Round Table

Stopping poliovirus vaccination after eradication: issues and challenges

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Since 1988 reported polio cases worldwide have declined by about 85% and the number of known or suspected polio-endemic countries has decreased from over 120 to less than 50. With eradication of poliomyelitis approaching, issues potentially affecting when and how vaccination against poliovirus can be stopped become extremely important. Because of the potential risks and benefits inherent in such a decision, the best available science, a risk–benefit analysis, contingency plans, a stock pile of poliovirus vaccines, and the endorsement by the global policy-making committees will all be needed before vaccination can be discontinued. The scientific basis for stopping polio immunization has been reviewed by WHO. This Round Table article summarizes the current state of knowledge, provides an update on the processes and timelines for certification, containment, and stopping vaccination, and highlights some of the unanswered scientific questions that will be addressed by further research. These include whether transmission of vaccine-derived poliovirus strains could be sustained so that poliomyelitis could re-emerge in a future unvaccinated population and whether prolonged excretion of vaccine-derived poliovirus from individuals with immune deficiencies could be a mechanism through which this could occur.

Keywords: certification, standards; immunization, trends; poliomyelitis, prevention and control; polioviruses, human 1–3, pathogenicity.

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Introduction

In 1988, the World Health Assembly adopted a resolution to eradicate poliomyelitis globally by the year 2000 (*1*). Responding to this mandate from the global community, WHO led the polio eradication initiative, with a focus on the following priority areas: development of policies, strategies and technical implementation guidelines for poliovirus eradication; coordination of partners to ensure adequate financial and technical support for the initiative; and establishment of infrastructure (human resources, communication, and transportation) within WHO and in polio-endemic countries to ensure that the corresponding activities will be carried out.

Substantial progress towards eradication has been reported from all WHO regions since 1988, e.g. poliomyelitis cases worldwide have declined by about 85%, and the number of known or suspected polio-endemic countries has decreased from over 120 to less than 50 (*2*). The WHO Region of the Americas eliminated poliovirus in 1991 and the entire Western Hemisphere was certified to be free of indigenous poliovirus by an independent international commission in 1994 (*3*). In the WHO Western Pacific Region, which includes the world's most populous country, China, indigenous poliovirus has not been isolated since 1997 and the region is in the final stages of poliomyelitis eradication (*4*).

As we approach global eradication, issues such as when and how vaccination against poliovirus can be stopped have become increasingly important both from a public health viewpoint and from a strategic industrial perspective, because poliovirus vaccine manufacturers may need lead time to adjust to changes in vaccination policy.

Background

Vaccines

Two excellent vaccines are available to control poliomyelitis: inactivated poliovirus vaccine (IPV), which was first licensed in the USA in 1955; and oral poliovirus vaccine (OPV) which replaced IPV as the preferred vaccine in most areas of the world in the early 1960s. The advantages and disadvantages of both vaccines have been reviewed extensively (*5, 6*). Although IPV, in which the virus has been formalin-inactivated and therefore rendered non-infectious, is very effective in inducing circulating antibody against

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poliovirus for individual protection, it is less effective than OPV in inducing mucosal immunity at replication sites in the gastrointestinal tract. Mucosal immunity restricts viral replication following exposure to poliovirus and is important for community protection. OPV, which contains live attenuated strains of each serotype, spreads from vaccinees and indirectly immunizes these secondary contacts; very rarely, OPV may cause vaccine-associated paralytic poliomyelitis. The ability of OPV to induce a higher level of mucosal immunity, plus the advantages of oral administration and lower costs, made OPV the vaccine of choice for the polio eradication initiative.

Certification of eradication

Following the example of the smallpox eradication programme and the certification process for polio eradication, which was pioneered by the Region of the Americas in the period 1990–94, WHO appointed an independent Global Commission for the Certification of Polio Eradication. In its inaugural meeting in 1995, the Commission outlined a process and specified criteria for certification (*7*). The process relies on each country establishing an independent national committee which will critically compile and review relevant data and present the country dossier to a regional commission. The latter, after reviewing this information from individual countries, has the responsibility to certify the entire region as polio-free. Once all six WHO regions have been certified as polio-free, the Global Commission will be able to certify the world as polio-free. The most important criterion for certification of a country, a region or indeed the world is the absence of poliovirus isolation for at least 3 years under conditions of adequate surveillance (*7*). The anticipated time frame for interrupting poliovirus transmission, and for certification, containment, and cessation of OPV administration is outlined in Fig. 1.

Laboratory containment process for polioviruses

After eradication, the only source of wild polioviruses will be laboratories. In June 1998, WHO circulated for public comment a proposed action plan and timetable for the safe handling and maximum containment of wild polioviruses and potentially infectious materials (*8*). This document was revised, based on the comments received, and was redrafted as the *Global action plan for laboratory containment of wild polioviruses* (*9*).

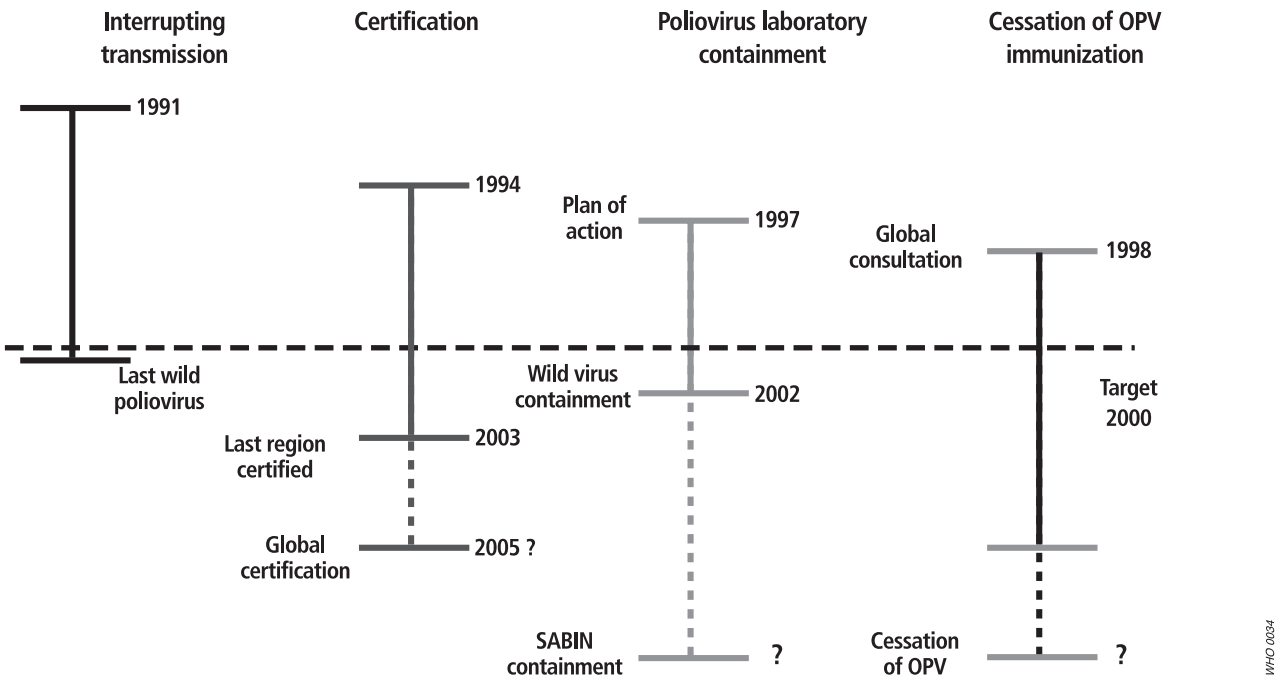
The current action plan is linked to the three major eradication stages: pre-eradication, post-global eradication, and post-OPV immunization. We are now at the pre-eradication stage when wild polioviruses are no longer circulating in many areas of the world and are decreasing in others. During this period, laboratories are requested to institute enhanced biosafety procedures for safe handling of all wild poliovirus materials. Countries are requested to identify and develop an inventory of laboratories that have such materials. The post-eradication period will begin one year after the last wild poliovirus has been detected. All laboratories listed on the national inventories as possessing wild poliovirus materials should elect to destroy such materials, transfer selected materials to designated WHO repositories, or implement high containment procedures. The post-OPV immunization period begins with the worldwide cessation of OPV administration and is expected to show a rapid increase of non-immune susceptible children. In this period, the laboratory biosafety requirements for wild poliovirus materials will increase from high containment to maximum containment, consistent with the need for increased safeguards against the inadvertent transmission of wild polioviruses from the laboratory to the community. Biosafety requirements for OPV and vaccine-derived viruses will increase to high containment to prevent the introduction and potential circulation of these viruses in unimmunized populations.

In addition to laboratory containment of polioviruses, a process has been put into place to contain the transgenic mice which express the human poliovirus receptor and which, unlike normal mice, are susceptible to poliovirus infection. The risk that escape of these transgenic mice to the wild would result in the establishment of a new animal reservoir of poliovirus is very low. Nevertheless, all laboratories working with these mice are adhering to procedures to minimize the possibility of their escape, both during maintenance and distribution of the animals (*10*).

Scenarios for stopping vaccination

The ultimate goal of any eradication programme is to stop using the intervention and to reap the financial benefits of eradication. As poliomyelitis eradication approaches, several strategies for stopping vaccination with OPV are under consideration. The susceptibility of the population to poliovirus will gradually increase following the discontinuation of vaccination — eventually to an extent when widespread epidemic transmission could take place. The most important issue is to safeguard the population, so that when and how to stop the administration of poliovirus vaccines may be the most critical and potentially far-reaching decision of the entire eradication initiative. Several options for stopping vaccination are being discussed: no change (e.g. continuation of universal childhood vaccination with OPV); change to an all-IPV programme either for a limited transition period or indefinitely; sequential removal of one or two of the Sabin-strains from OPV, or the use of monovalent OPV, based on epidemiological and strategic considerations; development of new vaccines; and discontinuation of OPV vaccination simultaneously worldwide or selectively country-by-country. The major advantages, disadvantages, potential long-term implications, and scientific gaps in knowledge of each of these options are outlined in Table 1. While each option requires further evaluation, the discontinuation of OPV in a synchronized effort worldwide remains the most plausible, perhaps

Fig. 1. **Timetable for polio eradication, certification, containment and stopping vaccination** (OPV = oral poliovirus vaccine)



after a series of global immunization days to maximize the population's immunity against poliomyelitis (*11*). The decision-making process will be greatly assisted by identifying relevant research questions and aggressively implementing a corresponding research agenda (Table 2).

Issues

Persistence of vaccine-derived poliovirus in populations

The following lines of evidence provide information on the potential persistence of vaccine-derived poliovirus in populations: Cuba and other countries have reported studies on persistence of the virus following mass campaigns with OPV; genomic sequencing of poliovirus isolates from polio-free countries indicates whether vaccine-derived virus circulated for extended periods; and surveys among religious groups objecting to vaccination and studies of poliomyelitis outbreaks provide information on the force of infection of vaccine-derived virus. However, it should be noted that currently available data are limited and further work is required on the transmissibility and persistence of vaccine-derived polioviruses (*12*).

Person-to-person transmission of OPV-derived polioviruses to household and other close contacts is well documented (*13*). The critical question is whether transmission could be sustained in this way (endemic transmission) in a population or whether widespread poliovirus infection (epidemic transmission) could re-emerge in a future unvaccinated population. Data are available from countries where mass OPV campaigns are the only means of providing OPV (with no supplemental doses between campaigns). Since 1962, Cuba has administered OPV exclusively in biannual mass campaigns conducted in February and April. OPV is not available and not used at any other time of the year (*14*). Several studies have demonstrated that vaccine-derived poliovirus persists for a limited period in Cuba; evidence of virus replication can be detected for not more than 3 months after a mass campaign (*15, 16*). This conclusion is supported by stool and serological surveys of children born after the end of a mass campaign and tested prior to the start of a mass campaign in the next year. However, poliovirus type 2 with a substantial genetic drift has been isolated from a sewage sample in Israel, suggesting prolonged "silent" circulation of this virus either in the population or in an individual (*17*).

Reports from countries such as Hungary and Romania indicate that vaccine-derived poliovirus circulation is limited in duration. Hungary used almost exclusively monovalent OPV from 1959 until the early 1990s. The monovalent OPVs were administered sequentially (types 1, 3, and then 2) in one-week campaigns separated by one month in the winter or autumn. Vaccine was not available between the campaigns. Surveillance detected polioviruses for up to 3 months after these campaigns (*18*). Almost all vaccine-associated paralytic poliomyelitis (VAPP) cases were clustered in the months after administration of monovalent type 3 OPV (*19*). Similarly, OPV

Table 1. **Advantages, disadvantages and long-term risks of strategies to stop poliovirus vaccination**

Strategy	Advantages	Disadvantages	Long-term risks	Scientific gaps
Continue OPV indefinitely	• Known risk profile (VAPP)[a] • Very effective in controlling and eliminating disease in developing and industrialized countries • Population immunity maintained	• VAPP[a] when wild poliovirus is no longer circulating • No financial benefits from eradication	• Lowest potential for renewed epidemic transmission (because of indirect effects of OPV with secondary spread)	
Use IPV indefinitely	• Least risk (no known adverse events) • Individual immunity preserved • Could be administered as a combination vaccine	• Most costly strategy • May require an additional injection to administer IPV • May require change in EPI schedule to administer IPV later in life • No financial benefits from eradication	• Accumulation of susceptible persons in the population because IPV has only direct effects • Continued production of IPV with wild-type poliovirus entails risk of the virus escaping	• Production relying on Sabin strains
Discontinue OPV in coordinated fashion after global NIDs	• Ultimate goal of the eradication programme is to stop vaccination • Stop OPV when population immunity is highest	• Uncertain potential for continued transmission of vaccine-derived virus, especially in developing countries • Loss of capacity to produce vaccine • Requires vaccine stockpile	• Rapid accumulation of persons susceptible to poliomyelitis • Potential for large epidemics after intentional or unintentional release of poliovirus from containment sources • Potential for vaccine-derived poliovirus to revert and acquire characteristics of wild-type virus (transmission, neurovirulence)	• Determine risk of continuous transmission of vaccine-derived virus in population (by development status, climate, sanitation and hygiene) • Risk of re-seeding populations with poliovirus by chronic carriers • Molecular determinants of neurovirulence and transmission • No animal model for measuring transmission
Discontinue OPV country-by-country	• Decision when to stop is delegated to individual countries • Stop OPV when population immunity is highest in country	• Most likely scenario to permit vaccine-derived virus to circulate – from an area that still vaccinates to re-seed an area that has stopped vaccination • Requires vaccine stockpile	• Rapid accumulation of persons susceptible to poliomyelitis • Potential for large epidemics of paralytic poliomyelitis after intentional or unintentional release of poliovirus from containment sources • Potential for vaccine-derived poliovirus to revert and acquire characteristics of wild-type virus (transmission, neurovirulence)	• Determine risk of continuous transmission of vaccine-derived virus in population (by development status, climate, sanitation and hygiene) • Risk of re-seeding populations with poliovirus by chronic carriers • Molecular determinants of neurovirulence and transmission • No animal model for measuring transmission
Selective removal of Sabin strains from OPV or use of monovalent OPV	• Maintain vaccination and population immunity against poliovirus types 1 and 3, while determining what happens with type 2 virus	• Substantial difficulties in gaining regulatory approval for ''bivalent OPV'' • Regulatory approval for monovalent OPV less challenging	• Removal of type 2 virus in OPV may increase the neurovirulence of bivalent OPV and increase the risk of VAPP[a] • Monovalent OPV may be associated with higher risk of VAPP[a]	• Study of Sabin type 2 virus in individuals, populations and the environment after its removal from OPV • Only an interim solution, a need to select a final strategy somewhat downstream
New poliovirus vaccine	• Continue vaccination and maintain population immunity • Less infectious virus seed will minimize risks if virus escapes	• Lengthy and costly process to gain regulatory approval • Uncertain what field trials are necessary • Cannot reap financial benefits of poliomyelitis eradication	• Uncertain, depending on the product developed	• Conducting the research needed will provide scientific knowledge that may be applicable to other vaccines

[a] VAPP = vaccine-associated paralytic poliomyelitis.

Table 2. **Research agenda for stopping poliovirus vaccination, 1999**

Broad objective	Individual objective	Country	Status	Collaborating institutions
Prolonged replication of poliovirus in individuals	Risk among vaccine-associated paralytic poliomyelitis cases	USA	Field work completed; manuscript in preparation	CDC
	Risk among immunodeficient individuals	USA	Field work in progress	JHU (Immunodeficiency Foundation)
		United Kingdom	Field work in progress	NIBSC, Medical Research Council
		Cuba	Field work completed	MOH, CDC, PAHO
		Tunisia	Field work in progress	Institut Pasteur, Tunis
	Risk among HIV-infected individuals	Kenya	Field work in progress	Kenya Medical Research Institute, CDC
		Guatemala	Field work in progress	MOH, JHU
Prolonged circulation of poliovirus in populations	Evidence of exposure to vaccine-derived virus following an OPV mass campaign	Cuba	Field work completed; manuscript in preparation	MOH, CDC, PAHO
	Disappearance of vaccine-derived virus from individuals and from the environment	Cuba	Field work completed; analysis phase	MOH, CDC, PAHO
	Molecular studies of vaccine-derived virus from acute flaccid paralysis cases	Bolivia, Brazil, Colombia, Mexico	Laboratory analyses completed	MOH, CDC
Prevalence of immunodeficiency disorders in developing countries	Persons with recurrent infections	Ethiopia, Guatemala, Pakistan	Field work in progress	MOH, JHU
		Haiti	Field work completed	MOH, CDC

[a] CDC = Centers for Disease Control and Prevention; JHU = Johns Hopkins University; NIBSC = National Institute for Biological Standards and Control; PAHO = Pan American Health Organization; MOH = Ministry of Health.

was administered only in campaigns in Romania until the 1990s. Clustering of VAPP cases occurred in close temporal association with these campaigns suggesting limited circulation of vaccine-derived poliovirus in the population (*20*).

The rate of nucleotide substitutions in the poliovirus genome can be used to estimate the duration of viral replication either in an individual or serially in a population. Poliovirus genomes appear to evolve at a relatively constant rate of 1% nucleotide substitutions per year (the so-called "molecular clock") (*21*). Communities with poor sanitation, no circulation of wild poliovirus, and substantial accumulation of susceptible unvaccinated or inadequately vaccinated children may be at highest risk for persistent transmission of vaccine-derived strains. Genomic sequencing has been conducted on 31 vaccine-derived strains from acute flaccid paralysis cases from communities in Bolivia, Brazil, Colombia and Mexico. All isolates demonstrated >99% similarity to the parent vaccine strains, suggesting no evidence of long-term circulation (O. Kew, personal communication, 1999).

Religious groups whose members object to vaccination (and reside within well-vaccinated general populations using either OPV or IPV) can be assessed to monitor secondary exposure to vaccine-derived poliovirus (and indirectly provide an indication of the force of infection of vaccine-derived poliovirus). Because population immunity to poliovirus is low in these populations, they are at risk for wild poliovirus transmission (*22*). Outbreaks in industrialized countries occurred in the Netherlands in 1977 (*23*) and 1992–93 (*24*), Canada in 1978 (*25*), the USA in 1972 (*26*) and 1979 (*27*), as well as in at least one developing country, Malaysia, in 1992 (*28*). In the Netherlands, IPV is used exclusively for routine vaccination. However, OPV was used in 1978 and 1992–93 to control poliomyelitis outbreaks in a religious group whose members object to vaccination. Serological surveys in the years following the first epidemic were consistent with the absence of poliovirus circulation in unvaccinated children from the religious group (*29*). Similar serological studies were initiated in a religious community in the USA after the 1992–93 epidemic in the Netherlands. These studies suggested that no one born after 1979 (the year of the last known poliomyelitis outbreak in this community) had antibodies to poliovirus types 1 and 3, but all had antibodies to poliovirus type 2 (*30*). A study was also conducted in British Columbia, Canada, in a religious community with links to the Dutch group, suggesting limited spread of vaccine-derived poliovirus to this unvaccinated group (*31, 32*).

Poliomyelitis outbreaks are invariably due to wild-type strains rather than vaccine-derived strains, suggesting that the vaccine-derived poliovirus may be less transmissible than wild-type strains, even if this is

difficult to quantify. Three recent outbreaks of poliomyelitis serve as examples: Samarkand in Uzbekistan in 1993–94 (*33*), Chechnya in 1995 (*34*), and Albania in 1996 (*35*). In Samarkand, OPV was not available for a 10-month period from November 1992 to August 1993; subsequently, a large outbreak of 74 cases of poliomyelitis due to poliovirus type 3 was observed (*33*). In Chechnya, OPV vaccination ceased abruptly in 1992 with the onset of the secessionist movement. An outbreak of 143 poliomyelitis cases occurred in 1995, caused by an imported type-1 wild virus; 84% of cases were less than 2 years of age (*34*). Immunity among unvaccinated children was, therefore, at low levels, implying quite limited, if any, community circulation of vaccine-derived virus. An outbreak of 138 poliomyelitis cases occurred in Albania in 1996 (*35*). The first case had onset of paralysis on 17 April, 10 days after the first of two rounds of a nationwide campaign that vaccinated 350 000 children (98%) aged 2–59 months. Attack rates were highest in infants too young to be vaccinated, followed by young adults and teenagers. Since wild poliovirus was apparently introduced concurrently with the OPV campaign and cases were concentrated in populations normally in close contact with children, type-1 OPV-derived strains (as well as types 2 and 3) must be substantially less transmissible than the outbreak strain.

Prolonged excretion of vaccine-derived virus in individuals

No long-term carrier stage in humans has been reported following wild poliovirus infection. However, prolonged excretion of wild poliovirus for 7 months has been demonstrated in two immigrant siblings in Finland (T. Hovi, unpublished data, 1999). Poliovirus excretion in an immune competent host is usually short-lived, seldom exceeding 2 months. In the early 1960s and 1970s, several instances of prolonged replication and excretion of vaccine-derived poliovirus (for up to 2 years) were reported, all among immunodeficient individuals (*36, 37*).

Patients with primary immunodeficiency disorders affecting the B-cell system appear to be at highest risk for prolonged poliovirus (and other enterovirus) replication and excretion (*38*). This group includes persons with either X-linked or sporadic agammaglobulinaemia (XLA), usually diagnosed in industrialized countries in infancy or early childhood (the prevalence of XLA in one industrialized country was estimated at 1 in 700 000 (*39*)); and common variable immunodeficiency (CVID), which occurs in approximately 1 in 50 000 Caucasians, but often remains undiagnosed for more than 5 years (*38*). Primary immunodeficiencies also occur in developing countries, but their prevalence is less well defined (*40*). In industrialized countries, patients with XLA or CVID, once diagnosed, receive regular intravenous immunoglobulin substitution therapy, which provides antibodies to poliovirus. Patients with XLA and CVID are prone to chronic echovirus and coxsackievirus infections of the central nervous system, and a new antiviral drug, pleconaril, is under trial for treatment of these enterovirus (including poliovirus) infections (*41, 42*).

Prolonged replication and excretion of vaccine-derived poliovirus among immunodeficient individuals, especially those with vaccine-associated paralytic poliomyelitis, is well documented (*43, 44*). One study in the 1960s in the United Kingdom reported that 28 of 30 antibody-deficient individuals given monovalent OPV excreted polioviruses for <1 month. Two individuals in this study developed long-term (>6 months) poliovirus excretion, one with type-1 and one with type-3 poliovirus (*36*).

A number of case reports show that, very rarely, patients with primary immunodeficiencies become long-term excretors, sometimes for years, after either receiving OPV prior to diagnosis of immunodeficiency or after community-acquired infection. For example, in 1977, a 3-year-old patient with agammaglobulinaemia was admitted to hospital in Japan suffering from poliomyelitis (*37*). Type-2 poliovirus was isolated from his stools. The patient had been diagnosed with agammaglobulinaemia in 1976, and poliovirus type 2 was isolated, retrospectively, from stool samples taken at that time. He had received OPV in 1975 and 1976. Excretion of the type-2 virus continued for 2 years after onset of poliomyelitis but became undetectable thereafter.

A 34-year-old patient with agammaglobulinaemia excreted vaccine-derived poliovirus type-2 over a 12-month period (*45*). He had no history of recent vaccination and probably acquired the infection from the community. Molecular analysis of the virus is consistent with prolonged replication (J. Martin, personal communication, 1999). In 1981, a 16-year-old immunodeficient patient with CVID was admitted to hospital in the USA with paralytic poliomyelitis (*46, 47*). The patient subsequently developed quadriparesis requiring mechanical ventilation and remained ventilator-dependent until his death in 1990. Poliovirus type 1 was isolated from the patient throughout the first year of his paralytic illness. These isolates differed in sequence from the Sabin vaccine strain by approximately 10%, suggesting poliovirus had replicated for about 7 years before the onset of the paralytic disease.

Excretion of poliovirus type 1 for a period of at least 5.5 years after onset of paresis of one arm and both legs in a child receiving immunoglobulin treatment for CVID has been documented (*48*). An isolate taken at onset of paresis showed 5.4 % change and an isolate taken 5.5 years after onset showed 8.5% change from the Sabin type-1 vaccine strain. Poliovirus excretion stopped spontaneously in this child 5.5–6 years after onset of paresis. The most recent OPV was administered to this child at least 3 years prior to onset of paresis, suggesting a potential excretion period of at least 8.5 years.

Recently, isolates of poliovirus have been obtained from a 27-year-old man with CVID

(National Institute for Biological Standards and Control, unpublished data). CVID was diagnosed when he was about 10 years of age. At that time he had already received OPV. Molecular analysis of poliovirus type-2 strains isolated by chance in 1995 and repeat samples in 1998 and 1999 showed >10% divergence from Sabin type 2, suggesting that this patient may have been excreting poliovirus for more than 10 years — a period consistent with his known vaccination history. He has no clinical signs of poliovirus infection. Attempts to stop his poliovirus excretion with oral immunoglobulin and/or pleconaril are in progress. This is to eliminate the risk that potentially virulent viruses would be able to spread efficiently in a non-immunized, susceptible population and to eliminate the potential risk of vaccine-associated paralytic disease in a patient with inherent continuous poliovirus replication.

Humoral immunodeficiencies may be severe, as in the patients described above, or more subtle. Patients with a selective IgA deficiency were immunized with OPV in a nationwide OPV campaign in Finland in response to a wild type-3 epidemic in 1984 (*49*). Stool samples were collected between days 2 and 35 and again at 6 months from eight patients who received a single dose of OPV. The IgA-deficient patients excreted virus for longer periods than immunologically competent controls but no long-term excretion (>6 months) was observed.

HIV infection as a potential risk factor for prolonged virus excretion

There are very limited data on secondary immunodeficiency as a risk factor for vaccine-associated paralytic poliomyelitis or prolonged poliovirus excretion (*46*). Current scientific data suggest that human immunodeficiency virus (HIV) infection is not a risk factor for paralytic poliomyelitis caused by wild-type virus or vaccine-derived virus (*50*). Only two case reports, from Romania (*51*) and Zimbabwe (*52*), have linked HIV infection and vaccine-associated paralytic poliomyelitis.

Studies are currently being conducted in Kenya to assess the likelihood of prolonged poliovirus excretion in a cohort of HIV-infected children; a similar study among adults is at the planning phase (Table 2).

Wild poliovirus/non-polio enterovirus recombinants

Parts of the poliovirus genome may be conserved through recombination with non-poliovirus enteroviruses. However, only recombinants carrying the wild-type poliovirus capsid can express poliovirus virulence because only these recombinants would be able to use CD155, the poliovirus receptor, and spread like wild-type poliovirus in the host. By definition, all such recombinants are still identified as wild polioviruses. Most recombinants that have been constructed by genetic engineering are impaired in replication (*53*). Even recombinants with wild-type poliovirus capsids would not necessarily have wild-type poliovirus virulence since growth in neuronal cells depends on interactions between cell factors and elements from the non-coding region of the virus genome. Recent experiments have shown that not all picornavirus non-coding elements can function well in cells of neuronal origin (*54*). On the basis of current evidence, recombinants are unlikely to pose a threat to the eradication programme.

Laboratory containment of polioviruses

From 1941 to 1976, 12 laboratory-associated cases of poliomyelitis were reported, including two deaths (*55*). Subsequently, no further cases have been reported, testifying to the effectiveness of vaccines and the advent of vastly improved laboratory facilities, technologies and procedures. However, because poliovirus may infect the gastrointestinal tract of immunized persons but not cause clinical disease, it is not possible to estimate the frequency of inapparent laboratory infections. A recent report illustrates the potential for such silent transmission (*56*). In 1992 a wild poliovirus type-1 strain used for IPV production was documented to have been transmitted from a worker in a vaccine production facility to his 18-month-old son. In another incident, a child was infected with a prototype strain of poliovirus type 3 commonly used in laboratories for research and vaccine production.

No evidence exists for poliovirus transmission to persons outside the laboratory through contaminated laboratory effluents being released into sewage, solid wastes being transported to landfills, or spent air being exhausted to the surroundings. Also, no evidence exists for the infection of others through contaminated workers' skin or clothing. Although theoretically possible, the probability of such transmission is difficult to document against the current background of high levels of immunity.

Thus, the risk of reintroducing wild poliovirus from the laboratory into the community is small, but not precisely measurable. We are now faced with the formidable task of locating the many laboratories that have stocks of infectious and potentially infectious wild poliovirus and ensuring that such stocks are destroyed or adequately contained in the laboratory. The key initial components to this task are national surveys of all medical/biological laboratories and the establishment of national, regional, and global inventories.

Virology laboratories with known poliovirus stocks and infectious materials can be relatively simply identified through surveys. The bigger challenge will be to identify all laboratories with potentially infectious clinical, epidemiological, research, or environmental specimens collected for other purposes, in a geographical area and at a time of wild poliovirus endemicity. Such laboratories may include those not usually associated with polioviruses, e.g. other microbiology, pathology, gastroenterology, nutrition, and environmental laboratories.

A primary function of the survey is to urge laboratories to dispose of all programmatically unnecessary wild polioviruses and potentially infectious materials, thus reducing the number of laboratories to be included in the global inventory. After poliomyelitis eradication, the high cost of constructing and maintaining high containment and maximum containment facilities is expected to further decrease the number of laboratories remaining in the global inventory. Because wild polioviruses are not required for diagnostic procedures, building containment facilities to house viruses that no longer serve a useful public health purpose is strongly discouraged. Completion of the national inventories is required before regional certification of eradication can be achieved.

As long as high immunization coverage continues, the consequences of transmission of wild poliovirus from the laboratory to the community will remain small. When OPV immunization stops, the consequences of such transmission could assume disastrous proportions. Reduction in the number of laboratories retaining wild poliovirus infectious materials and appropriate containment in those that do are critical. Success depends on the goodwill and thoroughness with which laboratories, institutions, nations, and regions exercise their responsibilities.

Intentional release of poliovirus ("bioterrorism" and biological warfare)

Whether current polioviruses are an effective weapon for bioterrorism or biological warfare is debatable (*57, 58*). After the world has stopped poliovirus vaccination, subsequent birth cohorts will rapidly increase the number of infants and children susceptible to poliovirus; however, population immunity to poliovirus will only decrease gradually (one birth cohort every year). The military could continue vaccination with IPV to eliminate any risk of paralytic disease among soldiers. However, if vaccination were discontinued, a completely susceptible population would emerge, and epidemics of unprecedented magnitude could result if wild-type virus were introduced — unprecedented because adolescents and adults are at higher risk for both paralytic consequences of infection and bulbar paralysis (*59, 60*). In addition, poliovirus might be engineered to be more neurovirulent, and this could change the ratio of paralysis to infection from the current 1:200 to much higher. In contrast to smallpox, even after the extinction of poliovirus, the poliovirus genome could potentially be synthesized in a well-equipped laboratory, transfected into appropriate cells, and produce infectious virus (*61*). All these scenarios for the intentional release of poliovirus remain, at present, highly speculative.

Future plans

A decision to stop poliovirus vaccination could potentially have serious public health consequences (e.g. the emergence of epidemics of paralytic disease), as well as substantial financial benefits. Consequently there needs to be an exhaustive review by groups of experts, policy-makers and the global community before any such step is taken. In addition, the decision should be endorsed by global policy-making bodies such as the World Health Assembly and the United Nations General Assembly.

To ensure that the best scientific evidence will be available to guide the decision-making process, an ambitious research agenda has been adopted and is currently being implemented. This agenda focuses on problems and areas where additional research would

Table 3. **Prolonged poliovirus excretion among immunodeficient persons, 1962–99**

Reference	Country	Year[a]	Age/Sex	Underlying immuno-deficiency disorder	Paralysis	Poliovirus serotype	VP1 nucleotide difference from Sabin progeny	Interval between last OPV dose and last positive specimen
MacCallum (*36*)	United Kingdom	1962	3 years/M	Hypogamma-globulinaemia	No	1	Not available	32 months
MacCallum (*36*), Martin (*62*)	United Kingdom	1962	20 years/F	Hypogamma-globulinaemia	No	3	2.3%	21 months
Hara (*37*)	Japan	1977	3 years/M	XLA	Yes	2	Not available	2 years
CDC (*47*)	USA	1981	17 years/M	CVID	Yes	1	10.0%	7.5 years
CDC[b]	USA	1986	11 years/F	CVID	No	2	10.8%	9.6 years
Misbah (*45*)	United Kingdom	1987	34 years/M	CVID	No	2	4.1%	>1 year
NIBSC[c]	United Kingdom	1995	25 years/M	CVID	No	2	12.1%	>10 years
CDC[b]	USA	1995	4 months/F	SCID	Yes	2	2.2%	3.7 years
Bellmunt (*48*)	Germany	1990	7 years/M	CVID	Yes	1	8.3%	ca. 8.5 years

[a] Year of onset of paralysis or first sample collection.

[b] Centers for Disease Control and Prevention, unpublished information.

[c] NIBSC, unpublished information.

help to fine-tune the risk estimates, or to determine the prevalence of conditions which may facilitate poliovirus replication and excretion in both industrialized and developing countries. Research is needed to provide further information in the following priority areas: the extent and duration of circulation of vaccine-derived poliovirus in populations; risk factors for prolonged replication of poliovirus among immunodeficient individuals; and assessment of the prevalence of immunodeficiency disorders in different populations (Table 2).

Conclusion

Recent progress towards global poliomyelitis eradication has led to a detailed re-examination of the issues that could affect the decision on "when and how to stop poliovirus vaccination". This decision must be based on the best available scientific evidence of the risks and benefits, as well as the availability of contingency plans and stockpiles of poliovirus vaccines, before the global policy-making bodies can endorse the discontinuation of poliovirus vaccination.

This article summarizes the current situation, provides an update on the processes and time frames for certification of eradication following containment of polioviruses and stopping of vaccination, and highlights some of the problems being addressed by an ongoing research agenda. Stopping poliovirus vaccination will remain work-in-progress until a decision is taken; now is the time to fully discuss the issues, answer questions, and seek consensus. ■

Résumé

Arrêter de vacciner contre la poliomyélite après l'éradication : problèmes et enjeux

Depuis 1988, le nombre de cas de poliomyélite rapportés dans le monde a baissé d'environ 85 % et le nombre de pays d'endémie connus ou supposés est tombé de plus de 120 à moins de 50. Comme l'éradication de la poliomyélite approche, les questions susceptibles d'influencer le moment et la façon d'arrêter de vacciner contre cette maladie prennent une importance cruciale. Du fait des risques et avantages potentiels qu'implique une telle décision, il faudra disposer, avant de pouvoir arrêter la vaccination, d'un dossier scientifique rigoureux, d'une analyse risque-avantages, de plans d'urgence, de stocks de vaccin antipoliomyélitique, et avoir reçu l'approbation des commissions mondiales en matière de politiques. Les bases scientifiques à l'appui de l'arrêt de la vaccination ont été examinées par l'OMS. Il est fondamental de savoir si la transmission des souches vaccinales excrétées pourrait se maintenir et donner lieu à une réémergence du poliovirus dans une future population non vaccinée. Plusieurs ensembles de données indiquent que la persistance de poliovirus dérivés de souches vaccinales est possible dans une population : Cuba et d'autres pays ont rapporté une persistance du virus à la suite de campagnes de vaccination de masse par le VPO ; le séquençage du génome d'isolats de poliovirus en provenance de pays indemnes de la maladie peut indiquer si du virus dérivé de la souche vaccinale a circulé de façon prolongée ; enfin, des enquêtes réalisées chez des groupes religieux opposés à la vaccination et des investigations sur des flambées de cas de poliomyélite fournissent des informations sur la capacité d'infection des virus dérivés de souches vaccinales. Jusqu'à maintenant, les faits semblent pencher pour une persistance limitée des poliovirus dérivés de souches vaccinales. Il faut cependant noter que les données dont on dispose actuellement ne sont pas exhaustives et que de nouvelles recherches sur la transmissibilité et la persistance de poliovirus dérivés de souches vaccinales sont nécessaires. L'excrétion prolongée de tels virus par des personnes atteintes d'un déficit immunitaire primaire pourrait être un des moyens de persistance des poliovirus dérivés de souches vaccinales. L'excrétion de poliovirus est habituellement de courte durée chez un hôte immunocompétent, et dépasse rarement 2 mois. Depuis le début des années 60, plusieurs cas de réplication et d'excrétion prolongées de poliovirus dérivés de souches vaccinales pendant 2 ans ou plus ont été rapportés, tous chez des personnes immunodéficientes. Les patients atteints de déficits immunitaires primaires portant sur le système des lymphocytes B semblent les plus à risque pour la réplication et l'excrétion prolongées de poliovirus (et d'autres entérovirus). On ne dispose que de données très limitées sur l'immunodéficience secondaire comme facteur de risque de poliomyélite paralytique associée à la vaccination ou d'excrétion prolongée de poliovirus. De nouvelles études sur la réplication prolongée des poliovirus chez les personnes immunodéficientes et l'évaluation des déficits immunitaires dans différentes populations devront être réalisées en priorité. La présente table ronde présente l'état actuel des connaissances, fait le point sur les processus et les échéances de la certification de l'éradication, du confinement du virus et de l'arrêt de la vaccination, et met en lumière certaines des questions scientifiques restant à résoudre et qui devront faire l'objet de nouvelles recherches.

Resumen

Suspensión de la vacunación contra el poliovirus tras su erradicación: problemas y desafíos

Desde 1988 el número de casos de poliomielitis notificados en todo el mundo ha disminuido casi un 85%, y el número de países donde se sabe o se sospecha que la poliomielitis es endémica ha disminuido de >120

a <50. Al aproximarnos a la erradicación de la poliomielitis, cobran gran importancia las cuestiones relativas al momento y la manera de interrumpir la vacunación contra el poliovirus. Considerando los riesgos y beneficios potenciales inherentes a tal decisión, antes de poder interrumpir la vacunación será necesario contar con lo siguiente: los mejores conocimientos científicos disponibles, un análisis de los riesgos y beneficios, planes de contingencia, reservas de vacuna contra el poliovirus, y la aprobación de los comités mundiales normativos. La OMS ha examinado la base científica disponible para interrumpir la inmunización contra la poliomielitis. Una cuestión crucial es si la transmisión de las cepas de vacuna excretadas puede prolongarse de manera que el poliovirus consiga reaparecer en una futura población sin vacunar. Varias series de pruebas aportan información sobre la posible persistencia en la población del poliovirus vacunal: Cuba y otros países notifican la persistencia del virus tras las campañas masivas de administración de OPV; la secuencia genómica de aislamientos de poliovirus procedentes de países donde no hay poliomielitis muestra si los virus vacunales han circulado durante periodos prolongados; las encuestas realizadas entre los grupos religiosos que se oponen a la vacunación y los estudios de los brotes de poliomielitis aportan información sobre la capacidad infecciosa del virus de las vacunas. Hasta el momento, las pruebas tienden a mostrar una persistencia limitada del poliovirus derivado de la vacuna. No obstante, hay que señalar que los datos actualmente disponibles no son exhaustivos y que son necesarios más trabajos sobre la transmisibilidad y la persistencia de los poliovirus derivados de la vacuna. Un medio de persistencia de los poliovirus vacunales podría ser la excreción prolongada de los mismos por individuos con inmunodeficiencia primaria. La excreción de poliovirus por un huésped inmunocompetente es generalmente breve, rara vez supera los dos meses. Desde principios de los años sesenta, se han registrado varios casos de replicación y excreción prolongadas de poliovirus derivados de vacunas durante dos años o más, todos en individuos inmunodeficientes. Los pacientes con trastornos de inmunodeficiencia primaria que afectan a los linfocitos B son al parecer los que más riesgo presentan de replicación y excreción prolongadas del poliovirus (y otros enterovirus). Hay muy pocos datos sobre la inmunodeficiencia secundaria como factor de riesgo de poliomielitis paralítica asociada a vacunas, o de excreción prolongada del poliovirus. Entre las investigaciones adicionales necesarias, es prioritario realizar nuevos estudios sobre la replicación prolongada del poliovirus entre los individuos con inmunodeficiencia, y evaluar los trastornos de inmunodeficiencia en distintas poblaciones. Este artículo de la mesa redonda resume el estado actual de los conocimientos, ofrece una puesta al día sobre los procesos y los plazos para la certificación, la contención y la interrupción de la vacunación, y destaca algunas de las cuestiones científicas pendientes que serán objeto de nuevas investigaciones.

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