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Poliovirus vaccination options for achieving eradication and securing the endgame☆

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Abstract

In 1988, the World Health Assembly resolved to globally eradicate poliomyelitis. As part of a four-pronged strategy with establishment of enhanced surveillance, institution of national immunization days, strengthening routine immunization, and carrying-out mopping-up activities, oral poliovirus vaccine (OPV) was selected as the vaccine-of-choice for eradication. Massive OPV use decreased the number of polio-endemic countries from >125 countries in 1988 to only 3 in 2012 and led to a >99.9% decrease in polio incidence in the corresponding period. In this communication, we will discuss polio vaccination options to accelerate eradication, to mitigate the risks during the planned withdrawal of type 2 OPV, and to secure eradication for future generations.

Introduction

After its launch in 1988, the Global Polio Eradication Initiative (GPEI) made rapid progress, reducing polio cases from an estimated 350,000 in 1988 to 719 reported in 2000 and eliminating wild poliovirus type 2. During the next decade, the number of polio-endemic countries decreased to 4, but no overall reduction in polio cases was accomplished [1]. The recent intensification of eradication efforts has decreased the number of polio-endemic countries to 3 (i.e., Afghanistan, Nigeria and Pakistan) and led to a record low number of cases in 2012 (222 as of February 6, 2013) [2].

Vaccination against poliomyelitis aims to maximize humoral immunity that confers individual protection against paralysis, and mucosal immunity that restricts viral replication

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Conflict of interest

All authors declare that they have no conflict of interest.

in the nasopharynx and the intestine, and thus reduces virus transmission. The presence of serum neutralizing antibody provides protection against paralysis. Intestinal immunity develops only when there has been exposure to live poliovirus (vaccine or wild) and high serum antibody titers correlate, but not always, with lower potential for re-infection and shorter duration of shedding following new exposure to live poliovirus [3–6].

This review presents current and potential new uses of available poliovirus vaccines to interrupt poliovirus transmission in the last reservoirs and secure the gains of eradication for future generations.

Old and new uses of oral polio vaccine (OPV)

Trivalent OPV

Trivalent OPV (tOPV), with attenuated Sabin strains of poliovirus types 1, 2 and 3, was the vaccine of choice for polio eradication in most countries because it induces both humoral and mucosal immunity, can immunize or boost immunity of close contacts through secondary spread, and is inexpensive and easy to administer [1]. Because of interference among the vaccine strains, children preferentially respond to type 2 after the first trivalent OPV dose. Studies in temperate developed countries found that 3 doses seroconverted ≥95% of infants to all types and provided long-lasting immunity, but only an average of 73%, 90% and 70% of children seroconverted to poliovirus types 1, 2 and 3, respectively, in tropical developing countries. A recent study in India also suggests shorter duration of mucosal immunity in developing countries [7]. Therefore more than 3 doses are required to prevent paralysis in >95% children living in tropical developing countries, and additional booster doses are needed to maintain intestinal immunity.

Rarely, Sabin strains can acquire the neurovirulence characteristics of wild polioviruses (WPV), which leads to an estimated 250–500 cases of vaccine-associated paralytic poliomyelitis (VAPP) annually [8]. In addition, low routine immunization coverage facilitates the emergence of circulating vaccine-derived polioviruses (cVDPV) which have the neurovirulence and transmissibility characteristics of WPV and the potential to establish endemic transmission, possibly negating the achievements of eradication [9]. From 2000 to 2012, 646 paralytic cases due to cVDPVs were reported, 86% of these derived from type 2 [2].

Monovalent and bivalent OPV vaccines

To improve the effectiveness of OPV in the last WPV reservoirs in Asia and Africa, GPEI introduced monovalent vaccines type 1 (mOPV1) and type 3 (mOPV3) in 2005. Both monovalent vaccines are more immunogenic per dose than tOPV against the respective serotypes [10,11]. However, the prevalent use of mOPV1 in campaigns during 2005–2008 may have facilitated a resurgence of WPV3 [12–14].

Bivalent OPV (bOPV) containing types 1 and 3 was licensed in 2009 after a clinical trial showed non-inferior immunogenicity against types 1 and 3 compared to the respective monovalent vaccines [15•]. Subsequently, bOPV has become a crucial tool for simultaneously closing immunity gaps to types 1 and 3. However, prevalent use of mOPV

and bOPV in mass campaigns in countries with weak routine immunization services has contributed to the emergence of type 2 cVDPVs [14,16].

New strategies of OPV delivery to accelerate eradication in certain settings

Currently the GPEI is tailoring the use of various OPV formulations in campaigns to the epidemiological situation at national and subnational levels. Additional strategies in use or under evaluation include:

1. Shortening intervals between rounds using monovalent and bivalent vaccines (from 4–6 to 1–3 weeks) to more quickly achieve high levels of population immunity. Lack of response to a given serotype should not prevent an immune response to another dose with the same serotype given shortly afterwards, whereas administration of a different serotype might interfere. This strategy has been implemented successfully during outbreak responses and in areas where the population can only be reached during short periods due to conflict or insecurity [17].
2. Expanding the target age for campaigns to children aged >5 years. Campaigns targeting expanded age groups (give age range) have been successfully implemented in multiple countries [18•,19,20,21]. Recent experience during outbreaks in which older individuals were paralyzed suggested that the higher cost and operational complexity of campaigns with a wider target age range could be potentially offset by faster outbreak resolution with fewer rounds, and that these campaigns did not negatively impact coverage among children aged ≤5 years (H. Everts, personal communication).

Phased OPV cessation: type 2 OPV withdrawal

To eliminate new cVDPV type 2 outbreaks and reduce VAPP, the Strategic Advisory Group of Experts on Immunization (SAGE) of the World Health Organization (WHO) has endorsed a phased cessation of OPV in routine immunization, starting with Sabin type 2 [22••]. The GPEI Strategic Plan 2013–18 includes plans for a global switch from tOPV to bOPV for routine immunization around 2016, provided prerequisites are met, including elimination of persistent cVDPV2 transmission in Nigeria and Somalia [23,24•].

Current and new uses of inactivated polio vaccine (IPV) to achieve polio eradication

Immunogenicity of IPV

The current formulation of IPV induces nearly 100% seroconversion rates and high antibody titers to all 3 serotypes following 3 doses, and >90% seroconversion rates after 2 doses when initiated after 8 weeks of age (Table 1). Intradermal administration of 2 or 3 fractional doses of IPV (1/5th of intramuscular dose) provided similar or lower seroconversion rates (Table 1). Interference with maternal antibodies and the need for longer intervals to mount adequate immune responses decrease the immunogenicity of fractional and full-dose IPV if administered at 6, 10 and 14 weeks.

Pharyngeal immunity appears to be similar after OPV and IPV administration, but IPV has limited effect on inducing intestinal immunity [25,26]. However, some studies have shown that IPV may 'prime' mucosal immunity because, although most persons who receive IPV shed vaccine virus following a challenge with OPV, the amount of virus shed and duration of shedding is decreased compared to naïve individuals [27]. In tropical developing countries, a supplemental dose of IPV administered to children previously exposed to OPV boosts humoral and intestinal immunity more effectively than a supplemental dose of OPV. In Cote d'Ivoire, seroprevalence among children aged 9 months increased following a booster dose of IPV for types 1 (85–97%), 2 (93–100%) and 3 (76–92%) poliovirus, but did not change substantially after tOPV administration [28]. In northern India, 90–100% of 6–9-month-old children became seropositive after a booster dose of IPV [29]. Another study in northern India found that the proportion of 10-year-old children shedding type 1 Sabin poliovirus 7 days after a bOPV challenge, decreased by ~75% among children who had previously received an IPV booster dose, and by 50% among children who had received a bOPV booster dose, compared to those who had received no booster (Jafari H *et al.*, personal communication).

Available IPV products and cost

GlaxoSmithKline and Sanofi Pasteur are the major producers of IPV, whereas the Bilthoven Biologicals (formerly the Netherlands Vaccine Institute) and the Statens Serum Institute currently produce smaller IPV quantities. Because of biocontainment requirements for facilities handling WPV, manufacturers in developing countries must purchase bulk IPV from these four suppliers for local filling of final product or establish IPV production using Sabin strains. Currently, most IPV is provided in combination vaccines with diphtheria, acellular pertussis, *Haemophilus influenzae* type b and/or hepatitis B vaccines (DTaP-Hib or DTaP-Hib-HepB).

IPV is substantially more expensive than OPV; the UNICEF procurement price is about $3 per dose of IPV compared with $0.15–$0.20 cents per dose of tOPV. The high manufacturing cost of IPV is partly scale driven. If production substantially increased from the current estimated capacity of ~80–120 million to 240–360 million annual doses, the cost of the vaccine could decrease by 30–50% per dose [30]. However, this surge in capacity will require 2–3 years lead time, plus manufacturers investment in infrastructure that is contingent upon future demand.

Fractional IPV (1/5 of a full dose) administered intradermally could reduce the cost of a 3-dose schedule by around 70%, becoming not only the cheapest option for the short term introduction of IPV, but also an option that could stretch current manufacturing capacity [31]. However, additional clinical trials, funding and support from manufacturers and regulatory authorities are necessary to better understand the immunogenicity of fractional IPV with different schedules and devices, and to fast-track regulatory approval processes.

Current use of IPV

IPV is administered through routine immunization services in polio-free countries where eliminating the burden of VAPP is a high priority. Some countries that switched from OPV

to IPV initially adopted a sequential/combination schedule with 1–2 IPV doses followed by 2–4 OPV doses. Since 2000, most industrialized countries have stopped administering OPV because high coverage with 3–4 doses of IPV prevents WPV circulation following importations. In addition, outbreaks in IPV-using countries were controlled with IPV/OPV campaigns [5].

Potential use of IPV for polio eradication

Use of IPV along with OPV in countries with ongoing poliovirus transmission could accelerate interruption of transmission by two mechanisms: first, reducing the number of vaccination contacts required to achieve adequate humoral immunity in a susceptible population; and second, boosting mucosal immunity and thus reducing WPV shedding (Jafari H *et al.*, personal communication).

Delivery through routine immunization

In Gaza and the West Bank, WPV circulation was interrupted in 1978 after addition of 2 IPV doses and 1 extra OPV dose to the 4 OPV doses previously provided through routine immunization services. [32]. However, the potential impact of this strategy is limited in polio endemic countries with low routine immunization coverage. In Demographic Health Surveys, coverage with 3 doses of diphtheria–tetanus–pertussis (DTP3) vaccine was only 36% in Nigeria (2008) and 60% in Pakistan (2006–2007), compared with the 90% coverage reported for Gaza and West Bank [33].

Operational challenges associated with the introduction of a new vaccine in routine immunization services would require additional resources and lead-time, including: first, revision of the immunization schedule nationwide; second, expansion of cold chain capacity, supplies for vaccine delivery and sharps disposal; and third, implementation of a communication plan to enhance acceptability by health workers and parents.

Delivery through campaigns

Adding IPV to OPV campaigns (and/or campaigns delivering other vaccines) would have several advantages over delivery through routine immunization services to accelerate eradication in endemic reservoirs: first, campaign coverage would likely be higher than routine coverage; second, coordination and implementation of campaigns is more feasible in the near term than fully strengthening routine immunization services in underserved areas; third, campaigns can be targeted and limited in area and population size and fourth, campaigns can reduce susceptibility in many age groups at once in contrast to the years it would take to cover the same age groups through routine immunization services.

On the other hand, provision of IPV in campaigns will face the following challenges:

1. Greater complexity and cost of campaigns. Delivery of an injectable vaccine requires skilled, trained healthcare workers who are scarce in low-income countries. Cold chain capacity will have to be restructured to handle freeze-sensitive IPV plus heat-sensitive OPV, and plans made for the management of adverse events following injection and disposal of sharps. Communications and

social mobilization strategies will also need to be updated to ensure acceptance of IPV and OPV.

2. Change in vaccine delivery. IPV will likely be delivered through fixed vaccination posts, which could reduce coverage below levels achieved with house-to-house campaigns distributing OPV.

The feasibility and success of campaigns with IPV can be maximized by applying lessons learned from successful campaigns with other injectable vaccines such as measles and meningitis. The use of jet injectors to deliver intradermal fractional dose IPV could reduce the cost per dose and increase doses available for distribution, minimize sharp wastage, and increase availability of vaccinators because non-healthcare workers can be trained to use them for vaccine delivery. Jet injectors might also enhance acceptance of vaccine [34].

IPV use after eradication of wild poliovirus

Rationale for the use of IPV

OPV withdrawal is essential to secure the gains of polio eradication, but is associated with a risk of outbreaks caused by cVDPVs, long-term VDPV excretion among persons with immunodeficiency disorders or reintroduction of WPV from containment failure. The risk of cVDPV emergence will be highest immediately after withdrawal of OPV, but the consequences of an outbreak will rise with increasing population susceptibility [35].

To mitigate the risks associated with OPV cessation, the SAGE recommended the universal introduction of at least one dose of IPV in routine immunization schedules at least 6 months before switching from tOPV to bOPV [22••,36]. Administration of IPV would have the following benefits: first, prevent paralysis upon exposure to a type 2 poliovirus; second, improve immunological response to mOPV2 or an additional IPV dose should a type 2 outbreak occur; third, reduce transmission of any reintroduced type 2 poliovirus; and fourth, potentially accelerate eradication of WPV types 1 and 3 by boosting immunity [22••,36]. A major prerequisite for the implementation of universal IPV use is the availability of affordable IPV options for low and middle-income countries. Lower cost options being pursued include reducing the number of doses, reducing the amount of antigen per dose and manufacturing IPV in developing countries.

Based upon seroconversion rates and priming in mucosal immunity observed in clinical trials, two doses of IPV could yield the above benefits against type 2 in >90% of vaccinated children [25,27]. On the other hand, a single IPV dose induces low seroconversion rates against type 2 (24–63%, Table 1) and data on its effect on oropharyngeal and intestinal immunity are scarce. However, data from some countries using sequential IPV-tOPV schedules in routine immunization show a high efficacy for one IPV dose in preventing VAPP [37,38]. Therefore, it is biologically plausible that IPV also protects against paralysis by WPV or VDPV. A recent study in Cuba also found that, after one IPV dose administered at age 4 months, 63% of infants seroconverted to type 2 poliovirus, but 98% of seronegative infants had been ‘primed’ and had a rapid antibody rise upon receipt of a second dose [39••]. If both seropositive and primed children are protected against paralysis, up to 99% of children could be protected after a full IPV dose, and 97% could be protected after

a fractional-IPV dose [39••]. This evidence suggests that a single IPV dose may provide sufficient population immunity to minimize the risk of cVDPV2 emergence and to mitigate the extent of outbreaks.

IPV use in routine immunization services

A cost-effective combination of bOPV and one dose of IPV with the current WHO schedule would be administration of bOPV at birth (if available), 6, 10 and 14 weeks together with DTP, and additional administration of IPV (fractional or full-dose) at 14 weeks (with DTP-OPV3) or 9 months (with measles). This schedule would reduce interference of maternal antibodies with IPV and would allow IPV to boost and close immunity gaps left by a 3-dose OPV schedule. The possible limitations of this schedule include a smaller effect on reducing VAPP, as the risk is higher with the first OPV dose [8], and lower population immunity in countries with high drop out between DTP1 and DTP3 doses (e.g., DTP1 coverage was 53% and DTP3 coverage was 36% in Nigeria in 2008 [33]).

Administration of two IPV doses would increase population immunity by increasing final antibody titers, and by allowing an additional opportunity for vaccination. Provision of a second IPV dose with measles vaccine could maximize IPV immunogenicity (Table 1, [40•]), but the impact may also be limited by high drop-out rates. Availability of IPV-containing combination vaccines manufactured in low-income countries could facilitate introduction of 2–3 IPV doses in routine immunization schedules by reducing the vaccine price and eliminating logistics and supplies required for an additional injectable vaccine.

By 2018–2019, additional antigen-sparing and lower cost IPV-containing vaccines could be available. Alum-based adjuvants have a straightforward development path because they are already used in combination products [41]. An oil-in-water adjuvant has been shown to allow reduction in IPV antigen by 90% in pre-clinical studies [42].

IPV derived from Sabin strains have reduced biosafety containment requirements and might allow IPV manufacture at lower-cost in developing countries. Institutions in Korea, Indonesia, India, Japan, China and the Netherlands are working on the development of Sabin IPV, which requires formulation adjustments and addition of adjuvants to compensate for reduced antigenicity and yield of types 2 and 3, and increased yield and immunogenicity of type 1. Combined DTaP-Sabin IPV vaccine was recently licensed in Japan [43,44].

IPV use for outbreak response

The current endgame strategic plan envisions eventual use of IPV in campaigns for outbreak control sometime after OPV cessation [23,24•]. Stand-alone IPV could be administered in combination with the relevant monovalent OPV formulation in outbreak areas, to achieve high population immunity as rapidly as possible. IPV alone could be distributed in areas surrounding the outbreak to raise population immunity and potentially limit spread of vaccine-related virus from the monovalent OPV response.

Additional research needed

Research necessary to guide implementation and evaluate the effectiveness of new uses of IPV and OPV includes:

- clinical trials comparing the immunogenicity of low-cost IPV options in different routes of administration to facilitate regulatory processes for label change;
- studies assessing the potential effect of low-cost IPV options on poliovirus transmission in developing countries;
- pilot projects with provision of IPV in routine and campaigns to assess vaccine acceptance and to evaluate the advantages and challenges of different delivery strategies;
- modeling studies considering the immunogenicity and coverage potentially reached with IPV delivery in different routine schedules and in campaigns, to support country policy decisions; and
- ecologic studies in developing countries switching to all-IPV routine immunization schedules to evaluate potential emergence of cVDPVs and risk of WPV importations.

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Table 1

Seroconversion rates following 1–3 doses of inactivated poliovirus vaccine (IPV) in different routine immunization schedules

Author year (Ref.)	Country	Schedule	*N*	% seroconversion[a]		
				Type 1	Type 2	Type 3
Intramuscular administration of 1 dose						
McBean 88 [45]	US	2 mo	309	42%	35%	54%
Simasathien 94 [46]	Thailand	2 mo	103	25%	39%	28%
Resik 10 [40•]	Cuba	6 wk	177	19%	36%	42%
Mohammed 10 [47•]	Oman	2 mo	186[b]	22%	32%	45%
Resik 13 [39•]	Cuba	4 mo	153	46%	63%	32%
Intramuscular administration of 2 doses						
WHO 97 [48]	Oman	6, 10 wk	136	71%	83%	81%
WHO 97 [48]	Thailand	6, 10 wk	141	40%	48%	79%
Cuba IPV group 05 [27]	Cuba	8, 16 wk	72	90%	89%	90%
Resik 10 [40•]	Cuba	6, 10 wk	177	63%	76%	93%
Mohammed 10 [47•]	Oman	2, 4 mo	186[b]	91%	91%	96%
Resik 13 [39•]	Cuba	4, 8 mo	153	100%	100%	99%
Intramuscular administration of 3 doses						
McBean 88 [45]	US	2, 4, 18 mo	219	99%	100%	100%
Simasathien 94 [46]	Thailand	2, 4, 6 mo	92	96%	95%	98%
WHO 97 [48]	Oman	6, 10, 14 wk	136	90%	96%	95%
WHO 97 [48]	Thailand	6, 10, 14 wk	141	67%	65%	94%
Dayan 05 [49]	P. Rico	6, 10, 14 wk	225	86%	86%	97%
Dayan 05 [49]	P. Rico	2, 4, 6 mo	230	100%	100%	99%
Cuba IPV Group 05 [27]	Cuba	6, 10, 14 wk	52	94%	83%	100%
Resik 10 [40•]	Cuba	6, 10, 14 wk	177	89%	96%	99%
Mohammed 10 [47•]	Oman	2, 4, 6 mo	186[b]	100%	100%	100%
Cadorna-Carlos 12 [50]	Philippines	6, 10, 14 wk	115	98%	98%	100%
Intradermal administration of 1–3 fractional doses						

Author year (Ref.)	Country	Schedule	*N*	% seroconversion[a]		
				Type 1	Type 2	Type 3
Resik 10 [40•]	Cuba	6 wk	187	5%	19%	8%
Resik 10 [40•]	Cuba	6, 10 wk	187	21%	55%	43%
Resik 10 [40•]	Cuba	6, 10, 14 wk	187	53%	85%	69%
Mohammed 10 [47•]	Oman	2 mo	187[b]	10%	17%	9%
Mohammed 10 [47•]	Oman	2, 4 mo	187[b]	70%	72%	72%
Mohammed 10 [47•]	Oman	2, 4, 6 mo	187[b]	97%	96%	98%
Cadorna-Carlos 12 [50]	Philippines	6, 10, 14 wk	115	99%	95%	95%
Resik 13 [39•]	Cuba	4 mo	157	17%	47%	15%
Resik 13 [39•]	Cuba	4, 8 mo	157	94%	98%	93%

[a]Cumulative seroconversion rates defined as children with antibody concentrations ≥4-fold the expected value based upon decline from baseline levels.

[b]Denominators varied for each serotype.Included studies conducted with enhanced IPV, with a sample size ≥50 and that provided information on seroconversion rates.