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Review of use of inactivated poliovirus vaccine in campaigns to control type 2 circulating vaccine derived poliovirus (cVDPV) outbreaks★

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Abstract

Delivering inactivated poliovirus vaccine (IPV) with oral poliovirus vaccine (OPV) in campaigns has been explored to accelerate the control of type 2 circulating vaccine-derived poliovirus (cVDPV) outbreaks. A review of scientific literature suggests that among populations with high prevalence of OPV failure, a booster with IPV after at least two doses of OPV may close remaining humoral and mucosal immunity gaps more effectively than an additional dose of trivalent OPV. However, IPV alone demonstrates minimal advantage on humoral immunity compared with monovalent and bivalent OPV, and cannot provide the intestinal immunity that prevents infection and spread to those individuals not previously exposed to live poliovirus of the same serotype (i.e. type 2 for children born after the switch from trivalent to bivalent OPV in April 2016). A review of operational data from polio campaigns shows that addition of IPV increases the cost and logistic complexity of campaigns. As a result, campaigns in response to an outbreak often target small areas. Large campaigns require a delay to ensure logistics are in place for IPV delivery, and may need implementation in phases that last several weeks. Challenges to delivery of injectable vaccines through house-to-house visits also increases the risk of missing the children who are more likely to benefit from IPV: those with difficult access to routine immunization and other health services. Based upon this information, the Strategic Advisory Group of Experts in immunization (SAGE) recommended in October 2020 the following strategies: provision of a

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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CRediT authorship contribution statement

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second dose of IPV in routine immunization to reduce the risk and number of paralytic cases in countries at risk of importation or new emergences; and use of type 2 OPV in high-quality campaigns to interrupt transmission and avoid seeding new type 2 cVDPV outbreaks.

Keywords

Outbreak response; Campaigns; Circulating vaccine-derived poliovirus; Inactivated poliovirus vaccine; Oral poliovirus vaccine

1. Introduction

The emergence and spread of type 2 circulating vaccine derived poliovirus (cVDPV) in multiple countries throughout Africa and Asia, that resulted in 533 paralytic poliomyelitis cases during 2017–2019 and 1079 in 2020, is a major setback for the Global Polio Eradication Initiative (GPEI) [1]. The fact that the source of these outbreaks is the Sabin oral poliovirus vaccine (OPV) makes it difficult for the GPEI to convey the message to health workers and affected communities that delivery of the same vaccine with high coverage is the best tool to control the outbreaks and prevent new emergences. Delivery of inactivated poliovirus vaccine (IPV) in combination with OPV in campaigns has been proposed to counteract the lower immunogenicity of OPVs in tropical settings and accelerate the control of type 2 cVDPV outbreaks [2,3]. However, because IPV does not provide intestinal immunity in individuals never exposed to live poliovirus, the potential role of IPV in interrupting poliovirus circulation is limited in settings with predominant transmission through the fecal-oral route. Furthermore, delivery of IPV with OPV in campaigns requires skilled health workers, more resources and longer time for implementation; and may reach lower coverage than OPV campaigns, especially among hard-to-reach populations, because injectable vaccines are difficult to administer through house-to-house visits.

This report summarizes immunogenicity data from clinical trials using OPV and IPV in combination or sequential schedules, and reviews operational data and reports of field experience with the use of IPV in campaigns. For the review we selected through a search in PubMed clinical trials and reports of campaigns that administered IPV and OPV and were published in peer-reviewed journals in English, acknowledging the journal limits for references. For the summary tables of immunogenicity data we chose clinical trials that compared OPV and IPV formulations currently in use, applied standardized tests for measuring polio antibody titers and had sufficient sample size to assess differences. Data reported to the World Health Organization Polio Information System (POLIS) was used for analysis of campaign performance. The information provided by this review guided the October 2020 recommendation by the Strategic Advisory Group of Experts in immunization (SAGE) to the World Health Organization of not using IPV for campaigns in response to type 2 cVDPV outbreaks [4].

2. Immunogenicity of IPV, OPV or OPV + IPV combinations

2.1. Natural infection

Poliovirus is transmitted via the oral-oral route or the fecal-oral route, through inhalation of droplets, or contamination of hands, food, utensils or water with nasopharyngeal secretions or fecal material from an infected individual [5]. Infection of naïve hosts with poliovirus results in viral replication and shedding in nasopharyngeal secretions for about 1–2 weeks and in stools for several weeks. Poliovirus replication stimulates the production of type-specific neutralizing antibodies in serum (Immunoglobulins M, G and A), and in nasopharyngeal and intestinal secretions (secretory immunoglobulin A), within 1–3 weeks [6].

Serum and mucosal antibody levels decline slowly with time and may become negative following initial infection, but are boosted upon new exposures or vaccination. The presence of antibodies in serum confers protection against paralysis even at low titers at the level of detection [7]. Even if antibodies decrease to undetectable levels, poliovirus-specific memory cells appear to provide life-long protection against paralysis. In contrast to humoral immunity, mucosal immunity is partial and wanes with time. Studies conducted in the United States in the 1950's found that shedding of vaccine virus following administration of OPV occurred in a smaller proportion and for shorter duration among children and adults who were seropositive from natural infection before the challenge OPV dose than in seronegative individuals [8,9].

2.2. Vaccination with OPV

OPV contains live attenuated poliovirus strains (single or combinations of Sabin strains types 1, 2, and 3 depending on preparation) that induce humoral and mucosal immunity in a way similar to infection from wild poliovirus [6,10,11]. About 10–25% of fully OPV-vaccinated children, depending on time since last dose, will still shed virus following an OPV challenge, especially with a high dose [9,10,12–14]. OPV-vaccinated individuals also shed poliovirus for a shorter time and at lower viral concentration than naïve and IPV-vaccinated individuals [9–12].

Provision of several doses of OPV through routine immunization offers long-term protection against paralysis and reduces probability and duration of viral shedding upon re-infection with poliovirus, thus contributing to the interruption of poliovirus circulation [13]. Sabin strains, especially type 2, may also spread and indirectly vaccinate contacts [15], which enhances the field effectiveness of OPV. For example, after OPV introduction in Yaoundé, Cameroon in 1979, the incidence of paralytic poliomyelitis decreased by 85% although only 35% of children 12 to 13 months old received three doses of OPV [16]. The major drawbacks of OPV are that Sabin strains cause vaccine-associated paralytic polio (VAPP) in rare occasions (about 4.7 cases per million births) [17], and that prolonged transmission of Sabin viruses in areas with poor vaccine coverage facilitates reversion of attenuating mutations resulting in emergence of cVDPVs, which have re-acquired the neurovirulence and transmissibility of wild strains [18,19].

Trivalent OPV has been the vaccine of choice for global polio eradication since the initiative was launched in 1988 when the three serotypes were circulating and cases were occurring in more than 125 countries. Because Sabin type 2 is more immunogenic, susceptible individuals usually respond to type 2 after the first dose, and may need several doses to seroconvert (become seropositive) to types 1 and 3. Following 3 doses of trivalent OPV ≥ 95% infants were found to seroconvert and develop long lasting immunity to all three poliovirus serotypes in temperate countries [20]. However, OPV is less immunogenic in tropical countries, probably because of higher prevalence of factors that interfere with vaccine take such as malnutrition, diarrhea or infection by other enteroviruses [20–22]. Three doses of trivalent OPV were found to seroconvert a weighted average of 73% (range, 36%–99%) for type 1, 90% (71% to 100%) for type 2, and 70% (range, 40%–99%) for type 3 [21].

To overcome the inferior immunogenicity of trivalent OPV in tropical countries the GPEI used several strategies: a) reduce the relative content of type 2 with a formulation containing a 10:1:6 ratio for types 1, 2 and 3 [23]; b) deliver multiple doses of OPV through routine immunization (RI) and immunization campaigns conducted nationally and sub-nationally [24]; and c) in the mid-to late-2000s, re-introduce monovalent OPV types 1, 2, and 3, and bivalent (type 1 and 3) OPV. Clinical trials during 2000–2015 have confirmed the higher per-dose immunogenicity of monovalent OPVs compared to trivalent OPV in several tropical countries [25–29]. Seroconversion after 2 doses administered between birth and 3 months of age were 90% for monovalent OPV1, 90–97% for monovalent OPV2, and 74–84% for monovalent OPV3; after 3 doses of monovalent OPV1 seroconversion was greater than 95% [26]. Two or 3 doses of bivalent OPV elicited non-inferior responses to monovalent OPV1 or OPV3 [25–28].

Use of monovalent OPV1 in campaigns during 2005–2008 in poliovirus reservoirs in Northern India and Northern Nigeria significantly decreased transmission of type 1 wild poliovirus, although this strategy resulted in the resurgence of wild type 3 during 2009 [30]. The addition of bivalent OPV to campaigns since 2009 together with implementation of strategies to improve coverage, were crucial to achieve high levels of population immunity to both serotypes and eliminate the final chains of endemic wild poliovirus from both countries [31,32]. But replacement of trivalent with bivalent OPV in campaigns in countries with poor routine immunization, also contributed to the emergence of type 2 cVDPV before the global switch to bivalent OPV in 2016 [18]. The widespread transmission of type 2 cVDPV outbreaks observed during 2019–20 is a consequence of the reduction in mucosal immunity to type 2 caused by the global switch to bivalent OPV, and the inadequate quality of campaigns delivering type 2 OPV conducted before and after the switch. Lapses in poliovirus surveillance also allowed some cVDPV outbreaks to remain undetected at the time of the switch [19].

2.3. Vaccination with IPV

IPV is administered via the intramuscular, subcutaneous, or intradermal route, and contains chemically inactivated poliovirus types 1, 2 and 3. Wild poliovirus strains are included in Salk IPV and Sabin strains in Sabin IPV. IPV induces high levels of neutralizing

antibodies in serum and elicits oropharyngeal mucosal immunity but has minimal effect on intestinal immunity in naïve individuals [10–12]. Vaccination schedules with IPV alone protect recipients from paralysis and reduce transmission of poliovirus through the oral-oral route (nasopharyngeal shedding), but are ineffective at stopping poliovirus transmission through the fecal-oral route, which plays a major role among young children and in settings with suboptimal sanitation [5].

IPV immunogenicity is affected by antigen content, presence of adjuvants, age at first dose, and interval between doses [20,33]. In clinical trials, a single dose of Salk IPV (containing 40:8:32 D Unit/per dose of types 1, 2 and 3) provided between 6 weeks and 4 months of age induced seroconversion in 19–57% infants for type 1, 26–80% for type 2, and 32–45% for type 3 [20,33]. Lower seroconversion rates were observed with IPV administration before 3 months of age because of interference of maternal antibodies and incomplete maturity of the immune system, although most of the seronegative infants were primed (i.e., exhibited an early immune response upon a challenge with a new vaccine dose) [34–36]. Two doses elicited seroconversion to all three serotypes in greater than 95% of infants and high antibody titers, when the first dose was given after 2 months of age and the second dose after a 4–6 month interval [36,37]. Primary vaccination with 3–4 IPV doses seroconverted 100% of children and elicited high titers at the end of the series [20,38,39].

Primary immunization with one or two doses of fractional IPV injected via intradermal route (0.1 mL or 1/5th dose) induced lower seroconversion rates and antibody titers than full-dose IPV, but differences were less significant with schedules that included three doses, or delay the first dose and include an interval between doses above 8 weeks [20,37,38]. Two fractional IPV doses administered at 3.5–4 months and at 8–9 months of age may induce greater than 95% seroconversion to the three serotypes [37]. The quality of the intradermal injection, which depends on the vaccinator technique and device used for injection, may also affect the immunogenicity of fractional IPV [40]. Loss of vaccine fluid on the skin and a small bleb size (below 5 mm) have been associated with inferior immune responses [40].

2.4. Sequential/combined schedules with OPV and IPV

Use of both vaccines can offset the limitations in safety and efficacy of each one, although at a higher cost per child vaccinated. Primary immunization series with combined or sequential OPV-IPV schedules may achieve higher seroconversion rates and antibody titers for all serotypes than series with trivalent OPV alone, depending on the time of IPV administration, the type and total number of OPV doses received, and the efficacy of OPV in that setting. As shown on Table 1, clinical trials found that addition of 1 or 3 doses of IPV to trivalent OPV with the WHO schedule of 6, 10 and 14 weeks of age (with or without a birth dose) increased seroconversion rates and final titers for types 1 and 3 in most settings, but the effect was often not clinically or statistically significant for type 2 because tOPV also achieved high seroconversion rates and titers [39,41–45]. Provision of an IPV dose after several doses of bivalent OPV provided protection for type 2 poliovirus in 49–80% of naïve infants (Table 1), and boosted titers for serotypes 1 and 3 without significantly modifying the high seroconversion rates achieved with bivalent OPV alone [39,42,43].

A supplemental dose with IPV plus OPV may have more impact on humoral immunity than OPV alone in populations that are under-vaccinated because of suboptimal coverage or use of monovalent OPVs, and in populations with low OPV efficacy. As shown on Table 2, a supplemental dose of IPV was more effective than trivalent and monovalent OPV3 in closing remaining humoral immunity gaps to serotypes 1 and 3 after 2–5 doses of trivalent OPV in Cote d'Ivoire, Gambia, Oman and Cuba [46–49]. In areas with persistent wild poliovirus circulation in India and Pakistan, IPV closed immunity gaps to type 2 and 3 caused by intensive use of bivalent and monovalent OPV1 in campaigns [22,50]. In Pakistan, an IPV booster was more immunogenic than bivalent OPV among malnourished infants 9–12 months of age, who already had lower seroprevalence for the three serotypes at baseline compared with normally nourished infants [22]. Also in Pakistan, addition of IPV to trivalent OPV as a booster dose was more immunogenic than monovalent OPV2 among children seronegative after four doses of different polio vaccines (trivalent OPV, bivalent OPV and/or IPV) [51]. Seroconversion to type 2 poliovirus after the booster at 22 weeks was 29% (38/133) after trivalent OPV, 61% (31/51) after monovalent OPV2 and 100% (47/47) after trivalent OPV plus IPV. Compared with a full IPV dose, a supplemental dose with fractional IPV induces lower or similar changes in seroconversion and boosting of titers, depending on the device used, but lower final antibody titers (Table 2) [49,52].

A supplemental IPV dose may also boost intestinal local immunity better than an OPV dose among children with intestinal immunity waning after vaccination, who live in poliovirus transmission reservoirs with decreased OPV efficacy [13]. Administration of an IPV booster to 10-year-old children in northern India, who had received multiple OPV doses up to 5 years of age, reduced shedding of type 1 poliovirus one week after a bivalent OPV challenge by 82%, whereas a bivalent OPV booster reduced shedding by 51%, compared with children who had received no booster (poliovirus detected in 7%, 19%, and 39% of the IPV, OPV, and control groups, respectively). However, neither IPV nor OPV had effect on type 1 poliovirus shedding after the bivalent OPV challenge among infants 6–11 months of age who had recently received several doses of OPV (poliovirus detected in 6%, 12%, and 4% of IPV, OPV, and control groups respectively) [13]. Among Pakistani infants 9–12 months of age who were given a booster with bivalent OPV alone or bivalent OPV plus IPV after having received an average of 10 OPV doses, a very small proportion shed poliovirus 7 days after a challenge with bivalent OPV, without significant differences between study arms (type 1 poliovirus detected in 2–5% and type 3 poliovirus in 3–7% of infants) [22]. Among children aged 1–4 years from Vellore, India, who had received a median of 10 OPV doses, an IPV booster reduced slightly shedding for both type 1 and 3 serotypes after a bivalent OPV challenge compared with control children who received no booster. Serotype 1 poliovirus was detected in 12% of IPV-boosted children versus 19% of control children ($P < 0.05$); serotype 3 poliovirus was detected in 8% versus 26% ($p < 0.0001$) [14].

3. Provision of OPV or IPV in campaigns

Delivery of vaccines in campaigns can quickly reduce susceptibility in multiple birth cohorts at once, which is essential to interrupt poliovirus circulation during outbreaks. The impact of vaccination campaigns, however, depends mainly on the promptness of campaign implementation after detection of the first case or outbreak confirmation and the coverage

reached, especially among children who have poor access to RI. Modeling analysis of polio campaigns has shown that delaying an outbreak response more than 30 days after confirmation of poliovirus circulation, results in more extensive outbreaks with more cases [53]. Coverage above 90%–95% may be required to interrupt wild and vaccine-derived poliovirus outbreaks, especially in areas with high force of infection [53,54].

3.1. Advantages and risks of OPV use in campaigns

OPV has been the vaccine of choice for preventive and outbreak response campaigns. OPV is ideal for campaign delivery because it is inexpensive, easy to administer, and well accepted by children. National Immunization Days and “mop-up” campaigns can be performed through house-to-house visits in a short time by deploying large numbers of volunteers with minimum training [24]. House-to-house vaccination has been demonstrated to be crucial to achieve high coverage in countries of Africa and Asia [55]. The ability of OPV to spread to un-vaccinated individuals may increase campaign impact on population immunity [16], but is also responsible for new cVDPV emergences when RI and campaign coverage is very low [18]. The risk of re-seeding new type 2 VDPVs with OPV campaigns continues to increase since the withdrawal of trivalent OPV in 2016, as new birth cohorts without intestinal immunity to type 2 poliovirus and waning immunity among those born before 2016 increase the pool of individuals participating in transmission of OPV strains [19].

3.2. Experience to date with IPV use in campaigns

A review of data reported through the WHO’s Polio Information System (POLIS) as of March 2021, found that between December 2013 and October 2020, 78 campaigns delivered either full (n = 73) or fractional (n = 5) dose IPV (Table 3). IPV campaigns were implemented initially in response to some type 1 wild poliovirus circulation, and since 2017, in response to some cVPDV2 outbreaks as well. Because of limitations of the available data, some IPV campaigns may have been for catch-up vaccination in birth cohorts that missed IPV in RI, and not for outbreak response. Pakistan, Afghanistan and Nigeria conducted 76% of the IPV-containing rounds (Fig. 1); other countries with rounds included Angola (1), Cameroon (1), China (4), Ghana (1), India (1), Kenya (1), Malaysia (1), Somalia (1), and Syria (6) (Table 3). IPV was co-administered with OPV (bivalent, trivalent, or type 2 monovalent) in 31 campaigns (40%) and given alone in 47 campaigns (60%). The target age for IPV was limited to above 6 weeks of age in all campaigns, with 46 campaigns (59%) including children below 5 years, 26 campaigns (33%) including children below 2 or 3 years, and 6 (8%) covering other age groups.

In general, IPV campaigns were small (Table 3). The GPEI guidelines recommend that an outbreak response for a cVDPV2 outbreak includes a small rapid response campaign (round zero) targeting about 100,000 to 500,000 children; followed by two larger scale rounds targeting at least 1–4 million individuals and additional small mop-up rounds in areas with poor performance [54]. The median target population of IPV campaigns was below 300,000 children and covered <15 districts. Only 13 campaigns targeted ≥ 1 million children and four campaigns ≥ 5 million. Most campaigns (55, 72% of 76 with dates of implementation) were conducted within 7 days, and 17 (22%) within 8–17 days. Three campaigns covering 0.2–6.5

million children required 23 to 29 days; and the national campaign in Angola (1.2 million) was completed in three phases over 99 days (Table 3).

3.3. Operational issues with IPV use in campaigns

Use of an injectable vaccine for polio campaigns require administration by healthcare workers instead of volunteers and delivery through fixed-posts instead of house-to-house visits. Also, more resources and complex logistics are required to handle supervision and management of safe injection practices and adverse events, transport of vaccines in cold chain, and sharps disposal. Reports from campaigns conducted in Kenya (2013), India (2016), Pakistan (2015–19), and Syria (2017–18) provide operational lessons learned with delivery of IPV plus OPV in campaigns [56–61].

Reports from the first IPV campaign conducted in Kenya (2013) demonstrated that it is feasible to conduct a campaign delivering two different polio vaccines, and that the population accepts administration of both vaccines without major concern about potential side effects [61].

Scarcity of healthcare workers in many countries with polio outbreaks is the major factor limiting the size and duration of campaigns with injectable vaccines. Deployment of skilled vaccinators from non-affected areas to the outbreak response areas allowed quick implementation of IPV-OPV rounds in Kenya, India, and Syria [56,58,61]. Quick successful implementation was also attributed to prior campaign experience, either because of frequent planned campaigns (India, Pakistan) or because of recent outbreak rounds in the same area (i.e., Syria and Kenya used IPV after several OPV rounds)[56,58,59,61].

The cost of adding IPV to OPV for campaigns was estimated in two outbreak response rounds conducted in 2013 in Kenya [61]. The total cost per child vaccinated reached $3.27 for the December round delivering IPV plus trivalent OPV compared with $0.50 per child during the November round delivering trivalent OPV alone. The vaccine cost alone was $2.09 for an IPV dose and $0.14 for an OPV dose.

Although fractional IPV could reduce the cost per vaccine dose, stretch a limited supply, and reduce the risk of adverse effects of poor intramuscular injection technique, it has been used rarely in campaigns during 2016–2020. Reports of campaigns in India and Pakistan highlighted the importance of selecting experienced vaccinators and providing additional training in achieving intradermal injections of good quality [56,59]. Use of jet injectors and syringe adaptors that guide the needle to its appropriate position in the skin, were well accepted by vaccinators, and jet injectors increased vaccination acceptance among caregivers. However, ease of use, quality of intradermal injections observed, and (when studied), immunogenicity, varied with devices [52,57,60].

3.4. Coverage with IPV use in campaigns

Information on the quality of IPV-containing campaigns reported on the POLIS database is limited. Only 27% of the 78 campaigns reported had administrative coverage data, and only 7 (9%) had information on missing children using lot quality assurance sampling (LQAS) surveys. Median administrative coverage was 99–100% in Pakistan and Afghanistan (range

65–111%), and only 68% (range 36–100%) in Nigeria (Table 3). Results from available LQAS surveys ranged from 0 to 100% of lots passing the 90% threshold for children with missed vaccination (results not presented), and, for campaigns that distributed IPV plus OPV, it was not possible to know which children received OPV only or OPV plus IPV.

Evaluations of IPV campaigns in Pakistan and Kenya described the challenges for vaccinators to reach target populations with fixed posts in rural areas. In Pakistan, a campaign delivering fractional IPV in four districts in Sindh had an estimated coverage of 90% (95% confidence interval = 88–92%), but social mobilization and coverage in outreach areas was likely lower than in urban areas [59]. In Kenya, a vaccine coverage survey found that IPV plus trivalent OPV reached more than 90% in refugee camps and surrounding communities, but vaccination sites had to become “temporary fixed posts” to reach vaccination targets, as caregivers requested vaccinators to bring vaccine closer to their homes. In a convenience sample of nomadic families settled near the villages and camps participating in the survey, <40% of children had received vaccine during the IPV round and during a previous round with trivalent OPV; the same children who had missed the trivalent OPV round were also missed by the IPV round [61].

3.5. Impact of IPV use in campaigns

IPV use in the United States in the 1950’s decreased the number of polio cases beyond expectations based upon the proportion of children vaccinated. The “herd effect” of IPV has been attributed to a direct effect on mucosal immunity in the nasopharynx and indirect effect in boosting intestinal immunity among individuals exposed to natural infection [62].

High coverage with IPV-only schedules has successfully prevented community transmission following importations for 20–50 years in countries with good sanitation with very few exceptions. Outbreaks in the Netherlands in 1978 and 1992 [63], and in Israel in 1988 and 2013 [64] caused between zero (Israel 2013) and 110 paralytic cases (Netherlands 1978). Most of the paralytic cases occurred among individuals who had not received IPV, and asymptomatic transmission among IPV-vaccinated individuals was documented. Administration of OPV, with or without IPV, was required to control the outbreaks [63,64]. Campaigns with IPV alone were conducted in Telangana, India in 2016, and in China in 2019 and 2020, following detection of VDPV2 in environmental samples (India and China in 2019) or in AFP case and contacts (in 2020 in another area in China). No new VDPV was detected after the campaigns [56,65].

Interpretation of the impact of adding IPV to OPV in campaigns on prevention of paralytic cases and slowing transmission often depends on assumptions used for statistical analysis or modeling, type of poliovirus, and period of time analyzed [2]. Shirref, Grassly, et al. looked at incidence of paralytic cases and prevalence of positive environmental samples 90 days before and after a campaign. For campaigns conducted during 2014–2016 in Nigeria, there was a slight reduction in type 2 cVDPV cases with IPV plus trivalent OPV whereas trivalent OPV alone had no effect. The incidence risk ratio (IRR) for cases detected 90 days before and after was 0.17 (95% CI 0.04–0.78, p = 0.02) for combined rounds and 0.59 (95% CI 0.18–1.97) for trivalent OPV rounds [2]. In Pakistan, campaigns that used IPV alongside any OPV during 2014–2017 had a significant impact on the detection of environmental

samples of type 1 wild poliovirus (prevalence ratio 0.63, 90% bootstrap CI 0.47–0.81), but not on incidence of poliomyelitis cases (IRR 0.62, 90% bootstrap CI 0.23–1.14) [66]. Using a deterministic model of poliovirus transmission, Duintjer Tebbens et al. found that adding IPV to the first or second round in Nigeria would result in a small reduction in polio cases (4–6%) at a much higher cost, compared with mOPV2-only rounds. The incremental benefit of IPV remained limited after 2017 [67,68].

4. Conclusions and recommendations for type 2 cVDPV outbreaks

Results from clinical trials and some field experiences suggest that provision of supplementary doses of IPV in combination with OPV in campaigns in populations with difficult access for RI or high risk of OPV failure could, in theory, close humoral immunity gaps and boost mucosal immunity to poliovirus with fewer vaccination encounters, thus accelerating interruption of transmission in outbreaks. However, several caveats need to be considered when interpreting the available data and assessing the potential use of IPV for VDPV2 outbreaks from 2021 onwards:

- Clinical trials have shown that IPV has a limited advantage over monovalent OPV2 or trivalent OPV on humoral immunity and paralysis protection against type 2 poliovirus, because of the high immunogenicity of the Sabin 2 strain in most settings.
- Since May 2021 children below 5 years have not been exposed to type 2-containing OPV in areas with new cVDPV2 outbreaks. Therefore delivery of an IPV dose in campaigns will not have the boosting effect on intestinal mucosal immunity observed in clinical [9,13,14] or field studies conducted in populations with prior exposure to live poliovirus [2,62]. For IPV to have any impact on intestinal mucosal immunity among children targeted by the campaigns, it should be provided after one or more rounds of type 2-containing OPV.
- Addition of IPV to polio campaigns increases the cost per child vaccinated, complicates the logistics of vaccine delivery and hinders the polio program’s ability to use strategies that make campaigns effective for controlling poliovirus outbreaks: 1) rapid implementation after detection; 2) scope large enough, and 3) high coverage, even among communities with difficult access to healthcare and RI services.

In October 2020, the SAGE recommended the introduction of a second dose of IPV at around 9 months of age into RI, which will induce type 2 antibodies in an additional 35–50% of children who receive the first dose at 3 months [4]. When the second dose is introduced, it will have an impact in reducing the potential number of paralytic cases in countries at risk for type 2 cVDPV importations or emergences but only if coverage is moderately high or high. IPV with OPV and other antigens should be considered in catch-up campaigns in low RI coverage areas and, particularly, among those cohorts that missed RI doses because of the global shortage of IPV during 2016–2018, a reduction in program performance during 2020–2021 due to the coronavirus pandemic, or conflict-related inaccessibility to services.

In countries experiencing cVDPV2 outbreaks during 2021, type 2 OPV is the best tool to quickly provide humoral and mucosal immunity to a large susceptible population. Monovalent Sabin OPV2 or novel OPV2 is indicated for countries with exclusive type 2 poliovirus transmission whereas trivalent OPV is reserved for countries with co-circulation of serotypes. In its meeting in October 2020, SAGE did not recommend addition of IPV to type 2 OPV campaigns because it will slow the implementation of the response, will have a small impact on reduction of paralytic cases at a high programmatic cost, and will not close immunity gaps persisting due to poor quality of vaccination activities [4]. Achieving high coverage with OPV campaigns through enhanced microplanning, social mobilization, and delivery strategies tailored to reach high-risk populations (mobile and underserved communities), are the most important ways to interrupt current cVDPV outbreaks and prevent re-seeding new ones.

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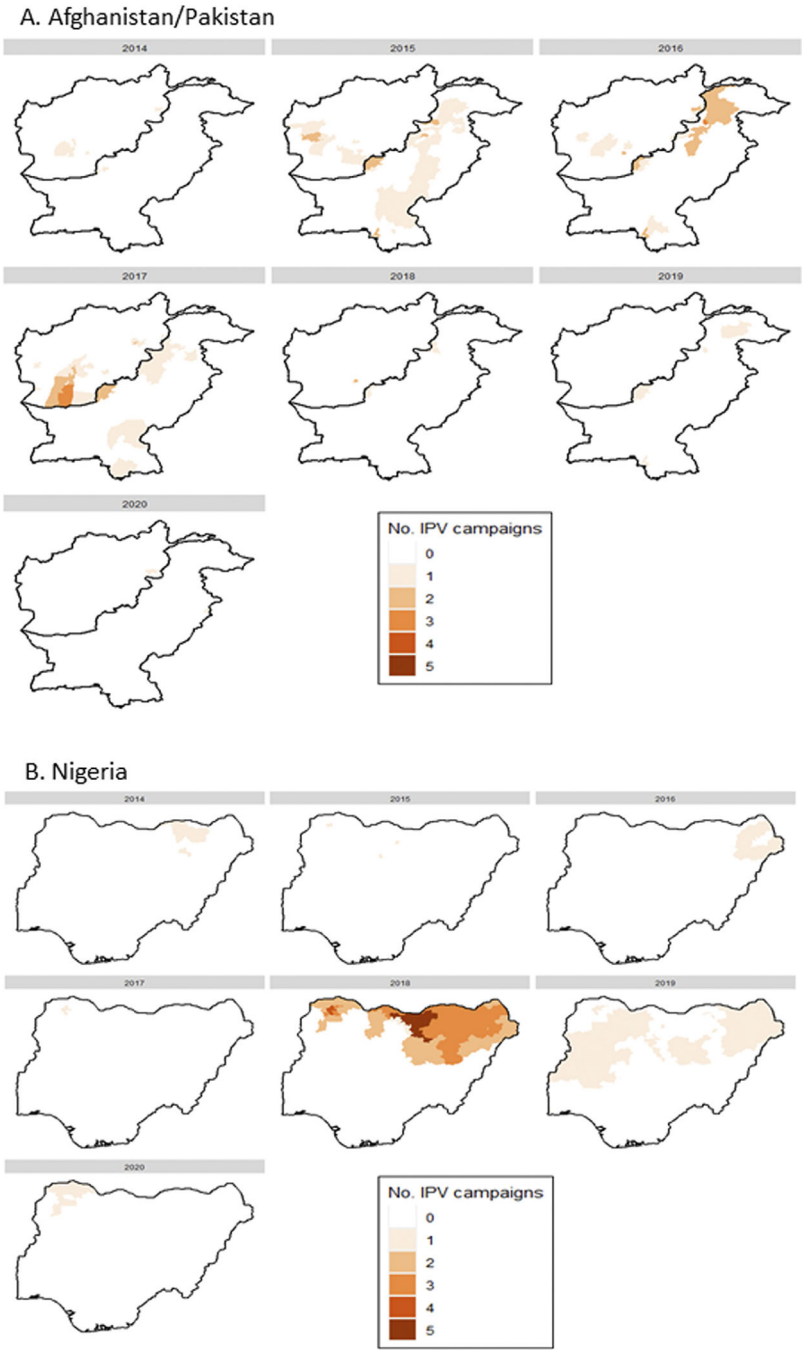

Fig. 1.

Table 1

Seroconversion and antibody titers after sequential OPV-IPV schedules for routine immunization.

Author, year, country [reference]	OPV type and schedule	IPV schedule	Time outcome measured	N	Seroconversion			Antibody titers*		
					P1	P2	P3	P1	P2	P3
Parent, 2002, Pakistan [41]	tOPV at 0–6–10–14 wk	None	24 wk	302	89%	96%	95%	213	440	174
	tOPV at 0–6–10–14 wk	6–10–14 wk		292	95 %[a]	97%	98%	470 [a]	818 [a]	905 [a]
	tOPV at 0–6–10–14 wk	14 wk		304	90%	96%	95%	286 [a]	513	344 [a]
Sutter, 2015,India [42]	tOPV at 0–6–10–14 wk	None	18 wk	163	98%	98%	76%	1152	181	228
	tOPV at 0–6–10–14 wk	14 wk		162	99%	99%	86% [a]	646	323	362
	bOPV at 0–6–10–14 wk	None		155	98%	25% [a]	94% [a]	406	406	228
	bOPV at 0–6–10–14 wk	14 wk		156	98%	72% [a]	95% [a]	45	28	362
Asturias, 2016, Latinoamerica [43]	bOPV at 6–10–14 wk	None	18 wk	200	100%	10%[a]	99%	≥1448	<8	≥1448
	tOPV at 6–10–14 wk	None		90	98%	98%	99%	≥1448	≥1448	≥1448
	bOPV at 6–10–14 wk	14 wk		199	100%	80 %[a]	100%	≥1448	28[a]	≥1448
	bOPV at 6–10–14 wk	14–36wk	40 wk	189	100%	100%	100%	≥1448	≥1448	≥1448
Saleem, 2018,Pakistan [39]	None	0–6–10–14 wk	22 wk	138	80% [a]	84% [a]	93% [a]	445	111[a]	446
	bOPV at 0–6–10–14 wk	None		144	97%	19% [a]	94%	≥1448	181[a]	588
	bOPV at 0–6–10–14 wk	14 wk		139	94%	53% [a]	98%	≥1448	32[a]	1261
	bOPV at 0–6–10–14 wk	14 wk		138	96%	49% [a]	94%	≥1448	39[a]	1176
	tOPV at 0–6–10–14 wk	None		134	94%	93%	85%	1152	724	294
Saez-Llorens,2016, Panama [45]	bOPV at 6–10–14 wk	14 wk (mIPV2)	18 wk	115	96%	93 %[b]	98%	≥1448	181[b]	≥1448
	bOPV at 6–10–14 wk	14 wk		115	91%	76%	98%	≥1448	36	≥1448
Lopez Medina, 2017, Latinoamerica [44]	bOPV at 6–10–14 wk	14 wk	18 wk	286	100%	79%	100%	≥1448	28	≥1448
	bOPV at 6–10–14 wk	14–36 wk	40 wk	535	100%	100%	100%	≥1448	≥1448	≥1448

bOPV – bivalent oral poliovirus vaccine; tOPV – trivalent oral poliovirus vaccine; IPV – inactivated poliovirus vaccine; mIPV2 – IPV containing 32 D–Ag units of inactivated type 2 poliovirus. DSJI – disposable syringe jet injector; NS – needle and syringe.

*Geometric Mean Titers reported in Parent's study; other studies reported median values. Titers were measured only in seropositive children except in the study by Asturias.

[a] $p < 0.05$ versus arm receiving tOPV only.

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[b] $p < 0.05$ versus arm receiving standard IPV.

Table 2

Seroprevalence and antibody titers before and after a booster dose with OPV or IPV among children previously exposed to OPV.

Author, year publ., country, [reference]	OPV doses at baseline	Booster dose	N	Percent of seropositive children						Titers (median or GMT)*					
				Pre- booster			Post-booster			Pre- booster			Post-booster		
				P1	P2	P3	P1	P2	P3	P1	P2	P3	P1	P2	P3
Moriniere, 1987, Cote d'Ivoire [46]	tOPV at 6–10–14 wk	IPV at 6 mo	186	73%	93%	67%	94 %[a]	100%	89 %[a]	166	618	61	1294	39	1591[a]
		tOPV at 6 mo	182	76%	91%	57%	85%	95%	65%	181	529	41	924	318	609
		IPV at 9 mo	177	85%	93%	76%	97% [a]	100%	92% [a]	321	437	123	1954	64	1977[a]
		tOPV at 9 mo	169	83%	91%	75%	85%	94%	75%	280	403	96	1589	270	779
Hanlon, 1987, Gambia [47]	tOPV at 2–3–4 mo	IPV at 1 yr	52	81%	95%	81%	88% [a]	99%	69% [a]						
		tOPV at 1 yr	58				81%	99%	56%						
Clarke, 2016, Gambia [52]	~5 OPV doses	IPV-NS at 9–10 mo	178	87%	96%	80%	98%	99%	98%	64	64	32	512	512	178
		IPV-DSJI at 9–10 mo	168	90%	99%	83%	99%	100%	96%	64	128	32	512	512	168
		fIPV-NS at 9–10 mo	177	86%	98%	74%	98%	99%	94%	64	64	16	256[b]	256[b]	177[b]
		fIPV-DSJI at 9–10 mo	177	90%	99%	76%	97%	100%	93%	64	64	32	256[b]	256[b]	177[b]
Sutter, 2000, Oman [48]	tOPV at 0–1.5–3–5–7 mo	IPV at 9 mo	205	98%	97%	88%	100%	100%	97 %[a]	576	1152	228	≥1448	≥1448	≥1448[a]
		tOPV at 9 mo	177	97%	99%	87%	99%	98%	88%	910	1448	228	1152	≥1448	288
		mOPV3 at 9 mo	205	97%	99%	93%	96%	99%	92%	910	1152	228	724	1152	288
Estivariz, 2012,India [50]	~ 7 mOPV1 (campaign) + 3 tOPV	IPV at 6–9 mo	183	100%	77%	47%	100%	99 %[c]	95 %[c]	≥1448	362	<8	≥1448	≥1448[c]	455[c]
		mOPV1 at 6–9 mo	175	99%	73%	50%	99%	73%	51%	≥1448	362	<8	≥1448	288	11[c]
Saleem, 2015, Pakistan [22]	~8 OPV + 2 tOPV (malnutrition)	bOPV at 9–12 mo	224	84 %[d]	71 %[d]	71 %[d]	92 %[d]	77 %[d]	75 %[d]	724[d]	409[d]	181[d]	≥1448	572	228
		bOPV + IPV at 9–12 mo	227	88%	76%	71%	98%	96%	92%	910	362	72	≥1448	≥1448	≥1448
	~8 OPV + 2 tOPV (normal nutrition)	bOPV at 9–12 mo	239	96%	85%	84%	98%	86 %[d]	86%	1152	910	362	≥1448	1152	455
		bOPV + IPV at 9–12 mo	238	92%	89%	83%	100%	100%	98%	≥1448	910	362	≥1448	≥1448	≥1448
Resik, 2015, Cuba[e] [49]	2 tOPV in campaigns	IPV at 12–20 mo	146	94%	98%	84%	99%	100%	99%	713	143	113	4499	2839	4499
		fIPV-NS at 12–20 mo	134	92%	95%	81%	96%	97%	95%	713	127	102	1423	1130	1130

Author, year publ., country, [reference]	OPV doses at baseline	Booster dose	N	Percent of seropositive children						Titers (median or GMT)*					
				Pre- booster			Post-booster			Pre- booster			Post-booster		
				P1	P2	P3	P1	P2	P3	P1	P2	P3	P1	P2	P3
		fIPV-DSJI at 12–20 mo	145	97%	99%	89%	99%	99%	97%	713	143	90	1423	566	1423
		fIPV-DSJI at 12–20 mo	153	92%	97%	90%	99%	98%	95%	566	149	113	898	1130	566
		fIPV-DSJI at 12–20 mo	151	93%	98%	88%	98%	99%	95%	713	148	90	1423	1130	1423

OPV - oral poliovirus vaccine; bOPV - bivalent oral poliovirus vaccine; tOPV - trivalent oral poliovirus vaccine; IPV – inactivated poliovirus vaccine; mIPV2 – IPV containing 32 D-Ag units of inactivated type 2 poliovirus; fIPV – fractional IPV (0.1 mL dose) via intradermal; DSJI – disposable syringe jet injector; NS – needle and syringe.

*Geometric Mean Titers reported in Moriniere's study; other studies reported median values.

[a] $p < 0.05$ versus booster with tOPV.

[b] failed non-inferiority comparison with booster with IPV-NS.

[c] $p < 0.05$ versus booster with mOPV1.

[d] $p < 0.01$ among the four study arms.

[e] Differences among groups not reported.

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Table 3

Operational characteristics of campaigns distributing IPV reported to the WHO's Polio Information System (POLIS), December 2013-March 2021.

Country (N)	Year(s)	Duration in days[a]	Vaccines distributed	Age Range[a]	Target population[a]	Target districts	Administrative coverage
Kenya (1)	2013	4	IPV	<5yrs	120,196	1	Not available
Afghanistan (23)	2014–2020	5 (0–29)	IPV(13) IPV + bOPV(10)	<5yrs (20); <2yrs(1); <9yrs(1); 4–5yrs(1)	93,283 (2,840–1,200,000)	4 (1–17)	101% (65–111%)[d]
Nigeria (12)[b]	2014–2019	5.5 (0–23)[c]	fIPV(2); IPV(4); IPV + bOPV(1); IPV + tOPV(3); IPV + mOPV2 (1) fIPV + mOPV2(1)	<5yrs(10); <3yrs(2)	540,824 (48,969–12,300,311)	18 (5–318)	68% (36–100%)[d]
Pakistan (24)[b]	2014–2020	7 (3–23)[c]	IPV(17); IPV + bOPV(6); fIPV + bOPV(1)[b]	<2yrs(16); <5yrs(8)	182,303 (16,404–6,159,023)	3 (1–45)	99% (78–107%)[d]
Cameroon (1)	2014	4	IPV	<5yrs	262,000	12	Not available
India (1)	2016	6	fIPV	<3yrs	291,305	2	Not available
Syria (6)	2017–2018	4 (2–8)	IPV(1); IPV + bOPV(3); IPV + mOPV2(2)	<2yrs(4)	275,178 (58,976–921,809)	21 (6–82)	86% (57–116%)
Somalia (1)	2018	4	IPV	<2yrs	290,691	31	103%
China (4)	2019	6 (6–7)	IPV(4); IPV + bOPV(2)	<5yrs(6)	482,442 (31,283–1,000,000)	9 (1–16)	98% (96–98%)
Ghana (1)	2019	4	IPV	18–47 mo	2,738,500	260	Not Available
Malaysia (1)	2019	1	IPV	<15 yrs	Not available	1	Not available
Angola (1)	2020	99	IPV	<3 yrs	1,201,381	170	Not available

IPV – inactivated poliovirus vaccine; fIPV – fractional IPV (0.1 mL dose) via intradermal; mOPV2 – monovalent oral poliovirus vaccine type 2; bOPV - bivalent oral poliovirus vaccine; tOPV - trivalent oral poliovirus vaccine. Data reported as median(range) or characteristic (number of campaigns).

[a]For campaigns with IPV + OPV combination, the duration, age range, target population reflect those of the IPV component. Minimal age for all campaigns was 6 weeks.

[b]One campaign in Pakistan and one in Nigeria used IPV in some districts and fIPV in other districts. Also some campaigns had different age groups in different areas.

[c]Missing end dates for some campaigns prevented calculation of duration.

[d]Missing administrative coverage data for some campaigns.