

Poliomyelitis eradication

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Abstract

Since the poliomyelitis eradication program began in 1988, the number of poliovirus infected continents and countries have decreased from five to two and from greater than 100 to 53, respectively. A nearly 90% reduction in the incidence of polio has been achieved with a corresponding decrease in virus genomic heterogeneity. Major challenges to eradication remain in south Asia and Africa in those areas with hot and humid climates, high population density, and high birth rates. Of particular concern are countries with ongoing social unrest and poor health infrastructure. With the approaching eradication of polio, post-eradication issues are now being addressed. The World Health Organization (WHO) draft plan for containment of wild polioviruses has been published for comment. Commissions and committees for certification of eradication have been established. Still under discussion is the question of the appropriate strategy for stopping oral polio vaccine (OPV) immunization. Studies are underway to determine whether vaccine-derived polioviruses will continue to circulate after OPV cessation and the potential disease consequences of that circulation. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Poliomyelitis; Humid climates; WHO; Vaccine

1. Introduction

In preparation for eradication achievement, in 1988, the World Health Assembly adopted the target of global poliomyelitis eradication by the year 2000. The World Health Organization (WHO) coordinates this global effort which is

supported through public and private partnerships and carried out by the polio endemic countries of the world. Remarkable progress has been achieved in the 10 years since the initiative began. Although significant challenges to eradication remain for those countries with ongoing social unrest and poor health infrastructure, global polio eradication is in sight. Increasing attention is being turned to the post-eradication issues of laboratory containment of polioviruses, certification of eradication, and cessation of immunization.

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2. Strategies for polio eradication

The global eradication initiative is built on four basic strategies: (1) routine immunization; (2) supplementary immunization through National Immunization Days (NIDs); (3) house-to-house mopping up and (4) surveillance (World Health Organization, 1997b).

2.1. Routine immunization

Routine immunization provides the foundation for a successful eradication initiative. The goal is to achieve and maintain high immunization coverage with all vaccines recommended for infants, including three or more doses of oral polio vaccine (OPV3).

2.2. Supplementary immunization

Supplementary immunization, through annual NIDs or sub-national immunization days (SNIDs) for all children under the age of 5 years, regardless of prior immunization history, interrupts virus transmission (Birmingham et al., 1997). In endemic countries, high-quality NIDs are needed for a minimum of 3 years.

2.3. Mopping-up

Mopping-up immunization campaigns break the final chain of wild poliovirus transmission in specific high-risk areas during the last phase of polio eradication. Mopping-up is surveillance driven, with OPV delivered house to house to all children in the targeted areas.

2.4. Poliovirus surveillance

Poliovirus surveillance guides immunization strategies, monitors eradication progress, and serves as the basis for certification (World Health Organization, 1998c). The cornerstone of surveillance for polio eradication is the detection, reporting and laboratory investigation of all acute flaccid paralysis (AFP) cases, regardless of presumed etiology, among children under 15 years of age. One AFP case confirmed by the laboratory

as poliomyelitis may represent several hundred to several thousand sub-clinical wild poliovirus infections. AFP surveillance is based on the assumption that the minimum number of infections required to sustain transmission in a population is (over time), equal to or greater than the number required for clinical expression (Eichner and Dietz, 1996). Despite the high ratio of sub-clinical to clinical polio cases, AFP surveillance has proven to be a highly effective tool.

The quality of polio surveillance is monitored by the sensitivity of AFP reporting and stool specimen collection. The target rate of non-polio myelitis AFP is at least one case per 100 000 population under 15 years of age. The target for completeness of specimen collection is two adequate stool specimens within 14 days of paralysis onset from at least 80% of AFP cases.

The key to effective poliovirus surveillance is the Global Poliovirus Laboratory Network (Hull and Dowdle, 1997), now consisting of 30 provincial (China), 82 national/sub-national, 15 regional, and six specialized laboratories. The specialized laboratories and some regional laboratories are fully equipped to provide virus genomic characterization, which is critical for programme guidance and monitoring of eradication progress. All network laboratories use standard WHO procedures (World Health Organization, 1997a,b). Quality assurance is provided by a process of formal laboratory accreditation by WHO. Non-accredited laboratories are required to send samples of AFP stool specimens to a fully accredited national or regional reference laboratory.

3. Eradication progress and challenges

Since the program began 10 years ago, the number of poliovirus infected continents and countries have decreased from five to two and from greater than 100 to 53, respectively. Currently, 53 countries are listed as endemic (19 with focal transmission and 34 with recent transmission) and 120 as polio-free. A nearly 90% reduction in the incidence of polio has been achieved with a corresponding decrease in virus genomic heterogeneity (Kew et al., 1995). During 1997,

5120 polio cases were reported. The 1997 total exceeds the number of cases confirmed in 1996 (4079), largely due to improved surveillance (World Health Organization, 1998d).

In 1994, the American region was certified as poliomyelitis free and remains so (Robbins and de Quadros, 1997). In the Western Pacific region, nine cases of virologically confirmed poliomyelitis were reported in 1997. All cases were from the Mekong River area of Cambodia and Viet Nam. The last case reported from the Western Pacific was in March 1997. In Europe, only six poliovirus type 1 cases were confirmed by isolation in 1997. All were in southeastern Turkey.

Major challenges to polio eradication remain in those areas with poor health infrastructure and at high risk of virus transmission. The greatest challenges are in the large, densely populated countries of south Asia, west and central Africa, and the Horn of Africa. These countries represent the majority of cases in the world and also pose the greatest risk of reseeding neighboring countries. Each of these reservoirs also contain countries or areas that are severely affected by conflict where implementation of polio eradication activities is particularly difficult.

In Africa, inadequate funding for health services and civil disturbances have resulted in very low levels of routine immunization coverage. Seven countries were unable to immunize even 50% of infants in the first year of life in 1997. Large and dense populations in these countries combined with low levels of population immunity have permitted free circulation of polioviruses.

By late 1998, NIDs have been conducted in all African countries with the exception of the DR Congo, Liberia and Sierra Leone. Nearly 60 million children were immunized with two doses of OPV during NIDs in 1997. Highest priority is being given to implementing NIDs in countries where political instability has either prevented or limited the scope of immunization campaigns. The need to train health workers, establish a cold chain, and surmount the increasing difficulties in transportation and communication increases the total cost of polio eradication in many African countries. The average cost of \$1 for immunizing a child during an NID may increase 2- to 3-fold

in countries with armed conflict and poor infrastructure.

No wild poliovirus was isolated in southern and eastern Africa during 1997, but surveillance in some countries is not yet geographically representative or sufficiently sensitive. Genetic analysis of poliovirus isolates have identified Nigeria and the Democratic Republic of the Congo (Zaire) as the major reservoirs of polioviruses on the African continent. These two countries represent 30% of the region's population.

In south Asia, NIDs have been conducted for 3 or more years in all countries but Afghanistan, which has conducted two national campaigns. Although very large numbers of children have been immunized (i.e. 127 million children in a single day in India) and reported coverage for the NIDs has exceeded 90%, wild poliovirus transmission still persists. The countries of south Asia provide ideal conditions for transmission of polioviruses—hot and humid climates, large populations, high population density, and high birth rates. The conditions prevalent in south Asia may dictate that extraordinary efforts will be necessary to interrupt poliovirus transmission. The number of polio cases reported in both Pakistan and India doubled between 1996 and 1997. While localized epidemics occurred in both countries, the increase is due primarily to better case finding resulting from improving surveillance. Interrupting poliovirus transmission in Pakistan and India is a priority, not just because of the numbers of cases involved. Poliovirus strains originating Pakistan and India continue to be imported into the Gulf countries, Europe and North America (Kew et al., 1995; Mulders et al., 1995). Continuing poliovirus transmission in south Asia, therefore, jeopardizes the progress achieved elsewhere in the world.

4. Polio post-eradication issues

The eradication of poliovirus in nature brings with it three major issues: ensuring laboratory containment of wild polioviruses; certifying that eradication has occurred and adopting a strategy for stopping immunization. The WHO draft plan for containment of wild polioviruses was pub-

lished for comment in June 1988. Certification commissions and committees have been established by WHO to judge if and when polio has been eradicated. Still under discussion is the question of the appropriate strategy for stopping OPV immunization.

4.1. Laboratory containment of polioviruses

Laboratories will be the only remaining source of the virus after polio eradication (Dowdle and Birmingham, 1997). Poliovirus biosafety concerns have been minimal since the introduction of polio vaccines, over 30 years ago. Technologies and biosafety practices have continued to reduce the risk of poliovirus laboratory infections and contamination of the environment. The probability of reintroducing wild polioviruses into the community through laboratory-associated poliovirus infection is now small, but the consequences of such an infection grow greater with time. After cessation of immunization, a chance reintroduction of wild poliovirus from the laboratory represents a threat to public health of global proportions.

Preventing a laboratory-associated reintroduction of poliovirus presents a formidable, but achievable, challenge. All wild polioviruses and potentially infectious materials (collected for other purposes at a time and place in which polioviruses were endemic) must be adequately contained, rendered non-infectious, or destroyed. A proposed Global Action Plan and Timetable for Safe Handling and Maximum Laboratory Containment of Wild Polioviruses and Potentially Infectious Materials was published by WHO for comment in 1998 to meet that challenge (World Health Organization, 1998b). The plan is linked to the major eradication objectives and consists of three phases.

4.1.1. Phase I

Pre-eradication covers the present era when wild poliovirus is decreasing or no longer circulating in many areas of the world. Beginning in 1999, nations must: (1) identify and develop an inventory of laboratories that have wild poliovirus infectious materials or potentially infectious materials; (2) institute in all such laboratories en-

hanced biosafety level-2 (BSL-2/polio) procedures for safe handling of all such infectious or potentially infectious materials and (3) establish a plan for implementation of Phase II biosafety requirements.

4.1.2. Phase II: post-eradication

This phase begins 1 year after detection of the last wild poliovirus, when the probability will be high that all human transmission has ceased (Eichner and Dietz, 1996). The plan proposes that all wild poliovirus infectious and potentially infectious materials will be placed under maximum containment (BSL-4). During the first year of Phase II, all laboratories possessing such materials will carry out one or more of the following three options: (1) implementation of maximum (BSL-4) containment procedures; (2) transfer of wild poliovirus infectious and potentially infectious materials to WHO-designated repositories; (3) render such materials non-infectious, or destroy them, under appropriate conditions.

Comments on the proposed plan received by WHO at the time of this writing strongly favor reducing the containment levels Phase II from BSL-4 to a modified BSL-3. Justification for the lower level of containment is that immunization of the population will continue until Phase III, thus lessening the risk to the community. Although the final plan will not be published by WHO until late 1999, it is likely that growing consensus for a modified BSL-3 recommendation will prevail.

4.1.3. Phase III: post-oral polio vaccine immunization

This phase begins with the world-wide cessation of OPV administration. Wild poliovirus infection and potentially infectious materials will be under maximum containment (BSL-4). Increased control of OPV and OPV-derived viruses will be required to prevent the theoretical circulation of these viruses in unimmunized populations. All facilities, including laboratories, clinics, immunization centers, physicians' offices, and other sites with OPV or OPV-derived viruses will be required to comply with the recommendations for high containment.

The reintroduction of wild polioviruses from the laboratory into the community is preventable. The major challenges to fully implementing the plan will be for nations to ensure that all laboratories are informed and comply with the laboratory containment requirements. The proposed plan and implementation guidelines will be piloted in several WHO regions. Based on these experiences and comments received, the final plan will be published by WHO in late 1999.

4.2. Certification of the eradication of poliomyelitis

WHO convened the first meeting of the Global Commission for the Certification of the Eradication of Poliomyelitis in 1995. The global commission established that certification is to be based on the principle that the risk of unrecognized virus circulation would rapidly diminish and approach zero after an appropriate period of time had passed during which no virus was detected despite excellent surveillance (World Health Organization, 1997a, 1998a). Regional certification commissions have been established in all WHO regions. Operationally, national certification committees in each country will present documentation of eradication to the appropriate regional certification commissions for approval. The regional certification commissions will certify eradication in the region as a whole then report to the global commission. Global certification requires that:

1. Indigenous wild polioviruses are absent for a period of at least 3 years. National committees must provide documentation that the surveillance systems within each country of the region are sufficiently sensitive to detect wild poliovirus circulation, should it occur. AFP surveillance is considered the gold standard for endemic or recently endemic countries. Industrial countries that have been polio free for many years and cannot effect AFP surveillance must provide documentation based on a continuation of surveillance and investigation of all suspect polio cases and geographically representative enterovirus surveillance.

2. Regional commissions have verified the documentation of national committees.
3. Appropriate measures are in place to detect and respond to any importation of wild polioviruses.
4. Containment of wild poliovirus and potentially infectious materials meets all requirements.

The global certification commission will require that all certification standards be met for at least a 3-year period after the last wild poliovirus is detected anywhere in the world.

4.3. Stopping immunization

Continued immunization against a disease is difficult to justify economically or ethically when the etiologic agent no longer exists. For polio, stopping immunization will prevent vaccine-associated paralytic poliomyelitis (VAPP) and injection-related adverse events for IPV. Stopping all polio immunization will result in global savings of US\$ 1.5 billion annually (World Health Organization, 1997b).

In March 1998, the World Health Organization convened a meeting of experts to review current knowledge and identify research needs to determine how and when polio immunization can be stopped (World Health Organization, 1998e). The meeting concluded that all vaccination against polio can and should stop when there is sufficient assurance of the global eradication of polioviruses, the containment of all laboratory poliovirus stocks, and evidence that vaccine-derived polioviruses will not circulate indefinitely. Mechanisms are in place to ensure the first two requirements of the recommendations are met. Remaining, however, are the data to demonstrate that vaccine virus circulation will not persist.

The choice of strategies for stopping immunization depends on whether vaccine-derived polioviruses continue to circulate after OPV cessation and the potential disease consequences of that circulation (Cockburn, 1961; Dove and Racaniello, 1997; Hull and Aylward, 1997). Although multiple studies have demonstrated transmission of vaccine-derived polioviruses from person to person in family situations, little is

known about circulation in the community, especially in settings of susceptible populations. (Fox and Hall, 1980; Fine and Carneiro, 1998). Potential limited sub-clinical spread within the community has been considered a positive attribute of the vaccine.

There is no current epidemiologic evidence to support the theory that OPV strains would continue to circulate and revert to wild type viruses. For 36 years mass campaigns have been the only method for immunizing children against polio in Cuba. Extensive virologic and serologic surveillance during the 10 months between mass campaigns did not demonstrate that vaccine-derived virus persisted beyond 2–3 months (Ochoa and Lago, 1987). Hungary also conducted only annual mass immunization campaigns in the early 1960s with findings similar to those in Cuba. Again, the vaccine viruses were not found in the community beyond 3 months (Domok et al., 1962).

Data from polio outbreaks also suggest limited transmission of vaccine-derived polioviruses, or at least that such viruses are substantially less transmissible than wild outbreak strains. Wild polio outbreaks have occurred in under-immunized populations in a number of instances where there has been ample opportunity for circulation of vaccine-derived strains. Preliminary data from genomic sequencing of vaccine-derived isolates from children with AFP in an under-immunized area in Brazil also failed to confirm any long-term circulation of vaccine-derived strains (World Health Organization, 1998e). Although encouraging, current data are inadequate to provide assurance that one or more vaccine-derived viruses will not persist.

The persistent excretion of vaccine-derived viruses by immuno-compromised individuals requires further investigation. Two of 30 immunodeficient individuals in a United Kingdom study excreted vaccine-derived virus for more than 6 months (World Health Organization, 1998e). Several reports describe the excretion of vaccine-derived poliovirus for periods ranging from 2 to 3.5 years (MacCallum, 1964; Yoneyama et al., 1982). The longest period of reported excretion has been a type 1 vaccine-derived poliovirus isolated from an immunodeficient patient with

VAPP. This virus was found to differ by about 10% in VP1 nucleotides from the Sabin strain (Kew et al., 1998). Based on the observation that poliovirus genomes evolve by genetic drift at a rate of about 1.2% per year, these findings are consistent with infection beginning about 8 years earlier. The frequency and the epidemiologic significance of long-term shedding of vaccine-derived virus by immunodeficient individuals remain to be determined, particularly in developing countries.

Nineteen studies are underway world-wide in 1998 to evaluate the potential for persistent circulation of vaccine-derived strains after OPV immunization is stopped and the potential for their reintroduction from immunodeficient individuals. These include further studies in Cuba, searches for vaccine-derived virus in high-risk environments where crowding and poor sanitation would facilitate poliovirus transmission, patients with primary and secondary immunodeficiencies, and retrospective studies of non-Sabin-like strains.

If vaccine-derived polioviruses do not persist, the least costly strategy for stopping polio immunization would be simply to stop OPV immunization (Cochi et al., 1997). Cessation would have to be synchronized among countries to prevent the potential risk of continued cross-border transmission to countries with rapidly increasing numbers of unimmunized cohorts. Another proposed approach would be the sequential deletion of the three Sabin types from the current trivalent OPV formulation. Type 2 poliovirus is the first to disappear in nature and would be the first vaccine strain removed. Type 3 would probably follow. However, because of earlier reports of increased risk of vaccine-associated poliomyelitis with monovalent type 3 vaccine, it is unlikely that such a scheme could be employed without additional safety and efficacy trials to gain regulatory approval. A third proposal would be to replace oral polio vaccine with IPV until the absence of circulating vaccine-derived virus could be assured. However, IPV administered in WHO's current infant immunization schedule (6, 10 and 14 weeks of age) is unlikely to provide adequate protection against poliovirus infection. Furthermore, low immunization coverage among the populations at highest risk for persistent circulation (e.g. low

immunization coverage, dense population) would severely limit the effectiveness of this approach. Finally, new genetically stable polioviruses could replace the current Sabin strains. Several promising genetically engineered candidates are available, but extensive evaluations would have to be done. If a new, stable OPV is to become available in a useful timeframe, preliminary plans must begin now. Regardless of which strategy is recommended for stopping immunization, stockpiles of OPV must be maintained for emergencies.

5. Discussion

The current timetable of polio eradication calls for interruption of poliovirus transmission worldwide by the end of the year 2000 (Fig. 2). Laboratory containment of polioviruses would begin 1 year after the last wild poliovirus was detected (2001) with containment complete 1 year later (2002). The last WHO region would be certified in the year 2003 with final global certification in approximately 2005. Cessation of OPV immunization would potentially occur a few years later, the exact time to be decided after global certification. Thus, OPV immunization can be expected to continue for at least another 10 years from today.

During these next 10 or more years, questions will continue to be asked. How can we be sure that polio is eradicated? How can we be certain of full compliance with laboratory containment? How can we be sure that the chosen strategy for stopping OPV immunization is without risks?

Proving the negative is, of course, impossible, but confidence grows greater with time. After more than 20 years since the last case of smallpox, there are those who feel that the virus may be still lurking out there somewhere, but the numbers of such skeptics continue to decrease with time.

We can never be certain that every specimen that possibly might contain infectious materials has been destroyed or placed under containment. The greatest danger, however, comes not from unsuspected or unknown clinical specimens, but from actively working with wild polioviruses. The risk of laboratory-associated infections or environmental contamination is greatest when the

virus is being grown, produced in large volumes, and manipulated in the laboratory. Experience with the smallpox virus predicts that poliovirus biosafety restrictions will be respected world-wide and that laboratory work can be safely performed under appropriate conditions of containment.

It is too early to pass judgement on a strategy for stopping OPV immunization. The data is not yet available from susceptible populations. Only in recent years, when it became apparent that polio could be eradicated and immunization stopped, has there been sufficient interest in gathering data to begin to answer this question. A number of studies are currently underway which in a year or so should give a much clearer picture of the risk of vaccine virus persistence in susceptible populations and the possible consequences of OPV cessation.

The year 2000 target date for interruption of poliovirus transmission is 28 months away from the date of this conference. Time is short, and many challenges remain. The goal is biologically feasible, but the final strategy must be tailored to meet the biological, political and financial requirements of the remaining reservoirs in south Asia, west and central Africa, and the Horn of Africa. Achieving this goal will require additional human and financial resources and a recommitment of all nations to completion of the task.

Finally we should revisit the origins of the current eradication initiative. After the initial success of the Expanded Programme on Immunization in the late 1980s, coverage began to fall. Launching the eradication initiative in the Americas therefore sought two objectives: to strengthen and further develop national health systems while ridding the world of polio (Aylward et al., 1998; Taylor and Waldman, 1998). Strengthening and further developing national health systems becomes increasingly important as the initiative enters into its most challenging phase of eradicating the virus in countries with little or no health resources and infrastructure. The eradication of polio offers the opportunity to strengthen health systems and enhance leadership development and managerial skills that can be readily adapted to meet the needs of other national public health priorities.

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