

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 oral poliovirus vaccine (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/etiology/chemically induced/prevention and control; Immunization programs; Disease outbreaks/Review literature (*source: MeSH, NLM*).

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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 (~97.7% 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

Fig. 1. Location of the four polio outbreaks associated with circulating vaccine-derived polioviruses (cVDPVs). Shown are the serotypes of the cVDPV isolates, the years of cVDPV virus isolation, and the number of reported polio cases associated with cVDPVs



Note: In each of these areas, the spread of cVDPVs followed the elimination of the corresponding serotype of indigenous wild poliovirus, but with the continued introduction of oral poliovirus vaccine into communities with growing immunity gaps. All of the cVDPV outbreaks were detected first by the laboratory, using sequence data and evolutionary analyses.

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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 in communities where the rates of OPV coverage were low.

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.

Insensitive surveillance is an additional risk factor for the spread of cVDPV. Apart from the outbreaks in the Philippines and Poland, VDPV circulation occurred in areas with very low rates of AFP case reporting. VDPV circulation in Hispaniola, Madagascar, and the Philippines apparently began 2–3 years before the first cases were detected. The genetic diversity of the cVDPV isolates from Egypt and Haiti suggested that the large majority of polio cases went unreported (24, 29), and the case counts probably seriously underestimate the impact of VDPV circulation in the two countries.

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 neurovirulent 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 $\geq 1\%$ 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 endemicity (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

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.

Résumé

Poliovirus circulants dérivés de souches vaccinales : état des connaissances

Au cours des quatre dernières années, on a observé des flambées de poliomyélite associées aux poliovirus circulants dérivés de souches vaccinales (PcDSV) sur l'île d'Haïti (2000-2001), aux Philippines (2001) et à Madagascar (2001-2002). Des études rétrospectives ont également décelé la circulation d'un PcDSV endémique en Egypte (1988-1993) et une propagation localisée probable d'un virus dérivé du vaccin antipoliomyélique buccal (VPO) en Biélorussie (1965-1966). Pour toutes les flambées dues à des PcDSV, la couverture insuffisante par le VPO et l'éradication préalable du poliovirus sauvage autochtone étaient les principaux facteurs de risque. Des campagnes de vaccination de masse par le VPO ont interrompu ces flambées. Pour améliorer la sensibilité de la détection des PcDSV, le réseau mondial de laboratoires pour la poliomyélite requiert désormais des tests supplémentaires pour tous les poliovirus isolés. Cette démarche a permis de reconnaître rapidement les flambées des Philippines

et de Madagascar, mais il n'y en a pas d'autres actuellement. L'interruption de la circulation du poliovirus sauvage dans la plupart des régions du monde ces dernières années a entraîné une augmentation spectaculaire du risque potentiel d'émergence de PcDSV. Ce risque semble le plus élevé avec la souche de type 2 du VPO, en raison de sa plus forte propension à se propager aux sujets contacts. L'émergence de PcDSV souligne bien l'importance cruciale d'éliminer le poliovirus sauvage dans les dernières poches où il circule, de maintenir la couverture universelle de la vaccination, d'arrêter d'administrer le VPO dès que tout risque est écarté et d'assurer une surveillance suffisamment sensible des poliovirus dans un proche avenir. Les régions où le risque de circulation du poliovirus sauvage a été le plus élevé et où les couvertures vaccinales doivent être les plus étendues pour supprimer l'émergence de PcDSV doivent tout spécialement retenir l'attention.

Resumen

Poliovirus circulantes de origen vacunal: estado actual de los conocimientos

En los últimos cuatro años se han declarado brotes de poliomiélitis asociados a poliovirus de origen vacunal circulantes (PVOVc) en La Española (2000-2001), Filipinas (2001) y Madagascar (2001-2002). Estudios retrospectivos han detectado también la circulación de PVOVc endémicos en Egipto (1988-1993) y la probable propagación localizada del virus derivado de la vacuna antipoliomiélica oral (OPV) en Bielorrusia (1965-1966). Las lagunas existentes en la cobertura de OPV y la previa erradicación del serotipo correspondiente al poliovirus salvaje autóctono fueron los factores de riesgo críticos de todos los brotes de PVOVc. Éstos fueron atajados mediante campañas de inmunización masiva con OPV. A fin de aumentar la sensibilidad de detección de los PVOVc, en 2001 la Red Mundial de Laboratorios para la Poliomiélitis implantó nuevos requisitos de análisis para todos los aislados de poliovirus sometidos a investigación. Este enfoque permitió reconocer rápidamente los brotes de PVOVc de Filipinas

y de Madagascar, pero no así otros brotes recientes. El riesgo potencial de aparición de PVOVc ha aumentado extraordinariamente en los últimos años, debido al cese de la circulación del poliovirus salvaje en la mayor parte del mundo. La cepa OPV de tipo 2 parece ser la que más riesgo plantea, debido a su mayor tendencia a propagarse a los contactos. La aparición de PVOVc subraya la importancia que revisten la eliminación de las últimas bolsas de circulación del poliovirus salvaje, el mantenimiento de unos niveles universalmente altos de cobertura con vacuna antipoliomiélica, la interrupción del uso de OPV tan pronto como la seguridad alcanzada lo permita, y el mantenimiento de sistemas sensibles de vigilancia del poliovirus en un futuro próximo. Hay que prestar especial atención a las áreas que presenten el máximo riesgo de circulación del poliovirus salvaje, y a aquellas donde deban mantenerse las mayores tasas de cobertura con vacuna antipoliomiélica para evitar la aparición de PVOVc.

ملخص

فيروس شلل الأطفال الجائل المشتق من اللقاح: الحالة الراهنة للمعارف

الأسلوب إلى سرعة التعرف على فاشيات فيروس شلل الأطفال الجائل المشتق من اللقاح في الفلبين ومدغشقر، دون التعرف على فاشيات أخرى حالية. وقد ازدادت المخاطر المحتملة لظهور فيروس شلل الأطفال الجائل المشتق من اللقاح ازدياداً جذرياً في السنوات الأخيرة مع توقف سريان فيروس شلل الأطفال البري في معظم أنحاء العالم. ويكمن أعلى مستوى من المخاطر في النمط الثاني من ذراري اللقاح القموي لشلل الأطفال بسبب شدة ميلها للانتشار إلى المسخالطين. وأدى ظهور فيروس شلل الأطفال الجائل المشتق من اللقاح إلى التشديد على أهمية التخلص من آخر جيوب فيروس شلل الأطفال البري الجائل، مع المحافظة على مستويات عالمية عالية من التغطية بلقاح شلل الأطفال، ووقف إعطاء اللقاح القموي بمجرد أن يصبح ذلك مأموناً، واستمرار الرصد الحساس لفيروس شلل الأطفال في المستقبل القريب. كما ينبغي إيلاء اهتمام خاص بالمناطق التي تشهد أعلى مستوى من مخاطر فيروس شلل الأطفال البري، والتي يستعجّل الوصول فيها إلى أعلى معدل للتغطية بالتمنيع بلقاح شلل الأطفال من أجل منع ظهور فيروس شلل الأطفال الساثر المشتق من اللقاح.

ملخص: شهدت الأعوام الأربعة الماضية فاشيات مرض شلل الأطفال مرتبطة بفيروس شلل الأطفال الجائل المشتق من اللقاح، وذلك في هايتي (٢٠٠٠-٢٠٠١)، والفلبين (٢٠٠١)، ومدغشقر (٢٠٠١-٢٠٠٢). كما اكتشفت الدراسات الاستيعابية سريان فيروس شلل الأطفال المتوطن المشتق من اللقاح في مصر (في الأعوام ١٩٨٨-١٩٩٣) واحتمال الانتشار الموسمي للفيروس المشتق من اللقاح القموي لشلل الأطفال في بيلاروس (١٩٦٥-١٩٦٦). وكانت الفجوات التي حدثت في التغطية بلقاح القموي لشلل الأطفال والاستئصال السابق للنمط المصلي لفيروس شلل الأطفال البري الداخلي المنشأ هي عوامل الخطر الحرجة في جميع حالات فاشيات فيروس شلل الأطفال الجائل المشتق من اللقاح. وقد أمكن وقف هذه الفاشيات بتأثير حملات التمنيع الجموعي بلقاح القموي. وفي عام ٢٠٠١ قامت شبكة مختبرات شلل الأطفال العالمية بتطبيق مزيد من الاشتراطات عند اختبار جميع مستفردات فيروس شلل الأطفال التي كانت قيد البحث، وذلك بغرض زيادة الحساسية لاكتشاف فيروس شلل الأطفال المشتق من اللقاح. وقد أدى هذا

References

1. Sutter RW, Kew OM, Cochi SL. Poliovirus vaccine — live. In: Plotkin SA, Orenstein WA, editors. *Vaccines*, 4th ed. Philadelphia (PA): WB Saunders; 2003:651-705.
2. Nathanson N, Fine P. Poliomyelitis eradication — a dangerous endgame. *Science* 2002;296:269-70.
3. Dowdle WR, De Gourville E, Kew OM, Pallansch MA, Wood DJ. Polio eradication: the OPV paradox. *Reviews in Medical Virology* 2003;13:277-91.
4. World Health Organization. Progress towards the global eradication of poliomyelitis, 2002. *Weekly Epidemiological Record* 2003;78:138-44.
5. Heymann DL. Polio eradication: finishing the job and protecting the investment. *Bulletin of the World Health Organization* 2004;82:1.
6. Fine PEM, Carneiro IAM. Transmissibility and persistence of oral polio vaccine viruses: implications for the global poliomyelitis eradication initiative. *American Journal of Epidemiology* 1999;150:1001-21.
7. Sabin AB. Properties and behavior of orally administered attenuated poliovirus vaccine. *JAMA* 1957;164:1216-23.
8. Benyesh-Melnick M, Melnick JL, Rawls WE, Wimberly I, Oro JB, Ben-Porath E, et al. Studies on the immunogenicity, communicability, and genetic stability of oral poliovaccine administered during the winter. *American Journal of Epidemiology* 1967;86:112-36.
9. Wright PF, Hatch MH, Kasselberg AG, Lowry SP, Wadlington WB, Karzon DT. Vaccine-associated poliomyelitis in a child with sex-linked agammaglobulinemia. *Journal of Pediatrics* 1977;91:408-12.
10. Sutter RW, Prevots R. Vaccine-associated paralytic poliomyelitis among immunodeficient persons. *Infections in Medicine* 1994;11:426-38.
11. Khetsuriani N, Prevots DR, Quick L, Elder ME, Pallansch M, Kew O, et al. Persistence of vaccine-derived polioviruses among immunodeficient persons with vaccine-associated paralytic poliomyelitis. *Journal of Infectious Diseases* 2003;188:1845-52.
12. Kew OM, Sutter RW, Nottay BK, McDonough MJ, Prevots DR, Quick L, et al. Prolonged replication of a type 1 vaccine-derived poliovirus in an immunodeficient patient. *Journal of Clinical Microbiology* 1998;36:2893-9.
13. Bellmunt A, May G, Zell R, Pring-Akerblom P, Verhagen W, Heim A. Evolution of poliovirus type I during 5.5 years of prolonged enteral replication in an immunodeficient patient. *Virology* 1999;265:178-84.
14. Martin J, Dunn G, Hull R, Patel V, Minor PD. Evolution of the Sabin strain of type 3 poliovirus in an immunodeficient patient during the entire 637-day period of virus excretion. *Journal of Virology* 2000;74:3001-10.
15. Halsey NA, Pinto J, Espinosa-Rosales F, Faure-Fontenla MA, da Silva E, Khan AJ, et al. Search for poliovirus carriers among people with primary immune deficiency diseases in the United States, Mexico, Brazil, and the United Kingdom. *Bulletin of the World Health Organization* 2004;82:3-8.
16. Domingo E, Holland JJ. RNA virus mutations and fitness for survival. *Annual Review of Microbiology* 1997;51:151-78.
17. Drake JW, Holland JJ. Mutation rates among RNA viruses. *Proceedings of the National Academy of Sciences of the United States of America* 1999;96:13910-3.
18. Gavrilin GV, Cherkasova EA, Lipskaya GY, Kew OM, Agol VI. Evolution of circulating wild poliovirus and of vaccine-derived poliovirus in an immunodeficient patient: a unifying model. *Journal of Virology* 2000;74:7381-90.
19. Liu H-M, Zheng DP, Zhang LB, Oberste MS, Pallansch MA, Kew OM. Molecular evolution of a type 1 wild-vaccine poliovirus recombinant during widespread circulation in China. *Journal of Virology* 2000;74:11153-61.
20. Minor PD, Dunn G. The effect of sequences in the 5' non-coding region on the replication of polioviruses in the human gut. *Journal of General Virology* 1988;69:1091-6.
21. Yoshida H, Horie H, Matsuura K, Kitamura T, Hashizume S, Miyamura T. Prevalence of vaccine-derived polioviruses in the environment. *Journal of General Virology* 2002;83:1107-11.
22. Minor PD, Almond JW. Poliovirus vaccines: molecular biology and immune response. In: Semler BL, Wimmer E, editors. *Molecular biology of picornaviruses*. Washington (DC): ASM Press; 2002. p. 381-90.
23. Sabin AB, Ramos-Alvarez M, Alvarez-Amezquita J, Pelon W, Michaels, RH, Spigland, I, et al. Live, orally given poliovirus vaccine. Effects of rapid mass immunization on population under conditions of massive enteric infection with other viruses. *JAMA* 1960;173:1521-6.
24. Kew OM, Morris-Glasgow V, Landaverde M, Burns C, Shaw J, Garib Z, et al. Outbreak of poliomyelitis in Hispaniola associated with circulating type 1 vaccine-derived poliovirus. *Science* 2002;296:356-9.
25. World Health Organization. Expanding contributions of the Global Laboratory Network for Poliomyelitis Eradication. *Weekly Epidemiological Record* 2002;77:133-7.
26. World Health Organization. Acute flaccid paralysis associated with circulating vaccine-derived poliovirus, Philippines, 2001. *Weekly Epidemiological Record* 2001;76:319-20.

27. Thorley B, Paladin F, Shimizu H. Poliomyelitis due to vaccine-derived polioviruses in the Philippines. In: *Abstracts of the XIIIth International Congress of Virology, Paris, 27 July to 1 August 2002*. Paris: International Union of Microbiological Societies; 2002.
28. Rousset D, Rakoto-Andrianarivelo M, Razafindratsimandresy R, Randriamanalina B, Guillot S, Balanant J, et al. Recombinant vaccine-derived poliovirus in Madagascar. *Emerging Infectious Diseases* 2003;9:885-7.
29. Yang C-F, Naguib T, Yang SJ, Nasr E, Jorba J, Ahmed N, et al. Circulation of endemic type 2 vaccine-derived poliovirus in Egypt, 1983 to 1993. *Journal of Virology* 2003;77:8366-77.
30. Kostrewski J, Kulesza A, Abgarowicz A. The epidemic of type 3 poliomyelitis in Poland in 1968. *Epidemiologic Reviews* 1970;24:89-103.
31. Kew OM, Nottay BK. Molecular epidemiology of polioviruses. *Reviews of Infectious Diseases* 1984;6 Suppl 2:S499-S504.
32. Kew OM, Pallansch MA, Nottay BK, Rico-Hesse R, De L, Yang C-F. Genotypic relationships among wild polioviruses from different regions of the world. In: Brinton MA, Heinz FX, editors. *New aspects of positive-strand RNA viruses*. Washington (DC): American Society for Microbiology;1990:357-65.
33. Martín J, Ferguson GL, Wood DJ, Minor PD. The vaccine origin of the 1968 epidemic of type 3 poliomyelitis in Poland. *Virology* 2000;278:42-9.
34. Korotkova EA, Park R, Cherkasova EA, Lipskaya GY, Chumakov KM, Feldman EV, et al. Retrospective analysis of a local cessation of vaccination against poliomyelitis: a possible scenario for the future. *Journal of Virology* 2003;77:12460-5.
35. Georgescu MM, Balanant J, Macadam A, Otelea D, Combiescu M, Combiescu AA, et al. Evolution of the Sabin type 1 poliovirus in humans: characterization of strains isolated from patients with vaccine-associated paralytic poliomyelitis. *Journal of Virology* 1997;71:7758-68.
36. Cherkasova EA, Korotkova EA, Yakovenko ML, Ivanova OE, Ereemeeva TP, Chumakov KM, et al. Long-term circulation of vaccine-derived poliovirus that causes paralytic disease. *Journal of Virology* 2002;76:6791-9.
37. World Health Organization. Laboratory surveillance for wild and vaccine-derived polioviruses, January 2002–June 2003. *Weekly Epidemiological Record* 2003;78:341-8.
38. Nathanson N, Martin JR. The epidemiology of poliomyelitis: enigmas surrounding its appearance, epidemicity, and disappearance. *American Journal of Epidemiology* 1979;110:672-92.
39. Nakano JH, Hatch MH, Thieme ML, Nottay B. Parameters for differentiating vaccine-derived and wild poliovirus strains. *Progress in Medical Virology* 1978;24:78-206.
40. Guillot S, Caro V, Cuervo N, Korotkova E, Combiescu M, Persu A, et al. Natural genetic exchanges between vaccine and wild poliovirus strains in humans. *Journal of Virology* 2000;74:8434-43.
41. Liu H-M, Zheng DP, Zhang LB, Oberste MS, Kew OM, Pallansch MA. Serial recombination during circulation of type 1 wild-vaccine recombinant polioviruses in China. *Journal of Virology* 2003;77:10994-1005.
42. da Silva EE, da Costa EV, Kew OM. OPV-derived polioviruses isolated from recent cases of acute flaccid paralysis in Brazil are closely related to the prototype Sabin strains. In: *Progress in polio eradication: vaccine strategies for the end game, Institut Pasteur, Paris (28–30 June 2000)*, Geneva: International Association for Biologicals; 2000.
43. De L, Nottay B, Yang CF, Holloway BP, Pallansch M, Kew O. Identification of vaccine-related polioviruses by hybridization with specific RNA probes. *Journal of Clinical Microbiology* 1995;33:562-71.
44. Yang C-F, De L, Holloway BP, Pallansch MA, Kew OM. Detection and identification of vaccine-related polioviruses by the polymerase chain reaction. *Virus Research* 1991;20:159-79.
45. Kilpatrick DR, Nottay B, Yang CF, Yang SJ, Da Silva E, Penaranda S, et al. Serotype-specific identification of polioviruses by PCR using primers containing mixed-base or deoxyinosine residues at positions of codon degeneracy. *Journal of Clinical Microbiology* 1998;36:352-7.
46. Balanant J, Guillot S, Candrea A, Delpoux F, Crainic R. The natural genomic variability of poliovirus analyzed by a restriction fragment polymorphism assay. *Virology* 1991;184:645-54.
47. van der Avoort HG, Hull BP, Hovi T, Pallansch MA, Kew OM, Crainic R, et al. Comparative study of five methods for intratypic differentiation of polioviruses. *Journal of Clinical Microbiology* 1995;33:2562-6.
48. Technical Consultative Group to the World Health Organization on the Global Eradication of Poliomyelitis. "Endgame" issues for the Global Polio Eradication Initiative. *Clinical Infectious Diseases* 2002;34:72-7.
49. World Health Organization. Introduction of inactivated poliovirus vaccine into oral poliovirus vaccine-using countries. *Weekly Epidemiological Record* 2003;78:241-50.
50. World Health Organization. *Conclusions and recommendations: WHO informal consultation on identification and management of vaccine-derived polioviruses*. Geneva: World Health Organization; 2003.