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Future of Polio Vaccines

Summary

Over the past half-century, global use of highly effective vaccines against poliomyelitis brought this disease to the brink of elimination. Mounting evidence argues that a high level of population immunity must be maintained to preserve a polio-free status of the entire world after wild poliovirus circulation is stopped. Shifting factors in the risk-benefit-cost equation favor the creation of new poliovirus vaccines to be used in the foreseeable future. Genetically stable attenuated virus strains could be developed for an improved oral poliovirus vaccine, but proving their safety and efficacy would be impractical because of the enormous size of the clinical trials required. New versions of inactivated poliovirus vaccine (IPV) that could be used globally should be developed. An improved IPV must be efficacious, inexpensive, safe to manufacture, and easy to administer. Combination products containing IPV along with other protective antigens should become part of routine childhood immunizations around the world.

Keywords

Oral Polio Vaccine (OPV); Inactivated Polio Vaccine (IPV); immunization; eradication; infectious disease control; global vaccination program

The remarkable concept of a vaccine against infectious diseases, realized more than 200 years ago, was arguably the most significant discovery in the history of preventive medicine. Subsequent development of numerous viral and bacterial vaccines dramatically reduced or completely eradicated a variety of dangerous infections of humans and animals. With the resulting epidemiologic changes that follow introduction of a vaccine, the balance between its cost, benefits, and risks have often required revisions in the way these products are used. The most dramatic example was the decision to discontinue routine smallpox immunization following elimination of variola virus circulation because the cost of vaccine administration and the risk of adverse reactions were considered excessive compared to the possibility of reintroduction of the virus into circulation. Two decades later, the evolving perception of the threat of bioterrorism led to the creation of a new generation of smallpox vaccines, this time with a significantly improved safety profile and based on the current manufacturing techniques. Thus, vaccines must co-evolve together with the pathogens and diseases they were intended to prevent.

Two vaccines against poliomyelitis introduced in the middle of the last century are among the most successful and widely used vaccines ever produced. The initial introduction of inactivated poliovirus vaccine (IPV) led to a dramatic reduction of polio morbidity in developed countries. In most of the world, it was soon replaced by live attenuated oral poliovirus vaccine (OPV), which became the main tool used in the worldwide effort to eradicate poliomyelitis that was launched in 1988. This campaign, which represents a mixture of dramatic successes and frustrating setbacks, is currently at least 9 years behind its original schedule. Nevertheless, new approaches and tools that were recently introduced leave hope that eventual success may be possible, and that circulation of wild polioviruses will soon be stopped. Therefore, it is imperative that review of the options for future worldwide protection against poliomyelitis be conducted immediately. Do we need vaccination after wild poliovirus circulation has been stopped? If so, what vaccine is optimal for post-eradication immunization programs? How

could polio vaccines be improved and made more safe, efficacious, cheaper, and easier to deliver? In this review, we attempt to address these questions.

Poliomyelitis and Poliovirus Vaccines

Poliomyelitis is an acute viral disease affecting motor neurons within the brainstem and spinal cord caused by three serologically distinct human polioviruses that are the prototypic members of the genus *Enterovirus*, family *Picornaviridae*, a large family of small, single strand RNA viruses. In temperate climates, polioviruses circulate in a seasonal pattern with peak activity in summer and fall, and transmission occurs by close personal contact, mostly via the fecal-oral route. Ingested polioviruses bind to well-identified cell surface receptors implant in the oropharynx and distal small bowel, penetrate the mucosa via specialized microfold cells (M cells) and other epithelial cells and replicate in underlying submucosal lymphoid tissues [1]. Viremic spread to systemic reticuloendothelial tissue and occasionally the central nervous system ensues although the final path by which polioviruses reach the spinal cord and brain remains unsettled [2–6].

While most poliovirus infections result in no illness or produce only self-limited symptoms, a small proportion (0.1 to 1%) of infections progress to motor weakness, which may range from mild weakness of a single extremity to complete quadriplegia with or without cranial nerve dysfunction [7–9]. Pregnancy [10–12], B cell immunodeficiency [13,14], and strenuous exercise during the incubation period [15,16] increase the risk of developing paralytic disease. The most serious complication of paralytic poliomyelitis is respiratory failure from paralysis of the diaphragm and intercostal muscles due to involvement of the motor centers of the brainstem (i.e., bulbar polio) and the spinal cord. Most patients experience some recovery of function in the weeks to months after acute disease, but residual motor deficits remain in about two-thirds of initially paralyzed patients, ranging from minor debility to permanent, flaccid paralysis.

The emergence of epidemic poliomyelitis in the Western world is interlinked with progressive urbanization of western society and improving sanitary standards that delayed the age of infection beyond infancy and the protection of passively acquired maternal antibodies [9]. In North America, successively larger epidemics of paralytic poliomyelitis occurred between 1894 and 1954 that galvanized public attention unlike any other disease [17]. The nationwide, grassroots appeal of the National Foundation for Infantile Paralysis (“March of Dimes”) raised millions of dollars that not only supported clinical care and rehabilitation care for poliomyelitis victims, but also scientific research with a goal of preventing paralytic poliomyelitis. With the support of the National Foundation, Enders, Weller, and Robbins succeeded in growing the Lansing strain poliovirus in human embryonic tissues, an achievement that opened the door to vaccine development [18]. In 1955, the formalin-inactivated poliovirus vaccine (IPV) developed by Jonas Salk at Pittsburgh was found to be effective in a monumental trial involving more than 1.8 million U.S. school children [19]. Rapid distribution of Salk IPV reduced the incidence of paralytic poliomyelitis in the U.S. from 13.9 cases per 100,000 in 1954 to 0.5 cases per 100,000 in 1961.

In the meantime, other investigators were studying live, attenuated polioviruses with a goal of maintaining sufficient gastrointestinal replication to induce immunity with viruses which remained avirulent for monkeys [20]. Several of these strains were extensively tested in humans in a number of international locations and ultimately three monovalent strains developed by Albert Sabin were licensed for use in the United States in 1961 and 1962. Within the next two years, more than 100 million OPV doses were given via community programs (“Sabin Sundays”) organized by local health departments and medical societies. Trivalent OPV was introduced in 1963 and thereafter rapidly replaced IPV for routine use in all but three countries

(Finland, Sweden and the Netherlands) because of superior immunogenicity, the ease of oral administration as opposed to intramuscular injection, induction of mucosal immunity, and the public health benefit of spread of live vaccine viruses from immunized to unimmunized contacts.[20] These advantages of OPV were considered to outweigh the known occurrence of vaccine-associated paralytic poliomyelitis (VAPP) that resulted from reversion of attenuating mutations in the vaccine viral genome and affected about 8–10 OPV vaccinees or their close contacts in the United States each year [21,22].

After the elimination of wild poliovirus circulation in the U.S. in 1979, it became apparent that even a small number of VAPP cases could not be tolerated if a safe and equally effective vaccine were available. The development of “enhanced potency” IPV vaccines in the 1980s met this need based on their ability to induce comparable or superior antibody responses compared with trivalent OPV [23,24]. During the past decade, IPV has replaced trivalent OPV in routine childhood immunization programs in most western countries with virtually no evidence of re-introduction of paralytic poliomyelitis.

The Global Poliomyelitis Eradication Initiative

By the mid-1970s, the success of OPV around the world sparked great optimism about the possibility of complete eradication of the disease. Sabin proposed that this could be accomplished by breaking the chains of transmission of wild polioviruses with massive use of OPV delivered on multiple national immunization days (NIDs) to a country’s entire population under the age of five, regardless of whether the children had received prior vaccine [25,26]. This would eliminate the reservoir of susceptible individuals and possibly exert interference against circulating wild polioviruses. The concept was proven to work in Brazil and the Dominican Republic, where two annual NIDs conducted three months apart led to complete elimination of wild poliovirus circulation. The success led the Pan American Health Organization to resolve in 1985 to eradicate polio from the western hemisphere, and in 1991, the last case of endemic polio was registered in Peru.

At about the same time, Rotary International became an advocate for global eradication of poliomyelitis, and in 1988 the World Health Assembly set the goal for complete eradication by the year 2000, supported by donations from several western country governments and a number of nongovernmental organizations and charities and collaborating with local public health ministries around the world. The same strategy proven to be successful in the Americas -- i.e., employment of national and sub-national immunization days coupled with rigorous acute flaccid paralysis (AFP) surveillance and virological confirmation of all polio cases, was used to eliminate poliomyelitis from individual countries and world regions. By year 2000, the worldwide incidence of poliomyelitis had declined from the estimated annual 350,000 cases in 1988 to about 1,000. During this time, wild type 2 virus disappeared completely from circulation. However, a number of unanticipated obstacles to stopping virus transmission developed, and progress of the eradication campaign has stalled, with a global incidence remaining between 1,000 and 2,000 for the last eight years. First, an outbreak of paralytic poliomyelitis caused by pathogenic vaccine-derived poliovirus (VDPV) occurred in Haiti and the Dominican Republic in 2000, lasting for about two years. The highly neurovirulent strains isolated from this outbreak were recombinants between a variant derived from Sabin OPV type 1 virus and some unidentified Group C enteroviruses [27]. Genetic instability of the Sabin vaccine strains had been known before; indeed, rare reversion of vaccine viruses to neurovirulence was always responsible for approximately one case of poliomyelitis per ~750,000 first-dose recipients of the vaccine [21], but the ability of these revertant viruses to sustain transmission was unknown. Therefore it came as an unpleasant revelation that vaccine poliovirus could revert and regain pathogenic properties indistinguishable from those of wild strains.

In the following decade, more than ten outbreaks caused by vaccine polioviruses of all three serotypes were identified [28]. The most extensive of these outbreaks, with over 100 confirmed paralytic cases, was registered in northern Nigeria in 2006 [28,29], and is still not contained as of this writing. Ironically, the responsible vaccine component is serotype 2, which had been eradicated previously from the global wild virus population. It occurred after suspension of local immunization in several states in 2003, followed by reintroduction of vaccine poliovirus into the community when the program resumed about a year later. As a result of the accumulated reservoir of susceptible individuals in which rapid circulation of the vaccine virus could occur, multiple evolutionary lineages of pathogenic VDPV arose and continue to spread. A similar, but much smaller, emergence of virulent viruses was observed previously under similar circumstances in the Soviet Union in the mid-1960s [30]. The more the vaccine strains circulate, the higher the likelihood that they will evolve and revert to or generate (by recombination with other non-polio enteroviruses) viruses with the same virulence properties as wild type. The ease with which pathogenic VDPVs appear in populations with diminished population immunity suggests that vaccine coverage must be maintained at the highest level, and no gaps in population immunity to poliovirus should be permitted.

An additional potential source of pathogenic VDPV strains in individuals persistently infected with vaccine poliovirus, usually as a result of B cell immunodeficiency. These individuals fail to clear the virus after immunization and may excrete its progeny for years [31]. The persisting virus continues to evolve and accumulate mutations, and variants with progressively increased fitness may be shed in the feces. Highly evolved VDPV strains have occasionally been isolated from environmental samples [32,33]. The origin of these strains is unknown; but they serve as a warning that OPV use is not compatible with ultimate polio eradication.

Perhaps the most puzzling obstacle to the eradication campaign became evident in the states of Uttar Pradesh and Bihar in northern India, where two serotypes of wild poliovirus continue to circulate with unusual robustness despite long-term, uninterrupted, massive immunization efforts. Seroconversion rates per dose of OPV are extremely low, requiring 10–15 consecutive immunizations per child to achieve levels of population immunity needed to stop transmission of the virus [34]. This low vaccine efficacy, coupled with very high birth rates, leaves a substantial proportion of infants and toddlers unprotected, and the overcrowded living conditions and poor sanitation in these states provide a fertile ground for virus circulation. The reasons for the high rates of vaccine failure are not entirely clear, but may include some environmental, genetic or nutritional factors and/or co-circulation of numerous other enteric pathogens that interfere with vaccine efficacy.

Finally, severe obstacles to the eradication campaign lie outside the realm of poliovirus biology or medicine. Inadequate immunization coverage exists in several remaining endemic areas of the world either because security issues in regions of military conflict prevent health care workers from reaching pediatric populations, or because cultural or political misinformation about the safety of the vaccine and the intent of the eradication campaign generates resistance in the population to accept the vaccine. Indeed, continuing poor coverage in northern Nigeria produced an explosion of almost 800 cases in 2008, accounting for almost half of the world's poliomyelitis burden. In recent years, viruses from Nigeria have re-infected at least 20 previously polio-free countries, both neighboring and distant, spread by travelers. The efforts required to continuously combat these outbreaks from introduced virus constitute an enormous financial and human resource burden on the eradication program.

New Approaches Needed to Finish the Job

The lack of progress toward global eradication of wild poliovirus in the last eight years contributes to program fatigue among both campaign workers and financial donors. If the

breakthrough is not achieved soon, the success of the entire campaign will be in serious jeopardy. Therefore, the program is actively searching for new approaches. One recent improvement is the use of monovalent vaccine for supplementary immunization activities in conjunction with continued use of trivalent OPV for routine immunization. The use of monovalent OPV eliminates interference between vaccine serotypes and results in significantly higher efficacy compared with trivalent OPV. This approach has closed gaps in immunity and reduced the numbers of susceptible children [35,36] in Egypt and Nigeria. Another approach currently under discussion is the supplementary use of IPV, which may induce higher seroconversion rates after a single administration than OPV in some populations [37], and may help tip the balance of vaccine efficacy in regions such as northern India.

It is hoped that these approaches, coupled with increased outreach and improved operational efforts in the remaining endemic communities, will successfully stop transmission of wild polioviruses. If and when that happens, the world will need to change its strategy for protection against poliomyelitis.

After Eradication?

Continued widespread use of OPV would continue to generate cases of VAPP amongst recipients, as well as circulating VDPVs that will inevitably lead to outbreaks. Therefore, OPV must be discontinued for eradication to be achieved [38]. The paradox is that withdrawal of OPV will also cause a rapid expansion of immunologically susceptible populations that will fuel the spread of outbreaks following reintroduction of virus. Reintroduction could result from undetected circulation of VDPVs, chronic excretors, imperfect surveillance, accidental release from research or vaccine manufacturing facilities, or deliberate distribution of natural or synthetic virulent poliovirus [39]. Computer modeling suggests that in a world where significant populations are left unprotected, polio outbreaks are inevitable [40]. Historically, population immunity against polio has always been quite high, either because of ubiquitous circulation of wild strains or because of effective immunization programs. In rare instances where isolated communities were or became highly susceptible to poliovirus, massive outbreaks of unusual severity occurred after poliovirus was introduced (or re-introduced) into circulation [41,42]. Thus, the only sustainable way to keep the world polio-free is to continue protection of the entire population. This means that polio vaccines will likely be used indefinitely, leaving only questions about what vaccines would be optimal for post-eradication immunization programs, and how they should be used.

Strategies for future immunization practices

Given the importance of maintaining immune protection of all the world's children while rejecting continued use of current OPV, an urgent need for new vaccine strategies has emerged. Several studies aimed at creation of a more stable and safer OPV generated new virus strains engineered to be attenuated by mechanisms that theoretically predict stable, non-reverting genetic properties. However, the regulatory requirements to demonstrate higher stability and safety of the new strains compared to conventional Sabin strains demand clinical trials of unrealistic size. Therefore, introduction of a new generation of live attenuated OPV appears to be impractical.

High-income countries such as the US, Canada, Japan, Australia, New Zealand, the UK and most of western Europe, have already shifted away from OPV to immunization with the more expensive IPV, well-proven to induce effective protective immunity. Alas, the current cost of this existing vaccine as well as the requirements for trained medical personnel to administer intramuscular injections, and the production scale-up that would be needed to provide this vaccine globally, currently prohibit a worldwide switch to IPV. Since the current IPV formulations are produced from the very wild-type virus being eradicated, containment and

safety issues at expanded production facilities would pose a major obstacle. Therefore a new generation of IPV that would be free from these shortcomings is needed [43]. Several companies are attempting to produce an IPV from the attenuated Sabin OPV virus in order to reduce safety concerns, with the expectation that production costs could be reduced by scale-up in quantity, utilization of fractional doses, adding adjuvants to boost immunogenicity, and/or using intradermal or alternative types of delivery methods. All of these ideas are currently being explored, either for conventional wild-type IPV (to reduce cost) or as potentially applicable to IPV derived from attenuated Sabin strains of poliovirus. The primary justification for development of Sabin IPV rests on the assumption that if the strains escape production facilities, the consequences may not be as grave as the escape of wild polioviruses used for manufacture of conventional IPV. The rapid emergence of virulent VDPVs from circulating Sabin virus could reasonably challenge this notion. In addition, the Sabin polioviruses manifest significantly altered immunogenicity, especially after formaldehyde inactivation, requiring higher doses of antigen and different proportions of antigens from the three different virus serotypes in order to achieve seroconversion rates in recipients equivalent to conventional IPV made from wild-type virus. At this time, it is not clear whether these problems can be overcome for production of an inexpensive, efficacious IPV from the Sabin OPV strains of poliovirus, and the justification for this massive technological effort remains questionable. Therefore, other alternatives must also be pursued.

An IPV made from stable, attenuated strains of poliovirus that are engineered to have a wild-type PV capsid, identical to the existing conventional IPV would be of great potential value. This latter property would ensure that the immunological characteristics of the new IPV would be unchanged from the current IPV, and would simplify use of existing biomarkers of vaccine efficacy. If the attenuating mutation(s) were all located in the non-structural genes of the virus, the structural and immunogenic properties of the virus particles, before or after formaldehyde inactivation, would be unaltered from those of the existing IPV. This would greatly facilitate meeting the vaccine regulatory criteria and would generate the same product with which we have many years of experience. Ideally, strains used for production of the next generation IPV should be unable to replicate outside of specially designed production substrates. About a half-dozen such viruses have been created in several research laboratories, and preliminary characterizations of their genetic stabilities and attenuation phenotypes in animal models are very promising [see review [43]]. However, more research is needed to determine their feasibility for mass production and suitability for human use. If such a product were to become available within the timeframe of the poliovirus eradication program, the reassuring safety of the seed stocks for production would obviate the need for high containment levels and possibly facilitate production in countries of the developing world, which could have broad economic and political advantages.

The addition of adjuvants to boost immunogenicity could reduce the dose (and therefore the cost) of vaccine antigen needed to induce a protective level of antibodies. The use of IPV in combination products together with other vaccines containing alum adjuvant partially achieves this objective, and also increases the overall public health value of such vaccines. Novel adjuvants might also increase the ability of IPV to induce mucosal immunity, resulting in a vaccine that would also reduce poliovirus transmission [44]. Similar explorations of alternative delivery methods and techniques, such as intradermal microneedles or patches, might alleviate the relatively high cost and logistical challenge of intramuscular injections of IPV.

Finally, modern biotechnology holds clear promise for development of totally novel vaccines based on fully synthetic products, or plant-derived vaccines, including edible products. These long-term possibilities should not be forgotten in the understandable rush to complete polio eradication, because they may represent the future of polio vaccines. In addition, the development of several anti-polioviral drugs [45] was called for by a Committee on

Development of a Polio Antiviral and Its Potential in Global Poliomyelitis Eradication at a workshop convened by the National Research Council of the National Academies, USA [46] in 2006. If such chemotherapeutic agents were to become available, they could markedly influence the cost/risk/benefit analysis of long-term continuous vaccine use.

Expert Commentary

Twenty years have passed since the World Health Assembly resolved to eradicate poliomyelitis. Much has been learned about the virus that causes this dreaded disease, as well as about the vaccine products used to combat it. Although the original eradication proposal relied on utilization of Sabin OPV to eliminate wild strains of poliovirus, followed by global cessation of OPV use to prevent generation and spread of newly virulent derivative viruses, current thinking acknowledges that massive vulnerability resulting from stopping all polio immunization could create a potentially explosive epidemiological setting in which unimmunized populations would be hostage to the very real possibilities of a natural or man-made disaster. A much safer scenario to ensure sustained absence of disease is to maintain population immunity by universal use of IPV. The main challenge to achieving this goal is the cost and logistics of distribution and administration of IPV. A number of modifications to the manufacture and delivery of this product that we summarily refer to as “the new generation of IPV”, appear to be feasible; concerted efforts in this direction are urgently needed.

However, technological advances in vaccine development will not result in universal global protection against poliomyelitis unless they are supported by a sustainable public health infrastructure for vaccine distribution and use. Open declaration of the need to prevent poliomyelitis beyond the current eradication program is essential to mobilize concerted efforts of public and private organizations to work together to achieve this goal. Most industrialized and many middle-income countries conduct reasonably efficient routine immunizations; the World Health Organization’s Expanded Programme for Immunization (EPI) is chartered to facilitate delivery of universal childhood vaccines in poor countries. Its track record in many countries remains mixed. Adding polio immunization by including IPV-containing combination vaccines into the EPI schedule could potentially produce synergy and improve protection against all vaccine-preventable diseases. Should cross-enhancement between these two major WHO-sponsored activities happen, international public health efforts will get a much-needed boost, the long-term success of the polio eradication initiative will be secured, and control of other infectious diseases will be promoted. This could potentially become the greatest legacy of the polio eradication program.

Five-year View

Provided that (i) polio immunization activities can be operationally improved and implemented efficiently in regions where vaccine coverage is still low, and (ii) vaccines with improved efficacy are used to terminate transmission in any remaining endemic regions, circulation of wild polioviruses will be stopped. To ensure continued protection against polio, middle and low-income countries will gradually switch their immunization programs to IPV, generating increased demand for this product. Existing manufacturers will ramp up production capability, and new manufacturers will emerge.

Making IPV affordable for low-income countries will require some changes to decrease its unit cost, improve biosecurity of its manufacture, and simplify delivery procedures. This will include research on feasibility of new seed strains of virus for preparation of IPV. In addition to technical modifications to the manufacturing process, infrastructure for global vaccine delivery in low-income countries must be modified to include universal use of combination

vaccines containing IPV. For all these changes to take place, open recognition of the need to continue vigorous immunization programs against polio is urgently needed.

Key Issues

- The global polio eradication program has relied exclusively on OPV to eliminate circulation of wild poliovirus strains; however, the initial grand success of this strategy stopped short of its goal of total eradication.
- Effective vaccine coverage has been significantly challenged by lack of security for health workers in some areas of military unrest and rejection of the vaccine in some regions.
- Trivalent OPV displays very low efficacy in some settings, presenting a significant obstacle to stopping wild poliovirus transmission in a few populations.
- Use of vaccines with increased efficacy (monovalent OPV and/or IPV) coupled with active outreach and enlisting help of local political and religious leaders could result in termination of wild poliovirus transmission.
- Sustained control of poliomyelitis will require maintenance of high levels of population immunity.
- Continued use of current OPV inevitably leads to generation of highly virulent circulating vaccine-derived polioviruses.
- OPV strains with improved stability could potentially be created by rational genetic manipulations; however, establishing the safety and efficacy of a new live, attenuated vaccine may not be practical because of the size of the required clinical studies.
- Universal global use of the current IPV is complicated by its relatively high cost and logistical challenges of its distribution and administration.
- Scaling up vaccine production, use of non-virulent strains, use of adjuvants to boost efficacy and reduce necessary antigen dose, novel delivery techniques, combination with other protective antigens – all represent avenues of research that could lead to creation of a new generation of IPV.
- The new generation of IPV would affect the cost-benefit balance and make it more attractive for global use as a universal childhood vaccine.

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