

Affordable Inactivated Poliovirus Vaccine: Strategies and Progress

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After polio eradication is achieved, the use of live-attenuated oral poliovirus vaccine (OPV) must be discontinued because of the inherent risk of the Sabin strains to revert to neurovirulence and reacquire greater transmissibility that could potentially result in the reestablishment of polio transmission. In 2008, the World Health Assembly mandated that the World Health Organization establish a strategy for developing more-affordable inactivated poliovirus vaccine (IPV) options for low-income countries. In 2012, the Strategic Advisory Group of Experts (SAGE) on Immunization recommended universal IPV introduction as a risk-mitigation strategy before the phased cessation of OPV (starting with Sabin type 2) and emphasized the need for affordable IPV options. In 2013, SAGE reiterated the importance of attaining the long-term target price of IPV at approximately \$0.5 per immunizing dose and encouraged accelerated efforts to develop lower-cost IPV options. This article outlines the 4-pronged approach that is being pursued to develop affordable options and provides an update on the current status and plans to make IPV affordable for developing-country use.

Keywords. inactivated poliovirus vaccine; affordability; intradermal administration; production optimization; adjuvant; schedule reduction; further attenuated poliovirus strains.

Following the resolution of the World Health Assembly (WHA) to eradicate polio by the year 2000, the Global Polio Eradication Initiative (GPEI) was launched to guide eradication efforts. Progress toward eradication has reduced the number of poliomyelitis cases by >99.9%, from >350 000 cases in >125 countries during 1988 to 416 cases in 8 countries during 2013 [1].

This progress is due to the massive use of oral poliovirus vaccine (OPV). OPV is the vaccine of choice for eradication because it induces superior mucosal immunity, is easier to administer, and is more affordable (approximately \$0.15/dose) [2]. However, OPV use is associated with a small risk (estimated to be 2–4 cases/million birth cohort per year [3]) of vaccine-associated paralytic poliomyelitis (VAPP), as well as the generation of vaccine-derived polioviruses (VDPVs)

[4], which makes OPV use ultimately incompatible with polio eradication.

The WHA endorsed in 2008 the eventual cessation of OPV for routine immunization following certification of global polio eradication and requested the GPEI to develop a strategy to provide affordable options for inactivated poliovirus vaccine (IPV) for use in developing countries [5]. Since 2008, new developments and scientific data led to a reframing of this recommendation into an endgame strategy. First, the introduction of real-time polymerase chain reaction, starting in 2008 [6], by the global polio laboratory network increased the timeliness and, more importantly, the sensitivity of detecting VDPVs, especially those attributable to type 2 poliovirus. After 2009, >95% of polio cases due to circulating VDPVs were attributed to type 2 virus [7]. Second, clinical trials showed that intradermal administration of a fractional IPV dose (ie, one that is one-fifth the size of the original dose) is feasible and effective [8, 9]. Third, bivalent OPV (bOPV), which contains poliovirus types 1 and 3, was found to be more immunogenic than trivalent OPV (tOPV) against types 1 and 3 poliovirus [10]. After bOPV first became available in 2009, it rapidly replaced tOPV as the vaccine of choice for most

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The Journal of Infectious Diseases® 2014;210(S1):S459–64

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DOI: 10.1093/infdis/jiu128

New Information and Tools	Proposed Endgame Strategy
<ul style="list-style-type: none"> Type 2 circulating VDPV represents a significant risk (>95% of circulating VDPV cases) bOPV is proven to be effective and widely available Some affordable IPV options will be available in a few years 	<ul style="list-style-type: none"> Phased removal of Sabin viruses from immunization programs, beginning with the type 2 Sabin virus Elimination of VDPV type 2 risk in parallel with WPV eradication through early tOPV-bOPV switch and early IPV introduction

Figure 1. Proposed Polio Endgame Strategy, Based on New Information and Tools. Abbreviations: bOPV, bivalent oral poliovirus vaccine; IPV, inactivated poliovirus vaccine; tOPV, trivalent oral poliovirus vaccine; VDPV, vaccine-derived poliovirus.

supplemental immunization activities designed to interrupt wild poliovirus transmission [11].

Based on these newly available tools and information, in 2012 the GPEI started discussions on a new roadmap to address, in parallel rather than sequentially, the short- and long-term risks of both wild poliovirus and VDPVs. The key vaccine strategies would rely on the substitution of tOPV with bOPV (which involves the withdrawal of poliovirus type 2) for routine immunization [12], preceded by the introduction of IPV for risk mitigation (Figure 1). This approach would accelerate VDPV type 2 elimination (since it would stop the massive exposure of populations to Sabin type 2), when other risk mitigation strategies are still available (including a restart option for tOPV, if needed) and when surveillance sensitivity and outbreak response capability are still high.

However, the price of IPV was identified as a primary barrier for universal IPV introduction (the 2012 price for purchasing from UNICEF was \$2.5/dose) [13]. The IPV price was substantially higher than the price of OPV, which was around \$0.15/dose (the tiered UNICEF price for low-income countries). In part this is because the IPV production capacity is much smaller than that of OPV, but primarily it is because much more viral antigen is required per dose of the inactivated vaccine.

In May 2012, the WHA requested the WHO to work with partners and manufacturers to enhance IPV affordability and availability [14]. In November 2012, the Strategic Advisory Group of Experts on Immunization (SAGE) recommended that all countries introduce at least 1 dose of IPV in their routine immunization programs, to mitigate the risks and consequences associated with the eventual withdrawal of the poliovirus type 2 component of OPV [15]. In November 2013, the SAGE noted that there is still a significant gap between the GPEI long-term target price (approximately \$0.50 per immunizing dose) and the IPV price for 2014–2018, even though the latter is likely to be approximately \$1.0 per full dose for countries eligible

Table 1. Priority Approaches for Achieving an Affordable Inactivated Poliovirus Vaccine (IPV) Strategy

Approach	Description
Reducing the number of IPV doses in routine immunization	Evaluate the use of 1 or 2 IPV doses
Sparing doses through intradermal administration	Develop intradermal device or microneedle patch to enable intradermal IPV, which uses one-fifth of a full dose
Using adjuvant	Use adjuvant to reduce antigen content per dose
Optimizing the production process	Enable IPV production in developing countries with less or noninfectious strain; reduce cost of production with process optimization

for support from the Global Alliance for Vaccines and Immunization. The SAGE encouraged the acceleration of efforts to achieve lower-cost IPV options and products [15]. In response to this programmatic need, GPEI has developed a comprehensive strategy to achieve a target price of approximately \$0.50/immunizing dose of IPV [16].

APPROACHES TO ACHIEVE AN AFFORDABLE IPV

The GPEI is pursuing the following 4 approaches to make IPV more affordable for low-income settings (Table 1): (1) reducing the number of IPV doses for routine immunization; (2) sparing doses through intradermal administration; (3) using adjuvants to reduce antigen requirements; and (4) optimizing the production process.

Reducing the Number of IPV Doses

The WHO position paper of 2010 recommended either a 3-dose IPV schedule, beginning at 2 months of age, or a 4-dose schedule if the primary series begins earlier (eg, with a 6-week, 10-week, and 14-week schedule, plus a booster dose with measles vaccine) [17]. However, if either 1 or 2 doses are sufficiently immunogenic, the number of doses in an IPV schedule could be reduced, with a lower cost of the schedule.

A number of studies now indicate that 2 doses of IPV can seroconvert >90% of subjects when initiated after 8 weeks of age (with an interval of ≥ 8 weeks between doses). It has also been found that the immunogenicity of 1 dose of IPV is highest (eg, >60% seroconversion against type 2) after 14 weeks of age because of reduced interference of maternally derived antibodies at this age [18]. There is also new evidence that even in the absence of seroconversion, a single dose of IPV (whether intramuscular or intradermal) can prime the immune system against poliovirus, measured by a rapid anamnestic immune

response following exposure to the antigen. A recent study in Cuba showed that a single dose of IPV administered at 4 months of age resulted in an immune response (measured as seroconversion or a priming immune response) to poliovirus types 1, 2, and 3 in 92.3%, 96.8%, and 91.1% of participants, respectively, in the group receiving the fractional dose, compared with 98.7%, 99.3%, and 98.7% in the group receiving the full dose [19]. This suggests that 1 dose of either fractional or full-dose IPV is sufficient to induce an immunity base (seroconversion or priming) against poliovirus in >90% of the population.

These results opened the way for additional options for the use of fewer doses of IPV in the routine immunization schedule in the context of mitigating the risks associated with withdrawal of the type 2 component of OPV. The SAGE therefore recommended in November 2013 that countries introducing 1 dose of IPV into the routine immunization schedule should administer that dose at or after 14 weeks of age and in addition to the 3–4 doses of OPV in the primary series [15]. Thus, the number of IPV doses used in the routine immunization schedule, in the context of the polio endgame, has been reduced considerably from the current 3–4 doses to 1 dose, with a concomitant reduction in cost.

Sparing Doses Through Intradermal Administration

Another approach to reduce the IPV dose requirement is with antigen sparing through intradermal delivery. A full course by intradermal administration is known to be more immunogenic than intramuscular administration for many vaccines, including IPV [20, 21]. Reducing the IPV dose through intradermal administration would decrease the cost of IPV administration; that is, if a 5-fold sparing of antigen is feasible, a single-dose IPV vial becomes a 5-dose vial.

Antigen sparing through intradermal administration of IPV has been evaluated extensively in the early years of IPV use [22–24] and more recently [8, 9, 25]. In general, the studies demonstrate that the immunogenicity of a primary series of at least 2 fractional doses of intradermal IPV (each of which is one-fifth the quantity of the full dose) is similar to that of a full-dose of intramuscular IPV, provided an appropriate schedule is used (administration starting at or after 2 months of age, with a minimum interval of 2 months between doses) [18]. In the near term, IPV is expected to be used in many countries as a booster at or after 14 weeks of age in conjunction with the third dose of OPV. Thus, it would be necessary to demonstrate the boosting effect following a single dose of intradermal IPV. The SAGE has recommended that the WHO and the GPEI work with vaccine manufacturers to develop both intramuscular and intradermal options and with regulatory authorities to initiate fast-track development of intradermal IPV [26]. The evidence suggests that intradermal administration can achieve the GPEI long-term price target of approximately \$0.50/immunizing dose, as the cost will be one-fifth of the price of a single-dose IPV vial.

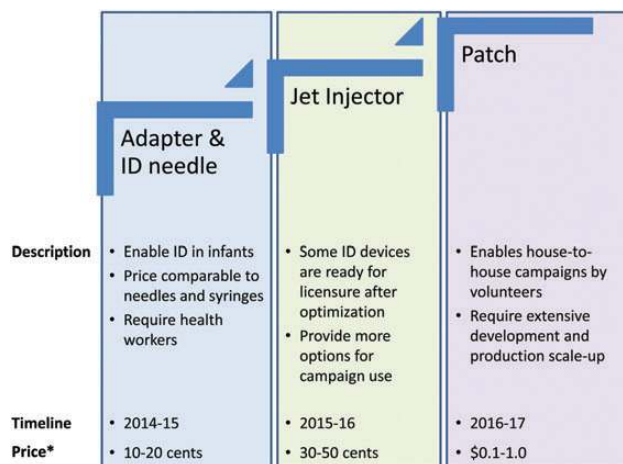


Figure 2. Stepwise approach to developing an intradermal (ID) inactivated poliovirus vaccine delivery system. *Excludes vaccine cost.

However, many countries have expressed a preference for intramuscular over intradermal vaccine because of operational challenges associated with intradermal injections with BCG needles and syringes [26]. To address this issue, the WHO is actively developing alternative intradermal delivery systems. At the end of 2013, 3 options are available for delivery: (1) microneedle adapters and intradermal needles; (2) needle-free jet injectors; and (3) microneedle patches. In the development of intradermal delivery systems, the WHO is considering a stepwise approach (Figure 2) to ensure the rapid availability of appropriate products.

Some needle adapters are already licensed and available on the market and have been evaluated in numerous clinical studies for their usability, safety, and immunogenicity [27–30]. In addition, new jet injectors without CO₂ gas cartridges, by Pharmajet, Bioject, and other companies, are being tested in clinical trials [8–10, 19]. These devices would simplify the intradermal administration of IPV in both routine immunization and mass vaccination campaigns. A number of suppliers of jet injectors indicated that the estimated cost per vaccine cartridge can be <\$0.50 when produced at commercial scale and that the injection device can be expected to be used >5 000 times.

In addition, the GPEI is supporting the development of microneedle patches with IPV. These patches contain hundreds of microscopic needles that dissolve or release the coated material into the skin. These patches could potentially allow persons without medical training to administer IPV vaccine in campaigns, going house to house as part of an outbreak response. Animal studies with multiple vaccines have shown that microneedle patches generate robust immune responses, similar to those by intramuscular injection [31–33]. A preliminary business model developed by patch suppliers suggests that these patches can be sold at a price of \$0.10–\$1.00 when

produced at the commercial scale (annual production of 5 million–50 million doses), exclusive of the cost of IPV.

Using Adjuvants to Reduce Antigen Requirements

Another approach to reduce IPV production cost is the use of adjuvant to enhance immunogenicity. A number of research groups have evaluated traditional adjuvants, such as aluminum, CpG oligodeoxynucleotides, and vitamin D3, for IPV and have reported that a 3–5-fold reduction in antigen content may be feasible [34, 35]. Recent studies in rats demonstrated that a >10-fold reduction of vaccine antigen is potentially feasible with the inclusion of an oil-in-water adjuvant with IPV [36, 37]. Aluminum hydroxide is widely used in pediatric vaccines and is likely to have the lowest regulatory hurdle for commercialization. Studies showed that aluminum hydroxide can enable a 2–3-fold reduction in rats [37, 38] and humans [39]. Currently, 2 Salk IPV suppliers are working on optimizing and developing an IPV formulation with aluminum adjuvant. Adjuvants can be used for both IPV stand-alone and combination vaccines. For example, the current IPV combination already contains aluminum in its DTP component, so antigen reduction of IPV components in these combination vaccines is theoretically feasible.

More recently, a study showed that alphavirus replicon particles (VRPs) may boost not only systemic responses but also induce mucosal responses after nonmucosal delivery with different antigens [40]. VRPs contain a truncated genome with information for viral replication and can infect cells once, but they are unable to propagate further due to the absence of the genes for the structural protein. VRPs are considered to be strong adjuvants because of this effect.

Adjuvant technology may enable the reduction of the antigen requirements to one-half to one-fifth of that in the current IPV. While this reduction will not translate directly into lower production cost, owing to vial-filling costs, the use of adjuvant has the potential to achieve a further reduction in the cost of IPV, bringing it closer to the GPEI target price of <\$0.50 if it enables a dose reduction of ≥ 5 -fold.

Optimizing the Production Process

The production cost of IPV can potentially be further reduced if the vaccine is produced in lower-cost settings (ie, developing countries). However, the currently licensed IPV relies on wild-type poliovirus (Salk) strains for production (except in Japan, where IPV is produced from Sabin strains). Wild-type IPV production poses an unacceptable biosafety risk for developing countries, where population immunity is seldom sufficiently high to prevent the spread of these strains, should these be released from an IPV production site. Thus, development of IPV from safer (ie, less transmissible) poliovirus strains and noninfectious methods of production have become a priority. In addition, producers in developing countries can take advantage of specific optimization techniques for current IPV

production processes to further reduce costs as they set up their IPV production processes.

To address the need for safer strains, manufacturers in China, Japan, and elsewhere are developing IPV by using Sabin strains (Sabin-IPV) [41, 42]. In 2012, 2 manufacturers obtained licenses to market Sabin-IPV in Japan [43], confirming the feasibility of this approach. In addition, the WHO has established a collaboration with the Netherlands Vaccine Institute (Bilthoven, the Netherlands) (now the Institute for Translational Vaccinology; Intravacc) to develop Sabin-IPV for potential technology transfer to manufacturers in developing countries. The preclinical development of the Sabin-based product has been completed, as well as phase 1 clinical trials both in adults and infants; the focus is currently on the transfer of this technology to manufacturers in developing countries [44].

Another option to reduce production costs is to further optimize production processes. Preliminary research in the laboratory-scale production model developed by the National Institute for Public Health and Environment (Bilthoven, the Netherlands) (now the Institute for the Translational Vaccinology; Intravacc) indicates that the current IPV production process can be further optimized by using specific techniques, such as increased cell densities, improvement of downstream processes, and use of animal-component-free media. This would potentially result in more efficient use of bioreactor capacity and, ultimately, reduce the production cost of IPV up to 3–5-fold [39]. Although these optimization approaches have been evaluated for Sabin-IPV, they could also be applied to Salk-IPV production. Currently, one new IPV vaccine manufacturer is evaluating the use of a new IPV production cell line (PER.C6*) to increase the cell density several-fold, potentially resulting in a much more efficient production process and lower cost [45].

FUTURE DIRECTIONS

In terms of longer-term prospects, the GPEI is also working with a number of institutions to develop IPV from alternative, further-attenuated strains, which may have lower biocontainment requirements for large-scale production. The approaches under evaluation include increased replication fidelity to reduce virus virulence, alteration of the nucleotide sequence to use a different (nonoptimal) codon set to reduce virus fitness, and modification of the internal ribosome entry site of the viral genome to reduce neurovirulence [46].

The program is also exploring the possibility of developing IPV by means of noninfectious production methods, which could eliminate the need for containment altogether. Two options are being explored. The first is a so-called packaging cell approach, in which the gene for poliovirus capsid precursor is removed from the virus strain (replicon) and added to the genome of the cell line, which allows the virus to replicate only in the specific cell line with the virus capsid precursor gene to

Table 2. Time Line for Affordable Inactivated Poliovirus Vaccine (IPV) Development

Variable	Activity or Phase		
	Eradication of WPV	Withdrawal of Poliovirus Type 2 From Vaccine	After Cessation of OPV Use
Expected timing	End of 2014	Middle of 2016	2019 or later
Product	Stand-alone full-dose IPV	Low-cost intramuscular or intradermal IPV	Low-cost intramuscular or intradermal IPV or hexavalent combination
Quantity (doses/year) ^a	Limited (approximately 10–20 million)	Substantial (≥100 million)	Large scale (≥200 million)

Abbreviations: OPV, oral poliovirus vaccine; WPV, wild poliovirus.

^a Excluding demand in countries already using IPV.

support viral replication [47]. The second is the development of virus-like particles (VLPs) of the 3 polioviruses for use as the vaccine antigen. VLPs are stabilized poliovirus capsids, which are antigenic but not capable of replication. Two vaccines against human papillomavirus (HPV), which use VLPs to generate capsid-specific neutralizing antibodies [48], are already available, and this concept can be applied to poliovirus vaccine.

These approaches may require substantial development efforts over a longer period, but they could enable manufacturers in developing countries to produce IPV without the risk of accidental release of viable polioviruses into the general population. While the use of safer poliovirus strains and noninfectious methods are not inherently more economical than Salk-IPV, cost savings are expected to come from enabling production in a lower-cost setting. Even so, these savings are difficult to quantify because of the many contributing factors and longer time frame for development.

DISCUSSION

The short-term goal of this program of work (24–36 months) is to complete the licensing trials for fractional-dose intradermal IPV options, especially for a boosting indication, with intradermal delivery systems. Intradermal IPV and its delivery methods (eg, needle adapters and jet injectors) have already been assessed and validated in multiple clinical studies, so it can potentially be licensed rapidly.

The development of intradermal IPV should be followed soon after by an adjuvanted IPV. However, adjuvanted IPV will be considered a new product and will require more time for full clinical development. In addition, the potential cost savings may be lower than that of the intradermal approach because the cost of the vial and the cost of filling it do not change. Still, adjuvanted IPV can be an important tool for national IPV suppliers as a method to expand their production capacity without substantial additional investments in equipment.

The intermediate goal of the program (within 5–10 years) is to develop affordable combination vaccines containing IPV, formulated with either Salk or Sabin strains. At that point,

countries may have a broad range of IPV options in their routine immunization systems, ranging from an IPV stand-alone (including fractional-dose or adjuvanted) product to a combination vaccine with adjuvanted IPV. In addition, intradermal patches could be available for use, including in house-to-house campaigns to respond to outbreaks in the post-eradication era or to improve population immunity in areas with low coverage. Table 2 illustrates the expected development time lines, the corresponding products, and the quantities of IPV needed in the different phases of the polio eradication endgame [49].

In summary, considerable efforts are under way by the GPEI to achieve the target set by the WHA and the recommendations of the SAGE for affordable IPV options for use in developing countries.

Notes

Supplement sponsorship. This article is part of a supplement entitled “The Final Phase of Polio Eradication and Endgame Strategies for the Post-Eradication Era,” which was sponsored by the Centers for Disease Control and Prevention.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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