunization with the inactivated poliovirus vaccine (IPV). These strategies probably minimized the epidemiological consequences of the frequent phenotypic reversion of the OPV strains.

Recent years have seen a rapidly changing risk profile from OPV exposure. In most of the world, population immunity to poliovirus is maintained only by immunization. Where polio vaccine coverage rates decline but OPV use continues, conditions may arise that increase the likelihood of person-to-person spread of vaccine-derived polioviruses (VDPVs). The duration and extent of spread are dependent on the magnitude of the immunity gap and the intensity of other risk factors favouring poliovirus circulation. This long-discussed hypothetical concern (6) has been realized by the recent occurrence of outbreaks of paralytic polio associated with circulating VDPVs (cVDPVs). Although several important themes are common to all of the outbreaks, each outbreak has taught its own important lesson about the parameters for the safe administration of OPV in a world free of circulating wild polioviruses.

**Recent cVDPV outbreaks**

**Hispaniola, 2000–01**

The immediate public health importance of cVDPVs was underscored by the occurrence of a polio outbreak associated with type 1 cVDPVs on the Caribbean island of Hispaniola in 2000–01 (Fig. 1) (24). The first indication of an outbreak was the isolation of poliovirus type 1 in the summer of 2000 from two patients with acute flaccid paralysis (AFP) in the Dominican Republic and Haiti. Because the indigenous wild poliovirus type 1 had been eradicated by the late 1980s, imported wild poliovirus was suspected. However, molecular characterization of the two case isolates, comparing sequences encoding the major capsid surface protein VP1 (>900 nucleotides), showed that they were unrelated to wild type 1 polioviruses previously endemic to Hispaniola or to any wild poliovirus currently found in other parts of the world (24). Instead, the Haitian and Dominican isolates were closely related (~97% VP1 sequence identity) to the Sabin type 1 OPV strain, and to each other (98.0% VP1 sequence identity). The degree of VP1 sequence similarity to the OPV strain was substantially lower than is normally observed (>99.5%) in isolates from cases of AFP or VAPP.

Active search for AFP cases detected a total of 21 confirmed polio cases (13 in the Dominican Republic in 2000, and eight in Haiti in 2000–01). It was possible to reconstruct the patterns of cVDPV transmission from the sequence properties of the isolates because of the rapid, stepwise evolution of poliovirus genomes (about 1% nucleotide substitutions per site per year). Relationships among VP1 sequences of the 31 type 1 VDPV outbreak isolates suggested that they were derived from an OPV dose given in late 1998 or early 1999 (24). The close sequence relationships among isolates from the Dominican Republic indicated that the outbreak there began with the importation of cVDPV from Haiti in the spring of 2000. By contrast, the Haitian isolates were more diverse, and appeared to have diverged into at least four separate lineages in 1999.

Circulation of VDPV occurred in an environment of low OPV coverage throughout Haiti (<30% nationwide, and as low as 7% in some areas) and in the affected communities of the Dominican Republic (20–30%). All but one of the patients were either unvaccinated children or incompletely vaccinated children. No mass OPV immunization campaigns in the form of national immunization days (NIDs) had been conducted in either country within the past 5 years. The outbreak stopped in both countries after mass administration of OPV in NIDs (24).

**Philippines, 2001**

The Hispaniola outbreak showed conclusively that low OPV coverage carried a risk of cVDPV emergence and prompted a reassessment by WHO of the strategies both for polio immunization and poliovirus surveillance. In 2001, the Global Polio Laboratory Network implemented additional testing requirements for all polioviruses under investigation, in order to increase sensitivity for detecting VDPVs (25). Soon thereafter, cVDPV was detected in the Philippines (26, 27). Specimens from three cases of AFP, reported during March to July 2001, tested positive for type 1 cVDPV. The isolates were closely related to the Sabin 1 OPV strain (~97% VP1 sequence identity), but even more so to each other (>99% VP1 sequence identity). The VP1 sequence relationships among the isolates suggested that the VDPV circulation began with an OPV dose given in 1998. Although the three cases occurred in separate communities (two
in Luzon, one in Mindanao), the close sequence similarities among the cVDPV isolates suggested that the virus had spread via a single, minimally branched chain, in contrast to the pattern of multichain transmission found in Hispaniola.

Wild poliovirus was last reported in the Philippines in 1993 (26), and no national immunization days (NIDs) had been conducted since 1997, although subnational campaigns had been conducted in 1998 and 1999 outside the affected areas. Nationwide routine OPV coverage had been approximately 80% during much of the 1990s; however, shortages of OPV in the 2 years before the appearance of cases probably led to gaps in coverage, particularly in slum areas (26). An important new lesson from the Philippines cases was that transient immunity gaps in very densely populated areas with poor hygiene/sanitation and tropical climates may permit cVDPV emergence.

Madagascar, 2001–02

Five cases of AFP associated with type 2 cVDPV were reported from two different communities in the southern province of Madagascar (28). The first case (onset in October 2001) was from the urban district of Toliara, whereas the remaining four cases (onsets in March to April 2002) were clustered in a rural village ~400 km from Toliara. None of the patients had been fully immunized against polio. The type 2 polioviruses isolated from patients and contacts from the two areas represented two geographically separate, genetically distinct, independent cVDPV lineages (28). The urban isolates differed from the Sabin 2 OPV strain at ~1% of VP1 nucleotides, whereas the rural isolates differed from Sabin 2 at ~2.5% of VP1 nucleotides.

OPV coverage was <50% nationwide in Madagascar, and wild poliovirus was last reported in 1997 (28). The detection of two distinct VDPV lineages in Madagascar underscored the point that cVDPVs can emerge independently in localities where gaps in polio immunity arise.

Evidence of past circulation of VDPVs

Egypt, 1983–93

From 1988 to 1993, 30 cases of polio associated with type 2 cVDPV were found in seven governorates of Egypt. The cases occurred at a time of low OPV coverage and after the apparent eradication of the type 2 wild poliovirus indigenous to Egypt (last known isolate, 1979) (29). The type 2 isolates were initially thought to be wild polioviruses, but recent molecular studies have shown them to be cVDPVs (29). The sequence properties of the isolates suggested that VDPV circulation in Egypt started with an OPV dose given in 1983, and that progeny from the initiating infection circulated for approximately a decade within Egypt. Like wild polioviruses, the type 2 cVDPVs established independent reservoirs of endemicity within the country. VDPV circulation ceased with rising OPV coverage, and VDPVs were last detected in Egypt in 1993.

The important lesson learned from the situation in Egypt was that cVDPVs can circulate indefinitely in countries with persistently low rates of polio vaccine coverage.
Poland, 1968
In 1968, a large polio outbreak in Poland immediately followed a field trial of an experimental type 3 OPV strain, USOL-D-bac (30). The environment in which the outbreak occurred was one of low population immunity to poliovirus type 3, because the Sabin type 3 component was never included in OPV and the replacement type 3 IPV failed to induce high levels of immunity (30). Although the epidemiological findings implicated a breach in quarantine of USOL-D-bac recipients during the field trial (30), conclusive evidence for the vaccine origin of the outbreak came from retrospective oligonucleotide fingerprinting (31) and nucleotide sequencing (32, 33) studies of outbreak isolates.

The outbreak in Poland is of current importance because it shows that vaccine virus progeny can circulate widely in developed countries with temperate climates and moderate population densities if immunity to at least one poliovirus serotype is low. Although the implicated vaccine virus was genetically distinct from Sabin 3 (32, 33), the outbreak in Poland is the only one known to be associated with any type 3 vaccine strain.

Other possible examples of VDPV circulation
A recent retrospective study found evidence for the circulation of type 2 vaccine-related virus in Belarus following local cessation of OPV use from 1963 to 1966 (34). In the months after the limited reintroduction of OPV in 1965, type 2 vaccine-related poliovirus was isolated from nine healthy unvaccinated children. The sequence properties of three of the four available isolates showed evidence of prolonged vaccine virus replication (6–9 months) (34). In Romania in 1980, a type 1 VDPV was isolated from a patient with “community acquired” VAPP (35). The patient was immunocompetent, but lived in a community with low rates of OPV coverage and poor hygiene/sanitation. In the Russian Federation in 1999, an immunocompetent 7-month-old orphanage child contracted VAPP associated with a type 1 VDPV (36). These findings reinforce the point that uniformly high rates of polio vaccine coverage are necessary to prevent the emergence of cVDPVs in industrialized countries that continue to use OPV.

Other current (25, 37) and retrospective (unpublished data) studies have found single VDPV isolates (all type 2) with genetic properties similar to those of the well-documented cVDPV outbreak isolates in other tropical developing countries.

Risk factors for cVDPV emergence and spread
The most significant risk factor for cVDPV outbreaks, like wild poliovirus outbreaks, is insufficient population immunity. The risk is also a function of other factors favouring poliovirus circulation: the number and density of non-immune susceptible persons, the birth rate, deficiencies in hygiene/sanitation, and the seasonal duration of tropical conditions (38). The previous elimination of indigenous wild poliovirus circulation increases the risk because non-immune susceptibles will accumulate rapidly in the absence of high rates of polio vaccine coverage and naturally acquired immunity. The cVDPV outbreaks are similar to outbreaks from imported wild poliovirus, except that the outbreak agents emerge endogenously. Virus excreted by OPV recipients may frequently recover the capacity for spread beyond immediate contacts, but spread is normally limited by population immunity. Outbreaks occur when the density of non-immune susceptibles rises to the point where the chains of cVDPV transmission can propagate (6, 38). The threshold point (per cent susceptible) for sustained person-to-person transmission of cVDPVs is probably lowest for type 2, and perhaps highest for type 3. The size of a cVDPV outbreak is a function of the size of the non-immune population and the potential for transport of outbreak virus to susceptible communities elsewhere. Countries that were (or are) major reservoirs for wild poliovirus circulation, and where the potential for person-to-person poliovirus transmission is greatest, are at particularly high risk for cVDPV emergence, and maintenance of high rates of polio vaccine coverage in these settings is essential.

Properties of known cVDPV isolates
The most important biological properties of cVDPV isolates are their increased capacity to cause paralytic disease in people and their capacity for sustained person-to-person transmission. When tested experimentally, cVDPV isolates have been found to be as neurovirological as wild polioviruses for transgenic mice expressing the human receptor for poliovirus (24, 27, 29). Like wild polioviruses, cVDPV isolates have been shown to replicate to high titres in cell culture at supraoptimal temperatures (24, 29). All cVDPV isolates characterized so far have antigenic properties that more closely resemble wild polioviruses than the original Sabin strains (24, 29). The antigenic differences from the Sabin strains are less pronounced for type 2 than for type 1 cVDPVs, possibly because selection against the Sabin 2 antigenic sites is less intense (39). Although these experimentally determined properties may correlate with clinically relevant properties, they are not unique to cVDPV isolates, as less highly evolved (OPV-like) vaccine-related polioviruses isolated from healthy individuals and VAPP patients may share some or all of these traits (20, 22, 39).

The extensive sequence divergence from the respective OPV strain is a distinguishing feature of VDPVs (12–14, 27–29). A vaccine-related isolate is considered a VDPV if it has diverged by $\geq 1\%$ of VP1 nucleotides from the reference OPV strain (25, 37). The demarcation of 1% VP1 divergence implies that replication of vaccine virus had occurred for ~1 year. It does not imply that isolates having <1% divergence would lack the capacity for person-to-person transmission in poorly immunized populations, as it is likely that the critical attenuating mutations of the Sabin strains generally revert well before nucleotide substitutions accumulate to the level of 1% (20–22). By this definition, nearly all minimally diverged “OPV-like” isolates would be excluded, and VDPVs that had replicated for at least 1 year would be included (25, 37).

All cVDPVs, but none of the iVDPVs (VDPVs isolated from immunodeficient chronic poliovirus excretors) described thus far appear to be recombinants with enteroviruses closely related to polioviruses (24, 27–29). The possible role of...
recombination in the phenotypic reversion of OPV is unclear. Recombination with other enteroviruses appears to be an indicator of circulation, as the cVDPVs in Hispaniola and Egypt had participated in successive rounds of recombination during the outbreaks (24, 29), as frequently occurs during the circulation of wild polioviruses (40, 41).

**Laboratory surveillance for VDPVs**

The occurrence of cVDPV cases also highlights the need for countries to maintain sensitive poliovirus surveillance into the foreseeable future. Laboratory-based surveillance for VDPVs began in 1997 in the Americas, with the sequencing of the VP1 genes of poliovirus isolates from AFP cases in the region (42). Unfortunately, this approach did not provide an early warning of the Hispaniola cVDPV outbreak because no polioviruses were isolated in the 5 years preceding the outbreak (24). Following that outbreak, intensive screening of recent poliovirus isolates for cVDPVs was initiated by laboratories within the entire WHO Global Polio Laboratory Network (25, 37). Since 2001, all vaccine-related poliovirus isolates from AFP cases have been screened for evidence of prolonged replication or circulation (25, 37).

Poliovirus isolates are identified according to their genetic properties by probe hybridization (43), diagnostic polymerase chain reaction (PCR) assays (44, 45), or PCR-restriction fragment polymorphism analysis (46). All isolates are also tested for antigenic change by using specific cross-absorbed sera in an enzyme-linked immunosorbent assay (ELISA) format (47) or panels of monoclonal antibodies in neutralization tests (47). Alternatively, isolates have been screened for recombinant sequences using PCR primers targeting non-capsid region sequences characteristic for each Sabin strain (D.R. Kilpatrick, unpublished observations). Any isolate having “non-vaccine-like”, “double-reactive”, or “non-reactive” antigenic properties or having a recombinant genome is further characterized by VP1 sequencing (25, 37). WHO is notified of any current isolates having >1% VP1 divergence, and both the case and the associated isolate are investigated further.

To date, over 7300 vaccine-related isolates from 1999–2003 AFP cases from all WHO regions have been screened for VDPVs (25, 37). The large majority (>95%) of isolates had “vaccine-like” antigenic properties and were usually not investigated further. Of the remainder, 44 were cVDPVs (all from the three recent outbreaks), 3 were iVDPVs isolated from immunodeficient chronic poliovirus excretors, 11 were uncategorized VDPVs, and 125 were antigenic variants of OPV-like virus (25, 37). A subset (1980) of the vaccine-related isolates was screened for the presence of recombinant non-capsid sequences of non-Sabin origin. A small proportion (<1%) of the isolates had non-Sabin sequences, and only one of these was an uncategorized VDPV. None of the other VDPVs were associated with more than one patient.

**The potentially higher risk of type 2 cVDPV**

Several observations indicate that the risk for emergence cVDPVs may be highest for poliovirus type 2 (6). The type 2 OPV strain appears to spread most readily to unimmunized people, as shown by its more frequent association with contact cases of VAPP (1) and by the much higher seroprevalence to poliovirus type 2 (relative to types 1 and 3) found among unvaccinated individuals in the United States and Europe (1, 6). Moreover, VP1 sequence comparisons (described above) found that vaccine-related isolates with the more divergent genomes (>0.5%) were most frequently type 2 (42). Limited, localized spread of type 2 vaccine-related virus may occur in some areas. Because paralytic attack rates for type 2 poliovirus infections are low (38), circulation of type 2 VDPVs is the most difficult to detect by AFP surveillance. Consequently, early detection of any future type 2 cVDPV outbreaks will require maintenance, and possible augmentation in some countries, of the current very high global standard for AFP and poliovirus surveillance (4, 25, 37, 48).

**A changing risk profile for cVDPVs**

Currently, the major risk for polio worldwide is from wild poliovirus infection (4). Most of this risk is localized to a few reservoir areas in Africa and Asia. In the rest of the world, the chief risk derives from continued use of OPV. It has been estimated that the global VAPP burden is 250–500 cases annually (1, 49), and most VAPP cases occur outside of the remaining reservoir areas. About half of all VAPP cases are associated with the type 2 OPV strain (1), whose wild counterparts were eradicated in 1999 (4, 25, 37, 48). It is likely that all polio cases will soon be associated with OPV use, causing the risk-benefit ratio for continued OPV use to shift dramatically.

Considerations for transition away from OPV use have focused largely on VAPP, for which the risk is quantifiable and the cases dispersed (49). More difficult to assess is the risk of outbreaks from cVDPVs. Here the potential risk may be very high. Fortunately, the recent cVDPV outbreaks were restricted to islands. However, if a cVDPV outbreak were to occur in a populous mainland country, the case burden could far outstrip that from VAPP, and could be of the scale of the past wild poliovirus outbreaks. Experience has shown that it becomes increasingly difficult to maintain high levels of polio vaccine coverage in countries and regions that have been certified as polio free. Thus, it is unlikely that the high rates of OPV coverage necessary to suppress cVDPV emergence in areas at greatest risk can be sustained much past global certification. Because OPV is the vaccine of choice for eradicating wild poliovirus, especially in tropical developing countries, its continued use in those settings is recommended until wild poliovirus circulation ceases (48, 49). Thereafter, all OPV use should be discontinued as soon as is safely possible (50).

**Implications of cVDPVs to the “endgame strategy” for global polio eradication**

Currently, the most urgent priority is to eliminate the remaining reservoirs of wild poliovirus endemcity (4, 5, 48, 50). In the remaining polio-endemic countries, the mass immunization campaigns currently under way to eliminate the last pockets of poliovirus circulation will also effectively prevent dissemination of cVDPVs. In polio-free areas with inadequate rates of routine OPV coverage, it is crucial to close the immunity gap. To achieve this, WHO has recommended maintenance or reinstatement of mass immunization campaigns in such areas (48). The appropriate frequency of the mass campaigns follows from the rate of accumulation of non-immune susceptibles in the highest risk populations of each area (6).

Recognition of the risks posed by cVDPVs and other VDPVs has prompted a reassessment of global strategies for maintaining polio-free status after wild poliovirus circulation has ceased (2, 3, 48, 50). The number of viable options for the “endgame strategy” using the existing polio vaccines now appear to be quite limited (2, 3, 48). WHO must develop a comprehensive strategy for the prompt cessation of OPV use as soon as
Circulating vaccine-derived polioviruses: state of the knowledge

Possible after global certification (50). Cessation of OPV use should be closely coordinated by WHO, as uncoordinated discontinuation by countries is likely to create unacceptable risks for emergence of cVDPVs. Synchronous cessation of OPV use immediately after coordinated mass OPV campaigns (in countries that had continued to use OPV) would maximize global immunity to polio at the time of OPV cessation (3, 48). Transition to IPV should be encouraged at the present time in developed countries in temperate zones where IPV efficacy is known to be high and where high rates of IPV coverage can be maintained through routine immunization (48, 49). The use of IPV in tropical developing countries presents special challenges because the rates of routine immunization are often inadequate, IPV efficacy is uncertain, and logistical and financial challenges persist (49). This option requires further, careful analysis (50). Stockpiles of polio vaccine must be established at strategic sites to enable a rapid response to the detection of any poliovirus infection in the post-OPV era (3, 48). Finally, sensitive field and laboratory surveillance must be maintained until there is compelling evidence that the risk of any poliovirus re-emergence is negligible (3, 48, 50).

Conflicts of interest: none declared.
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