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## Pre-eradication vaccine policy options for poliovirus infection and disease control

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### Abstract

With the circulation of wild poliovirus (WPV) types 1 and 3 continuing more than a decade after the original goal of eradicating all three types of WPVs by 2000, policymakers consider many immunization options as they strive to stop transmission in the remaining endemic and outbreak areas and prevent reintroductions of live polioviruses into non-endemic areas. While polio vaccination choices may appear simple, our analysis of current options shows remarkable complexity. We offer important context for current and future polio vaccine decisions and policy analyses by developing decision trees that clearly identify potential options currently used by countries as they evaluate national polio vaccine choices. Based on a comprehensive review of the literature we (1) identify the current vaccination options that national health leaders consider for polio vaccination, (2) characterize current practices and factors that appear to influence national and international choices, and (3) assess the evidence of vaccine effectiveness considering sources of variability between countries and uncertainties associated with limitations of the data. With low numbers of cases occurring globally, the management of polio risks might seem like a relatively low priority, but stopping live poliovirus circulation requires making proactive and intentional choices to manage population immunity in the remaining endemic areas and to prevent reestablishment in non-endemic areas. Our analysis shows remarkable variability in the current national polio vaccine product choices and schedules, with combination vaccine options containing inactivated poliovirus vaccine (IPV) and different formulations of oral poliovirus vaccine (OPV) making choices increasingly difficult for national health leaders.

### Introduction

Launched in 1988, the Global Polio Eradication Initiative (GPEI) successfully eradicated wild poliovirus (WPV) type 2 (WPV2) in 1999.<sup>(1,2)</sup> However, in spite of intensive efforts to achieve the eradication of all three types of WPVs and interruption of transmission in India in early 2011, through 2012 types 1 and 3 (WPV1 and WPV3) continued to circulate in parts of three endemic countries (Afghanistan, Nigeria, and Pakistan).<sup>(3,4)</sup> Endemic countries

export viruses to other countries, which caused outbreaks and in some cases led to sustained re-established transmission in other countries (e.g., Angola, Chad and Democratic Republic of the Congo, which sometimes also got exported).<sup>(3)</sup> Figure 1(a) shows the progress made toward the eradication of WPV types 1 and 3 since 2000 and the decline in the number of endemic countries that reported confirmed cases (red boxes), with the designation of endemic referring to countries that never completely interrupted indigenous transmission of all WPVs within their national borders. Figure 1a also shows the number of non-endemic countries (blue diamonds) that experienced an outbreak (defined as one or more cases of paralytic polio) due to reintroduced WPV1 or WPV3 and Table 1 lists the more than 50 countries that reported WPV cases between 2000 and 2012.<sup>(3-5)</sup> Figure 1(b) shows the distribution of the countries listed in Table 1 according to the total number of years in which they reported cases between 2000 and 2012 (cases officially reported through January 2, 2013).<sup>(3)</sup> Outbreaks that persist for >12 months imply re-established transmission. In 2010, an outbreak in Tajikistan,<sup>(7)</sup> which also impacted Turkmenistan, Kazakhstan, and the Russian Federation, demonstrated the ability of the WPVs to infect susceptible individuals far from endemic areas, sequentially spread, and cause outbreaks in polio-free countries, and underscored the need for vigilance in both vaccination and surveillance.<sup>(8,9)</sup>

Table 2 lists countries that reported cases of a circulating vaccine-derived poliovirus (cVDPV), which can emerge when oral poliovirus vaccine (OPV) coverage levels become sufficiently low to allow susceptible individuals to continue to transmit infections.<sup>(10-12)</sup> This risk of cVDPVs represents a significant concern for post-eradication risk management, and in order to completely end all cases of paralytic poliomyelitis, ultimately the world will need to coordinate the cessation of OPV.<sup>(13-16)</sup>

Achieving eradication of WPVs requires eliminating their circulation everywhere contemporaneously, which requires all countries to protect large proportions of their populations with a poliovirus vaccine.<sup>(17,18)</sup> Delays in achieving the eradication of WPVs increase costs. Dynamic disease and economic modeling helped national and global policy makers appreciate the strong economic justification for global polio eradication,<sup>(19,20)</sup> the reality that control is neither risk nor cost-free,<sup>(21)</sup> and issues related to post-eradication policies and decisions.<sup>(14-16,21-31)</sup> Countries face increasing complexity as they select their poliovirus vaccine(s) for national use, particularly with the current availability of monovalent OPV (mOPV) and bivalent OPV (bOPV) formulations and changing formulations for inactivated poliovirus vaccine (IPV). Global discussions about OPV cessation options also impact national choices.<sup>(16)</sup>

The most recent World Health Organization (WHO) recommendations about routine vaccination strategies focus on the potential for importation and transmission of WPVs,<sup>(32)</sup> and they provide limited guidance to help countries manage their population immunity. We recognize that choices of poliovirus vaccine and schedule represent national decisions, and based on a comprehensive review of the literature, we: (1) identify the current vaccination options that national health leaders face for polio vaccination, (2) characterize current practices and identify factors that appear to influence national and international choices, and (3) assess the evidence of vaccine effectiveness considering sources of variability between countries and uncertainties associated with limitations of the data.

## Methods

To characterize current national poliovirus vaccine choices and potential options, we reviewed the existing national schedules reported to the WHO.<sup>(33)</sup> Similar to the approach we used to explore post-eradication policy options<sup>(21)</sup> and global policy options,<sup>(16)</sup> we developed decision trees that identify categories of current policies and list the possible decision options within those categories from the perspective of a national policy maker. In the process of reviewing the literature and developing decision trees to summarize the options, we identified a number of critical factors that may influence policy choices, including vaccine performance.

We comprehensively reviewed the evidence related to vaccine performance measured as the seroconversion achieved as a function of vaccine formulation and schedule. We focused on seroconversion data as opposed to seropositivity endpoints from clinical trials because seroconversion provides the most controlled measure of the fraction of vaccine recipients that becomes protected from poliomyelitis disease, presumably for life.<sup>(34)</sup> Seroconversion measures the probability that an individual experiences an immunological response from the vaccine (i.e., take), although we emphasize that it does not address protection from asymptomatic infection and transmission to provide population immunity, which represents another essential consideration for vaccine policy choices.<sup>(11,35)</sup> In contrast, seropositivity measured prior exposure to vaccine or live viruses may reflect some level of pre-existing immunity either from residual maternal antibodies (particularly in the case of vaccines administered shortly after birth) or natural exposure to live polioviruses, including WPV and OPV-related viruses excreted by OPV recipients (particularly in WPV-endemic settings or settings of intense OPV use).

We searched PubMed titles and abstracts using the keywords “polio” or “poliovirus” and “seroconversion,” “efficacy,” “antibodies,” “immunogenicity,” “response,” or “trial” and found 2,654 articles published in English between January 1, 1978 and December 31, 2012 and we reviewed unpublished reports and guidelines provided by the US Centers for Disease Control and Prevention (CDC) and the WHO. We excluded studies published before 1978 because the current enhanced-potency IPV (eIPV) did not become available until the late 1970s<sup>(36)</sup> and we wanted to rely on reasonably recent serology methods. Based on abstract review from this search and references cited in previously published reviews of the two vaccines,<sup>(36-38)</sup> we identified 266 studies published in English that potentially provided seroconversion results. We excluded 158 studies that did not report seroconversion results and instead mainly reported seropositivity levels and/or (geometric) mean antibody titers after vaccination. We also excluded 42 studies that we could not obtain, 9 studies that reviewed or included data from other studies, and 6 studies that only considered the effect of booster doses or cumulative seroconversion after more than 4 doses. We also excluded studies that provided only results for fewer than 20 subjects (n=3), considered only non-enhanced-potency IPV (n=2), or provided only class-specific seroconversion results (i.e., IgA) (n=1), which left 45 studies to code in our analysis. We extracted seroconversion results from these studies, in some cases using our judgment to determine whether to separately list or combine arms in the case of groups with relatively small differences (i.e., stratifications reported in studies include different schedules, vaccine formulations, levels of

pre-existing (maternal) antibodies, risk groups, and/or administration with other vaccines or drugs). Consistent with a review of monovalent vaccines,<sup>(39)</sup> we stratified by temperate versus non-temperate climate settings as a rough proxy for many factors that may affect seroconversion rates in different places (e.g., prevalence of enteroviruses and enteric bacteria, SES, climate, quality of vaccine delivery systems, level of maternal immunity, genetics).<sup>(37)</sup>

In the process of reviewing the existing quantitative seroconversion evidence, we assessed the data quality and identified data gaps and significant sources of uncertainty. Notably, we assigned grades that provide information about seroconversion rates for the current vaccine formulations. We evaluated various grading options,<sup>(40,41)</sup> and eventually collapsed our assessments into three grades. We assigned a grade of 1 if the study used the current formulation of the vaccine and appropriate methods. As discussed by Patriarca et al.<sup>(37)</sup> changing the ratio of the three vaccine components in a trivalent formulation may alter responses, and could effectively impact the immunogenicity of tOPV. Similarly, the potency of eIPV matters, and some studies considered eIPV vaccines with lower potency than the current standard of 40, 8, and 32 D-antigen units for types 1, 2, and 3, respectively, or considered the fractional eIPV vaccines.<sup>(42-45)</sup> Thus, we placed the most weight in our assessment on the vaccine formulation and the information that it provides for the current vaccines. We assigned a grade of 2 if the study did not use the current formulation of the vaccine (i.e., 10:1:6 for tOPV, 10:6 for bOPV, and 40:8:32 for eIPV), but otherwise used appropriate methods. We assigned a grade of 3 if we identified methodological issues that led to questions about the reliability of the data or the study did not report sufficient information to determine the adequacy of the serological methods. We consider serology methods inadequate if they use an antibody titer of <1:4 or >1:10 as the minimum titer for seropositivity, if they do not define seroconversion (in initially seropositive subjects) by a fourfold rise in antibody titers, or if they include the decay of maternal antibody titers for vaccine schedules that administer the first dose before 3 months of age. Although the laboratory procedures, assays, and reference strains used also may affect the results,<sup>(46,47)</sup> we did not consider this limitation because in many studies we could not determine whether the methods conformed to current standards. We also did not include the design of the study as a factor in the grading.

## Results

We identified the policy options for the two main components of immunization strategies that countries use to increase population immunity: routine immunization and supplemental immunization activities (SIAs). Countries continue to evaluate their policies and change their schedules as vaccine options change, and we see an increasing shift toward IPV adoption, particularly in the context of using combination vaccines. As countries consider the impact of switching from OPV to IPV for routine vaccination to avoid cases of VAPP or as OPV cessation approaches,<sup>(14,16)</sup> they may consider sequential schedules of IPV and OPV, multiple different IPV formulations in combined and uncombined forms, costs, and different potential delivery schedules and dosing regimens (e.g., fractional doses). Notably, IPV use initiated before global WPV eradication may influence national immunization choices for the transition and post-eradication time periods (e.g., current IPV-using countries

will most likely continue their use after global eradication, at least for some period of time).<sup>(16,21)</sup> We explicitly include and examine the potential role of SIAs as a strategy that countries use to enhance disease control and population immunity,<sup>(9)</sup> and we cover the options for countries from the perspective of both developing and developed countries, which go beyond the topic of routine immunization covered in the WHO position paper.<sup>(34)</sup> Since achieving high levels of population immunity in many countries requires the use of SIAs and countries differ significantly in their experiences, we emphasize the importance of national leaders considering all of the relevant options.<sup>(9)</sup>

### Routine Immunization

The categories of choices for routine vaccination include deciding whether to include a birth dose, selecting the timing for it, selecting the specific type(s) of vaccine for use in primary immunization and for boosters, determining the formulation(s) and method(s) of delivery, determining a primary immunization number of doses and schedule, and number and timing for booster doses, as shown in Figure 2. Routine immunization represents a planned activity, accounting for an expected part of an annual national health budget and relying on access to vaccine based on contractual relationships that generally ensure a secure supply (i.e., at least in the absence of any disruptions in production). In order to ensure supply, countries may also wish to support the development of a vaccine stockpile.<sup>(48)</sup> National health leaders may constrain vaccine and schedule choices by the availability of sufficient supplies of the various types of vaccine products licensed within the country, cost, and the schedules of other vaccines they might wish to administer during the same times. Given that tOPV contains three different and competing serotypes of live poliovirus and that IPV (i.e., also a trivalent vaccine) induces a prime-boost type of immune response, individuals must receive multiple doses of poliovirus-containing vaccines, with delivery of the doses containing multiple serotypes occurring at intervals of 4 or more weeks. Thus, routine immunization requires multiple contacts with health services, with the vaccine administration time and costs and parental preferences for fewer needle sticks representing important considerations for any national health system. Countries continue to gradually move toward the use of combination IPV products (e.g., DTaPIPv, DTaPHibIPV, DTaPHepIPV, DTaPHibHepBIPV) or parallel administration of OPV along with one or more other vaccines (e.g., bacille Calmette-Guerin (BCG), DTP, HepB, measles, Hib, and rotavirus) during a child visit. These shifts continue to impact the availability of vaccine products, including access to stand alone IPV, which could potentially impact national choices related to outbreak response.<sup>(48)</sup>

Over 50 countries currently include a birth dose (or zero dose) of OPV in their schedules, because the birth dose may induce early protection, improve the seroconversion rates of subsequent doses, and protect against VAPP by providing a first dose when many infants still benefit from protection from maternal antibodies.<sup>(32,49)</sup> Maternal antibodies interfere with IPV, and consequently the WHO does not recommend the use of IPV for a birth dose or for children under 6 weeks of age (i.e., maternal antibodies probably explain the reduced efficacy observed with IPV vaccination given at 6 weeks compared to 2 months).<sup>(50-52)</sup> Thus, Figure 2 only includes OPV as an option for the birth dose. All countries that include a birth dose in their schedule use tOPV, but in Figure 2 we include other theoretical options (e.g., bOPV, mOPV) and we use dashed lines to indicate these. The rapid changes occurring

in the poliovirus-containing vaccine market suggest that countries will most likely continue to consider new options not currently represented in the Figure (and subsequent figures), so we included “Others” as a reminder that at any time other options may become available. We define primary vaccination as the first three doses of polio vaccination received after 3 weeks of age. To allow for consistent comparisons, we define boosters as any doses received after the primary schedule, although we note that this includes some doses given to children under 2 years of age that might not represent optimal timing for boosters,<sup>(53)</sup> and that some countries might count as a fourth dose in their primary schedule.

Although Figure 2 shows numerous permutations of vaccine choices for routine immunization, currently countries only use the trivalent formulations (i.e., tOPV, IPV stand alone or in a combined formulation, or sequential schedules involving both). The selection of vaccine strongly correlates with income, with lower-income countries using tOPV and higher-income countries using IPV-containing vaccines to avoid VAPP. Figure 2 includes the other options to emphasize that countries may consider other choices, but the reasons for using trivalent formulations for routine immunization stem from the need to provide protection from all types of live polioviruses that pose a potential threat. Although WPV2 disappeared from indigenous circulation in 1999, the threat of type 2 cVDPVs represents a real issue (Table 2). Thus, until the point of coordinated cessation of one or more OPVs (e.g., tOPV or all formulations containing OPV type 2), routine immunization programs must protect individuals from all three serotypes.<sup>(16)</sup> Following the successful eradication of any single WPV type, which already occurred with WPV2, global health leaders may consider the option of ceasing the use of OPV of the eradicated type(s).<sup>(16)</sup> However, such an action must be coordinated globally and should only occur after (1) disruption of transmission of any currently circulating cVDPV viruses of that type, (2) development of appropriate outbreak response plans, and (3) creation of a mOPV stockpile of that type that can be used to rapidly respond to any cVDPV outbreak.<sup>(15,16,54)</sup>

The WHO position paper recommended that countries continue to follow their established national schedules and use tOPV for routine immunization, unless they have high socioeconomic status (SES), tertiary sewage treatment systems, and DTP3 coverage >90-95%, in which case the recommendations include the options of schedules using IPV only, sequential IPV/tOPV, sequential tOPV/IPV, or tOPV.<sup>(32)</sup> Given the complexity of the existing choices, we depict the options related to using: (1) only tOPV and (2) any IPV in the national routine immunization schedule (including sequential schedules) in Figures 3 and 4, respectively, which include the very large spectrum of options countries currently use.<sup>(33)</sup> Many countries that only list OPV for their official routine immunization schedule apply specific exclusion criteria, particularly related to immunocompromised individuals, and they use IPV to vaccinate the small number of individuals who meet the criteria. Table 3 indicates the numbers of countries that include such exclusion criteria and those that do not by schedule, and it also shows the total number of countries using the indicated primary schedules that also give a birth dose of tOPV. Although the private market may provide IPV in countries that only list OPV for their routine immunization, this is not captured in our analysis. Currently all countries maintain a primary schedule that seeks to vaccinate children as they reach specific ages, except Cuba, which delivers OPV universally in mass immunization campaigns twice a year as its routine immunization strategy.<sup>(55)</sup> All countries

currently use a primary immunization schedule with at least 3 doses, except Japan, for which the current schedule includes 2 doses of tOPV, although Japan began a transition toward adoption of IPV in late 2012. We defined primary immunization as up to 3 doses that start after 15 days of age and we counted any doses beyond these as boosters. Table 4 shows the number of countries that use any IPV-containing vaccine for routine vaccination in their schedule by schedule, which demonstrates that many countries include combination formulations of IPV in their schedules, at least as an option, which adds significant complexity to Figure 4 relative to Figure 3. Several countries use sequential schedules that include both tOPV and IPV-containing vaccines, with South Africa representing the only country that currently includes IPV-containing vaccines in its primary immunization schedule that also gives a birth dose of tOPV. As depicted in Figure 4, countries vary significantly with respect to their choices of vaccines and schedules for boosters.

Table 5 summarizes the evidence from seroconversion studies for OPV identified in our review of the literature.<sup>(42,49,50,56-89)</sup> Numerous studies from countries of all income levels around the world demonstrate the ability of OPV to induce seroconversion, although they also reveal important variability and generally lower rates in less temperate settings. All OPV studies share the limitation that seroconversion may occur not as a result of direct vaccination but from exposure to live polioviruses (i.e., WPV or OPV-related), as reported for unvaccinated subjects in several studies<sup>(60,62,63,71,73,90-92)</sup> As shown in Table 5, the existing studies show a wide range of seroconversion estimates for a birth dose, with particularly low rates in two recent studies in India for unknown reasons.<sup>(65,66)</sup> However, this difference disappears after subsequent doses<sup>(75)</sup> and several studies found increased cumulative seroconversion rates with the addition of a birth dose to the primary immunization schedule.<sup>(62,63,75)</sup> Despite this variability, the WHO recommends a birth dose for all countries with moderate or high potential for WPV transmission, determined mainly by relatively low levels of routine immunization coverage, poor sanitation, and/or lower SES.<sup>(32)</sup>

With respect to primary immunization with tOPV, the data in Table 5 suggest that after receiving all 3 doses, in temperate countries seroconversion rates for all three serotypes approach 100%, while non-temperate countries show more variability and generally lower rates. (As discussed in the methods, we excluded numerous studies from the analysis that reported approximately 100% seropositivity because they did not report seroconversion rates.<sup>(93)</sup>) Possible explanations for lower seroconversion in lower-income countries include competition with other enteric pathogens, diarrheal disease, interference with high levels of maternal antibody (including those received during breastfeeding), environmental conditions not conducive to effective vaccination, and vaccine quality issues due to problems in the cold chain.<sup>(32)</sup> For two doses, similar variability according to setting arises, with estimates as low as 24% seroconversion for type 1 in Ghana,<sup>(60)</sup> but 100% seroconversion with just two doses for type 2 in the United States.<sup>(74)</sup> The data collected after individual doses show important trends with respect to the different serotypes, with the first dose of tOPV formulations tending to induce relatively greater protection for type 2 than types 1 and 3, which demonstrates the known interference between type 2 and types 1 and 3<sup>(37)</sup> even with the standard formulation. Although in theory vaccine formulations might be adjusted to optimize seroconversion rates for the different types, in practice this would depend on

investing resources to change formulations and relicense the product, which would lead to significant costs and delays. Thus, we assume that vaccine reformulation currently represents more of a theoretical option than a practical option. The studies in Table 5 considered a large array of schedules, all with at least 4-week intervals between doses, but few studies<sup>(57,74,75)</sup> directly compare different schedules with the same number of tOPV doses and none of them show substantial differences between the schedules.

Booster doses provide a way to make up for missed doses earlier in life and increase antibody levels in previously immune individuals, which may reduce their potential to participate in poliovirus transmission.<sup>(34,94)</sup> In the context of understanding population immunity for polio, waning immunity represents an important source of uncertainty, and studies of polio antibodies provide relatively limited data.<sup>(34,94)</sup> Although immunity from paralytic disease appears life-long following a successful vaccination, a few studies that explored waning show that antibody concentrations decrease over time,<sup>(95-97)</sup> which suggests the possibility that individuals may become relatively more susceptible to infection and participate more in the transmission of infection as the time since their last live poliovirus infection or IPV vaccination increases. With the increasing use of IPV, the dynamics of waning immunity might also change due to the absence of boosting via exposure to secondary OPVs.

Table 6 summarizes the evidence from seroconversion studies for immunization strategies involving enhanced potency IPV identified by our literature review,<sup>(42-45,50,55,63,69,87, 98-101)</sup> Many studies provide evidence of seroconversion using IPV-containing vaccines for routine immunization. A recent study reported significantly higher rates of seroconversion for IPV delivered using a 2, 4, 6-month primary schedule than for a 6, 10, 14-week (i.e., 1.5, 2.5, 3.5-month) schedule<sup>(101)</sup> and studies that investigated early administration of the first dose typically found lower seroconversion rates than those administering the first dose at a later age in similar settings. These results suggest that countries should consider their choice of primary schedule carefully when using IPV, because substituting IPV in for a first dose may lead to the need to shift the immunization schedule such that the first dose occurs at least 2 months after birth. Unlike OPV, which causes infection to produce a local immunological response in the mucosa and systemic antibody production, IPV stimulates good systemic antibody production but very limited, if any, mucosal immunity.<sup>(34,94)</sup> For the 6, 10, 14-week schedule used by many developing countries, the WHO suggests the need for an additional booster dose given the inferiority of the schedule.<sup>(34)</sup>

IPV use in middle- and low-income countries remains limited, in large part due to the relatively high cost of IPV compared to OPV. However, the existing studies in Table 6 suggest that 3 doses of eIPV administered after 2 months of age can lead to seroconversion in a high fraction of recipients to all three serotypes. The experience with intradermally-administered fractional IPV doses remains mixed, with good results in Oman<sup>(45)</sup> and the Philippines<sup>(100)</sup> but sub-optimal seroconversion in Cuba<sup>(44)</sup> after 3 doses, perhaps owing to the different schedules and/or devices used.

Table 7 summarizes the evidence from seroconversion studies for immunization strategies that used sequential IPV and OPV strategies, which all involving 4 or more total doses.



(50,63,69,89) Developed countries that transitioned from OPV to IPV often used an IPV/OPV sequential schedule, which yielded high levels of seropositivity in both temperate<sup>(36)</sup> and non-temperate settings (Table 7). A sequential schedule beginning with IPV and followed by OPV induces both mucosal and humoral immunity while significantly reducing (or completely preventing) VAPP.<sup>(102)</sup> Studies that explored the potential impact of administering OPV and IPV simultaneously<sup>(50,63,69,89)</sup> suggest that simultaneous schedules may offer important opportunities to address immunity gaps, albeit at a cost.<sup>(34)</sup> IPV costs and availability continue to influence national vaccine choices, and a recent study showed success with respect to seroconversion with fractional doses administered intradermally.<sup>(45)</sup> Efforts to find more cost-effective strategies for producing and using IPV continue to explore dose sparing options with subcutaneous delivery and/or improved adjuvants.

The evidence from Tables 5-7 relate only to the ability of the vaccines to protect individuals from contracting paralytic polio. In addition to protecting individuals from disease, national decision makers must also protect the population from the possibility that any introduced WPVs or VDPVs can establish transmission. This depends on the ability of the vaccines to reduce excretion upon infection or reinfection<sup>(34,35)</sup> and managing the levels of population immunity.<sup>(9)</sup> While both IPV and OPV provide good protection against oropharyngeal excretion, OPV remains superior in its ability to induce enteric mucosal immunity, which reduces fecal excretion.<sup>(103,104)</sup> Experience with IPV in reducing WPV transmission in developed countries suggests that oropharyngeal transmission may represent an important route of transmission in temperate climate settings with good hygiene.<sup>(34-36)</sup> Since fecal-oral transmission may represent the dominant route of transmission in developing countries with tropical climates and poor hygiene settings, which also obtain lower routine immunization coverage and lower seroconversion, many developing countries elect to conduct SIAs to maintain high population immunity levels.

### Supplemental Immunization Activities (SIAs)

Figure 5 shows the categories and options for SIAs, which include choices about whether to conduct SIAs, the vaccine formulation(s) to use, the number of rounds, the target age group and coverage, and the geographic scale (e.g., National Immunization Days (NIDs), Sub-NIDs (SNIDs)). Very limited recommendations exist with respect to providing criteria for determining when to conduct preemptive SIAs (i.e., SIAs intended to close an identified potential immunity gap prior to an outbreak),<sup>(105)</sup> and we believe this represents an important area for additional tools and guidance. With respect to the decision about whether to conduct SIAs in Figure 5, we anticipate that countries will first assess whether their routine immunization program provides sufficient population immunity. If population immunity is too low they will decide to conduct SIAs (Yes), if population immunity is sufficient then they will decide not to conduct SIAs (No), or they might conduct targeted SIAs in high-risk areas as needed to address a specific immunity gap or respond to a threat (e.g., concern about importation of a virus from a bordering country) (As needed).

Typically only the countries that use tOPV for routine immunization perform SIAs, and consequently tOPV represents the main vaccine used. However, with the licensure of mOPV1 and mOPV3 vaccine products in 2005, these vaccines became available as tools for

use in SIAs to specifically decrease immunity gaps for a specific serotype. Using mOPV instead of tOPV for an SIA round increases the immunological protection against the serotype of the mOPV,<sup>(59)</sup> but it does not provide protection against the other two serotypes.<sup>(9,16)</sup> Thus, using mOPV or bOPV for SIAs implies a relative shift in the overall population immunity profile compared to using only tOPV, and health leaders should carefully consider the impacts on population immunity. Evidence suggests that bOPV provides non-inferior response to mOPV1 and mOPV3 use for the respective serotypes, while providing superior response to the type 1 and type 3 seroconversion induced by tOPV.<sup>(66)</sup>

Countries could also potentially use IPV in SIAs, although we could not find any evidence of this occurring to date. Increasing evidence suggests that IPV can both boost mucosal immunity in subjects previously infected with a live poliovirus<sup>(36,106)</sup> and help close humoral immunity gaps among previously susceptible individuals,<sup>(50,63,69,89,107,108)</sup> although additional studies will need to evaluate its impact on poliovirus transmission and operational issues. Given that WPVs still continue to circulate and pose a threat, countries must decide whether to conduct NIDs, SNIDs, or no SIAs and link their decisions to population immunity, and we suggest that a model of population immunity might help inform their decisions.<sup>(9)</sup>

Based on the data from Tables 5-7, Table 8 summarizes cumulative seroconversion rates for the possible vaccinations that countries might consider for routine immunization. The data provide some indication of effectiveness, but countries should carefully consider the relevance of the evidence to their own situations, because we see substantial variation between studies and large ranges for many estimates. As shown in Table 8, the strictness of grading inclusion criteria applied affects the best estimates. Overall, the evidence suggests that seroconversion rates remain lower in non-temperate than in temperate settings. Serotype 2 consistently leads to the highest seroconversion rates, followed by type 1 and 3, but the difference between types reduces as seroconversion improves (e.g., going from non-temperate to temperate, or from 3 to 4 doses). While the impact of the birth dose on cumulative seroconversion with tOPV remains relatively small, Table 8 clearly shows the impact of the age at the first dose for eIPV regardless of the grading restrictions. We did not systematically review take rates for sequential schedules, but the evidence suggests that sequential vaccination performs similar to IPV-only vaccination or better.<sup>(36)</sup>

Countries that conduct SIAs typically give single doses of OPV vaccine administered during each round to all people in the target population, regardless of vaccination history. Thus, the fraction that remains susceptible after exposure to multiple SIA rounds depends on the average seroconversion rate obtained with each dose, as estimated in Table 8. We calculate these from the cumulative seroconversion rates from Table 5 observed after 3 or 4 doses, excluding birth dose schedules since they may behave differently. With the current widespread use of mOPVs and bOPV for SIAs, Table 8 also includes available estimates from recent trials that compared these with tOPV<sup>(59,65,66)</sup> with relatively high per-dose take rates observed before 1978 for temperate climates reviewed elsewhere.<sup>(39)</sup>

## Discussion

With most countries in the world currently free of all three types of WPVs and cVDPVs, maintaining high levels of population immunity for polio represents a critical issue that nations should continue to prioritize due to the known risk of outbreaks following reintroduction of a live poliovirus and continued exportation of WPV1 and WPV3 from endemic and reinfected countries. The 2010 outbreaks in Tajikistan and Congo served as painful reminders that the absence of observed cases over a period of several years does not guarantee the maintenance of sufficiently high levels of population immunity to keep any future imported viruses from causing an outbreak. They also substantiated the need for a population immunity model applicable to countries with relatively low routine immunization coverage.<sup>(9)</sup> Complete eradication of WPVs continues to represent the best strategy to minimize the risk of WPV importation<sup>(9,25)</sup>

Countries face a large number of choices to maintain high levels of population immunity, including whether to use IPV or OPV for routine immunization and whether to conduct periodic SIAs. Endemic countries or countries experiencing frequent WPV introductions face more complicated choices, because they must determine the number of SIAs to conduct with mOPVs, bOPV, and/or tOPV, or potentially with IPV, to pre-empt or respond to serotype-specific threats. Recent experience with efforts that focused on using mOPV1 to reduce the burden of WPV1<sup>(109)</sup> between 2006-9 in India led to increased susceptibility to types 2 and 3 and outbreaks of WPV3 and to cVDPV2 cases.<sup>(3,110)</sup> Similarly, the shift to the nearly exclusive use of mOPV1 and mOPV3 in SIAs instead of tOPV between 2006-9 in Nigeria,<sup>(12,111)</sup> which did not achieve high levels of coverage, increased susceptibility to type 2 and led to the largest documented cVDPV type 2 outbreak to date.<sup>(112)</sup> We suggest that understanding population immunity emerges as the key to prevention and to determining optimal policies,<sup>(9)</sup> although we note that practical considerations such as costs, supply constraints, combination vaccines and harmonization with other childhood vaccines all remain important factors that we identified in our review as likely to influence national decisions. National and global immunization policy makers can use the decision trees and context presented here to identify and evaluate their poliovirus immunization options and to estimate the expected seroconversion.

Additional research, policy development, and discussion play important roles in encouraging simplification of vaccination strategies for both routine immunization and SIAs. The remarkable range of existing schedules provides some indication that vaccine choice and schedule decisions might benefit from optimization at the national and global levels. The evolution of different combination vaccine products continues to complicate choices, since national health leaders will need to consider the optimal timing of a vaccine containing multiple antigens. At the same time, the inclusion of IPV in combination vaccines may make it easier to protect children from polio at a time when parents do not see cases of paralytic polio impacting their children, and consequently they may not perceive a great need for the vaccine.

With current discussions about coordinated global cessation of type 2 OPV (OPV2),<sup>(16)</sup> we expect that many countries that do not use IPV now will begin to explore the potential role

of IPV in their immunization programs. Currently, manufacturers do not produce sufficient quantities of IPV to supply enough doses to meet a complete global switch from OPV to IPV, but they could do so in the future. In addition, the significantly higher vaccine and delivery costs associated with IPV compared to OPV make it a relatively poor option with respect to its cost-effectiveness.<sup>(14)</sup> However, current efforts underway to develop cheaper and more abundant supplies of IPV may soon support the introduction of at least a single dose of IPV in all countries that wish to provide some protection from paralysis to those who receive the IPV from a potentially reintroduced type 2 live poliovirus. We find the national and global vaccination options remarkably complex, and we hope that this paper provides some useful context for national policymakers with respect to identifying their current polio vaccination options.

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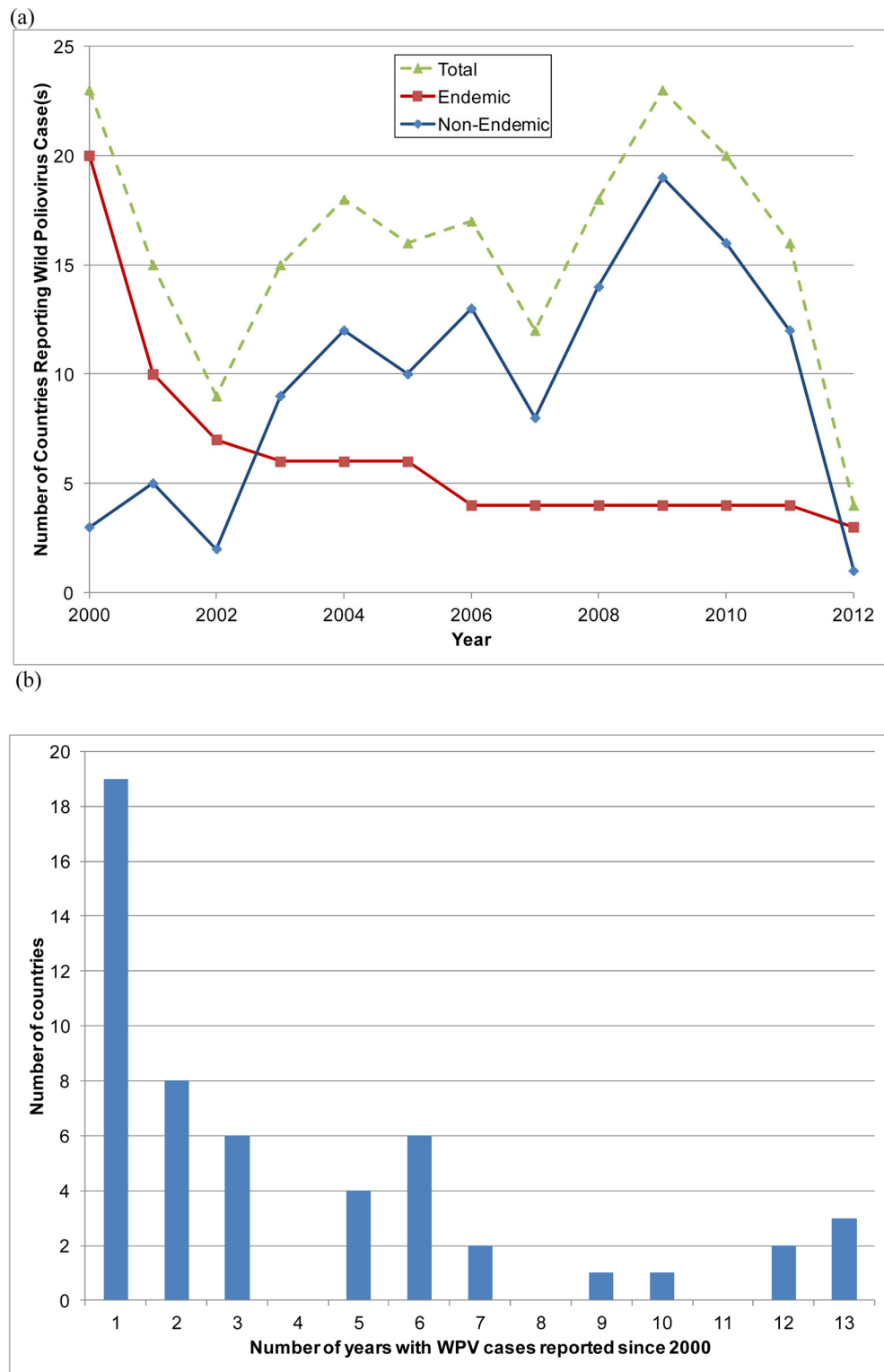


Figure 1.

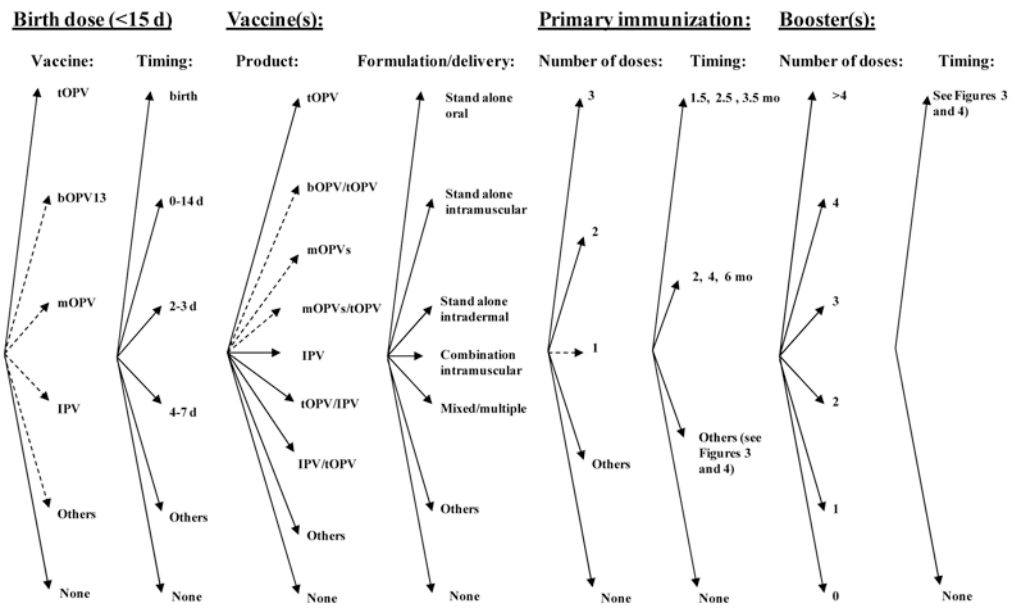
Number of countries (a) reporting cases of wild polioviruses (WPVs) by year and endemic status and (b) distribution of number of years individual countries reported cases between 2000 and 2012.<sup>(3)</sup>

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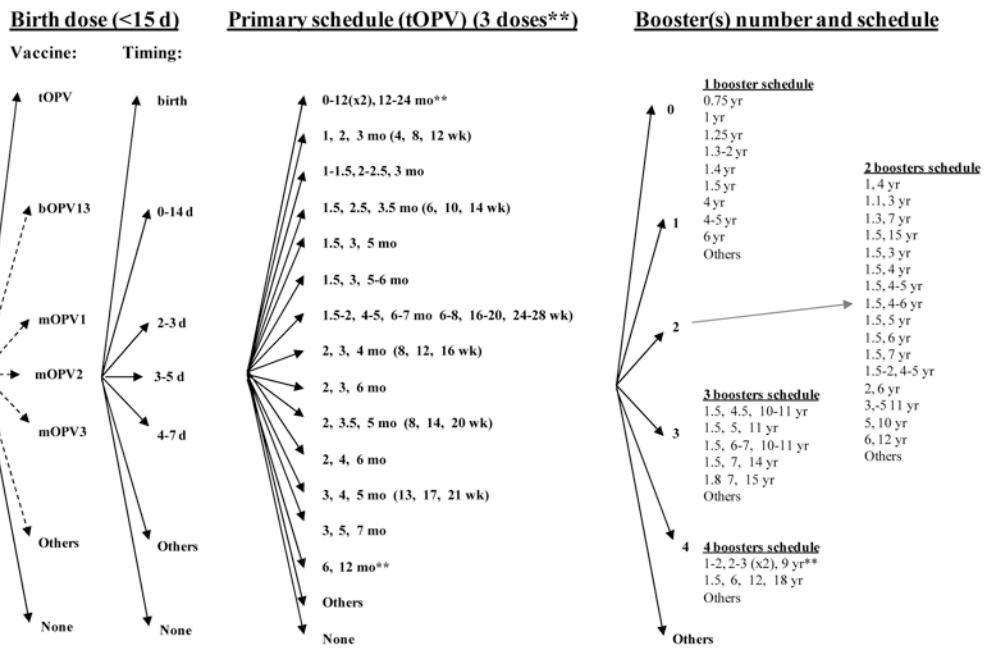
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**Figure 2: Decision tree of national poliovirus routine immunization policy choices\***

\* Some countries that use OPV apply exclusion criteria from OPV vaccination and use IPV for the small number excluded individuals.



**Figure 3: Decision tree for routine immunization national schedules that only use tOPV, based on current national schedules<sup>(33)</sup> \***

\* Always delivered as standalone oral formulation. Some countries that use OPV apply exclusion criteria from OPV vaccination and use IPV for excluded individuals.

\*\* Cuba vaccinates all children under 3 years of age in two annual campaigns, and Japan currently lists a schedule with only 2 doses.

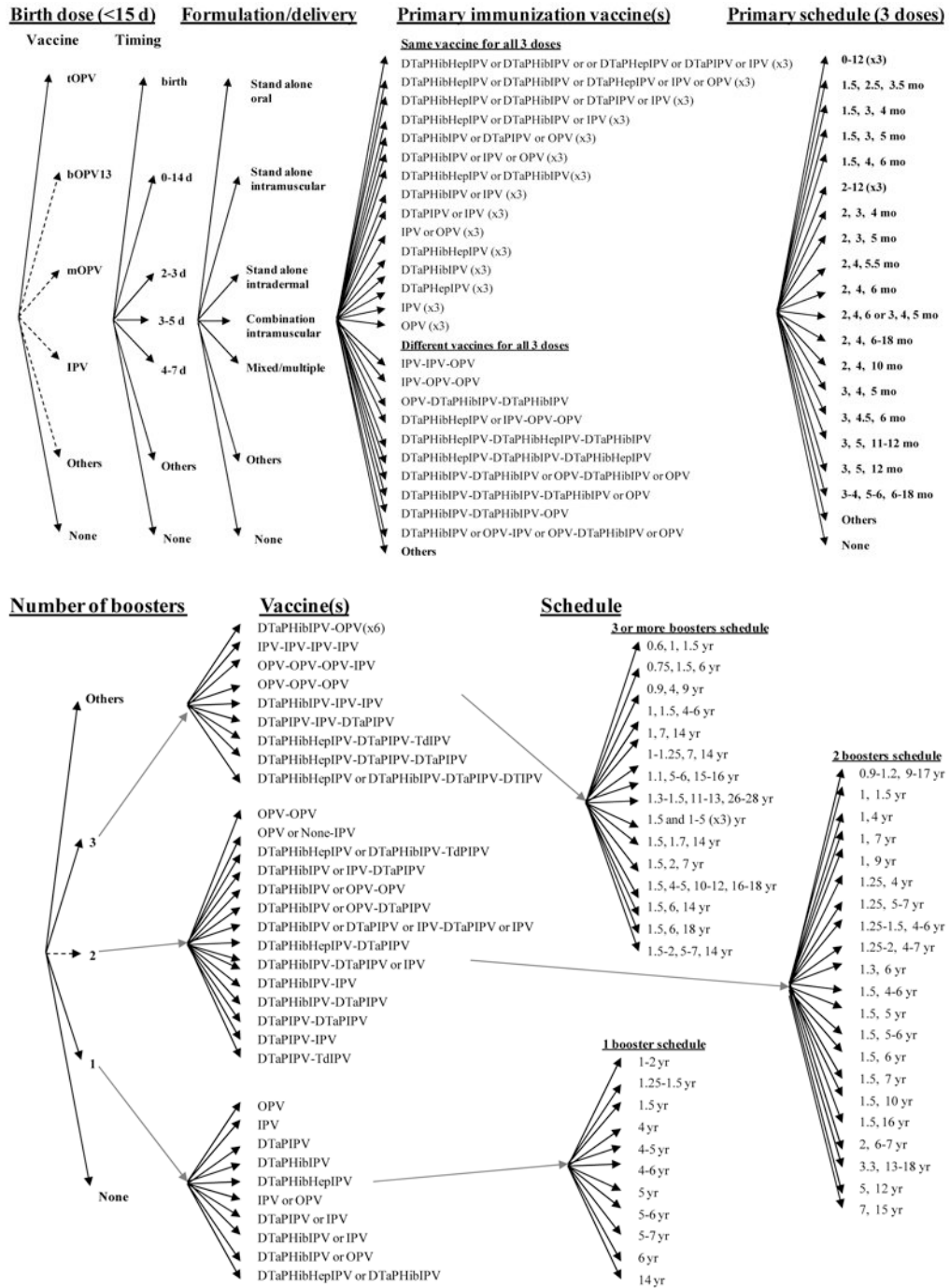
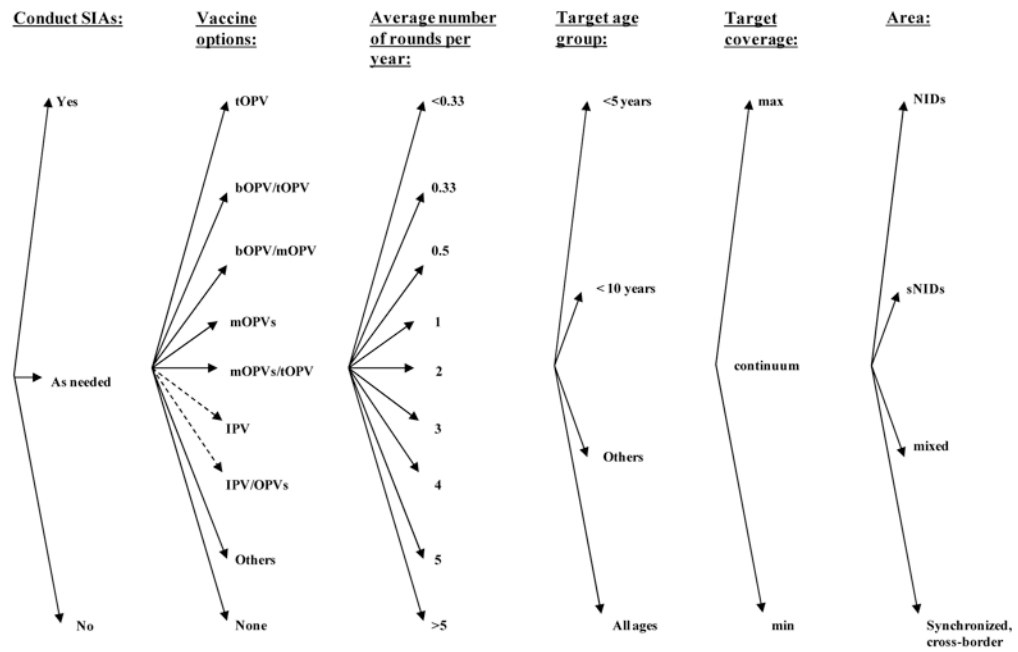


Figure 4: Decision tree for routine immunization national schedules including any use of IPV, based on current national schedules<sup>(33)\*</sup>

(a) Birth and primary immunization options.

(b) Booster options.

\* Some countries that use OPV apply exclusion criteria from OPV vaccination and use IPV for excluded individuals (applies above for some schedules that include OPV).



**Figure 5: Decision tree of supplemental immunization activity (SIA) policy choices and options\***  
 \* Some countries that use OPV apply exclusion criteria from OPV vaccination and use IPV for excluded individuals



**Table 1.**Countries that reported WPV cases since 2000 (as of January 2, 2013) <sup>(3-5)</sup>

Country	Endemic until	Endemic (E) years WPV cases reported	Non-endemic (N) years WPV cases reported*	Total years E/N	Latest WPV3	Latest WPV1
Afghanistan	Endemic	2000-2012		13/0	11-Apr-10	25-Nov-12
Nigeria	Endemic	2000-2012		13/0	10-Nov-12	20-Nov-12
Pakistan	Endemic	2000-2012		13/0	18-Apr-12	20-Nov-12
India	2011	2000-2011		12/0	22-Oct-10	13-Jan-11
Niger**	2006	2000-2006	2007-2012	7/6	30-Oct-11	15-Nov-12
Egypt**	2006	2000-2004		5/0	7-Dec-00	3-May-04
Somalia	2003	2000-2003	2005-2007	3/3	6-Oct-02	25-Mar-07
Angola	2002	2000-2001	2005-2011	2/7	17-Nov-08	7-Jul-11
Sudan	2002	2000-2001	2004, 2005, 2007-2009	2/5	16-Dec-08	27-Jun-09
Ethiopia	2002	2000-2001	2004-2006, 2008	2/4	NA	27-Apr-08
Chad	2001	2000	2003-2012	1/10	10-Mar-11	14-Jun-12
DRC	2001	2000	2006-2011	1/6	24-Jun-09	20-Dec-11
Nepal	2001	2000	2005-2008, 2010	1/5	15-Oct-08	30-Aug-10
Côte d'Ivoire	2001	2000	2003, 2004, 2008, 2009, 2011	1/5	24-Jul-11	6-Aug-09
CAR	2001	2000	2003, 2004, 2008, 2009, 2011	1/5	9-Aug-09	8-Dec-11
Benin	2001	2000	2003, 2004, 2008, 2009	1/4	1-Dec-08	19-Apr-09
Ghana	2001	2000	2003, 2008	1/2	NA	8-Nov-08
Congo	2001	2000	2010-2011	1/2	29-Sep-00	22-Jan-11
Bangladesh	2001	2000	2006	1/1	23-Oct-99	22-Nov-06
Iraq	2000	2000		1/0	NA	28-Jan-00
Mali	<2000		2004, 2005, 2008-2011	0/6	23-Jun-11	1-May-10
Burkina Faso	<2000		2002-2004, 2008, 2009	0/5	NA	25-Oct-09
Cameroon	<2000		2003-2006, 2009	0/5	15-Oct-09	6-Dec-06
Guinea	<2000		2004, 2009, 2011	0/3	3-Aug-11	3-Nov-09
Kenya	<2000		2006, 2009, 2011	0/3	NA	30-Jul-11
Mauritania <sup>§</sup>	<2000		2001, 2009, 2010	0/3	NA	28-Apr-10
Togo	<2000		2003, 2008, 2009	0/3	NA	28-Mar-09
Indonesia	<2000		2005, 2006	0/2	NA	20-Feb-06
Liberia	<2000		2009, 2010	0/2	NA	8-Sep-10
Myanmar	<2000		2000, 2007	0/2	NA	28-May-07
Sierra Leone	<2000		2009, 2010	0/2	NA	28-Feb-10
Uganda	<2000		2009, 2010	0/2	NA	15-Nov-10
Yemen	<2000		2005, 2006	0/2	NA	2-Feb-06
Zambia	<2000		2001, 2002	0/2	NA	27-Feb-02
Algeria	<2000		2001	0/1	NA	13-Oct-01

Country	Endemic until	Endemic (E) years WPV cases reported	Non-endemic (N) years WPV cases reported*	Total years E/N	Latest WPV3	Latest WPV1
Botswana	<2000		2004	0/1	NA	8-Feb-04
Bulgaria	<2000		2001	0/1	NA	24-Apr-01
Burundi	<2000		2009	0/1	NA	12-Sep-09
Cape Verde	<2000		2000	0/1	NA	13-Dec-00
China	<2000		2011	0/1	NA	9-Oct-11
Eritrea	<2000		2005	0/1	NA	23-Apr-05
Gabon	<2000		2011	0/1	NA	15-Jan-11
Georgia	<2000		2001	0/1	NA	2-Sep-01
Iran	<2000		2000	0/1	NA	18-Dec-00
Kazakhstan	<2000		2010	0/1	NA	12-Aug-10
Lebanon	<2000		2003	0/1	NA	23-Jan-03
Namibia	<2000		2006	0/1	NA	26-Jun-06
Russian Federation	<2000		2010	0/1	NA	25-Sep-10
Saudi Arabia	<2000		2004	0/1	NA	17-Dec-04
Senegal	<2000		2010	0/1	NA	30-Apr-10
Tajikistan	<2000		2010	0/1	NA	4-Jul-10
Turkmenistan	<2000		2010	0/1	NA	28-Jun-10

NA indicates onset of most recent case occurred prior to 2000

<2000 indicates country declared non-endemic before 2000

\* All cases are importation related

\*\* In 2005, no endemic circulation occurred in Egypt or Niger but their status remained endemic, all cases in Niger from 2005 onward relate to importations

§ 2001 wild virus of unknown origin; 2009-2010 viruses are importation related

**Table 2.**

Countries that reported circulation vaccine-derived poliovirus (cVDPV) cases associated with 2 or more cases of acute flaccid paralysis (AFP) since 2000, cVDPV type, years of cases reported, dates of last reported outbreak case and total paralytic polio cases as of January 2 2013.<sup>(10,11)</sup>

Country	cVDPV type	Years with cVDPV cases	Latest case	Total cases
Afghanistan	2	2010, 2011,2012	15-Nov-12	9
Cambodia	3	2005, 2006	15-Jan-06	2
Chad *	2	2010	10-Nov-10	1
Chad	2	2012	20-Oct-12	12
China	1	2004	11-Nov-04	2
DOR/Haiti	1	2000-2001	12-Jul-01	21
DRC	2	2008-2012	04-Apr-12	64
Ethiopia	3	2009-2010	4-Nov-10	7
Ethiopia	2	2008-2009	16-Feb-09	4
India	2	2009, 2010	18-Jan-10	17
Indonesia	1	2005	26-Oct-05	46
Kenya *	2	2012	25-Jun-12	1
Madagascar	2	2005	13-Jul-05	3
Madagascar	2	2001-2	30-Apr-02	5
Mozambique	1	2011	2-Jun-11	2
Myanmar	1	2006, 2007	6-Dec-07	5
Niger *	2	2010-2011	11-Nov-11	4
Niger *	2	2006	3-Oct-06	2
Nigeria	2	2005-2012	16-Aug-12	381
Pakistan	2	2012	4-Nov-12	12
Philippines	1	2001	26-Jul-01	3
Somalia	2	2008-2012	23-Jul-12	18
Yemen	2	2011	5-Oct-11	9

\* Niger 2006, 2010, Chad 2010, and Kenya 2012 cVDPVs are linked to the outbreak in Nigeria

\*\* Nigeria experienced multiple separate initiating events<sup>(12)</sup>

**Table 3.**

Distribution of countries using OPV for routine immunization by schedule and count of those giving a birth dose (n=129)<sup>(33)</sup>

Primary schedule (mo)	Number of countries		Birth dose given **
	OPV only	OPV*	
1.5, 2.5, 3.5	64		40
2, 4, 6	18	17	5
2, 3, 4	13	1	8
3, 4, 5	4		1
2, 3.5, 5	2	1	1
1-1.5, 2-2.5, 3	1		1
0-12(x2), 12-24(x1) ***	1		
1, 2, 3	1		
1.5, 3, 5	1		
1.5, 3, 5-6		1	
1.5-2, 4-5, 6-7	1		
2, 3, 6	1		
3, 5, 7		1	
6, 12 ****	1		
Total	108	21	56

\* Country applies exclusion criteria for some risk groups and uses IPV to vaccinate excluded individuals

\*\* Includes 53 countries that give the dose at birth, 1 country each that give the dose at 0-14 (<15) days, 2-3 days, or 4-7 days.

\*\*\* Cuba

\*\*\*\* Japan

**Table 4.**Distribution of countries using any IPV-containing vaccines by schedule (n=65)<sup>(33)</sup>

Vaccine	Number
<b>IPV only for all 3 doses</b>	
2, 4, 6 months	1
2, 4, 6-18 months	2
3, 4, 5 months	1
3-4, 5-6, 16-18 months	1
<b>Combination IPV option for all 3 doses**</b>	
2, 4, 6 months	19
2, 3, 4 months	9
3, 5, 12 months	5
1.5, 3, 5 months	2
3, 4.5, 6 months	2
3, 5, 11-12 months	2
0-12 (x3) months	1
1.5, 3, 4 months	1
1.5, 4, 6 months	1
2-12 (x3) months	1
2, 3, 5 months	1
2, 4, 5.5 months	1
2, 4, 10 months	1
3, 4, 5 months	1
3, 4, 5, or 2, 4, 6 months	1
<b>IPV or OPV for all 3 doses***</b>	
2, 4, 6 months	1
<b>OPV only for all 3 doses***</b>	
2, 3, 4 months	1
<b>IPV-IPV-OPV</b>	
3, 4, 5 months	1
3, 4.5, 6 months	1
<b>IPV-OPV*-OPV*</b>	
2, 4, 6 months	2
<b>IPV-OPV-OPV</b>	
2, 4, 6 months	2
<b>Combination IPV option (x2)-OPV</b>	
3, 4, 5 months	1
<b>Combination IPV option-OPV*-OPV*</b>	
2, 4, 6 months	1

Vaccine	Number
<b>Combination IPV option-OPV-OPV</b>	
2, 4, 6 months	1
<b>OPV-Combination IPV option (x2) ****</b>	
1.5, 2.5, 3.5 months	1

\* Country applies exclusion criteria for some risk groups and uses IPV to vaccinate excluded individuals

\*\* Countries that include any form of a combination vaccine (DTaPHepIPV, DTaPHibIPV, DTaPHibHepIPV, DTwPHibHepBIPV, DTaPIPV) as an option or as the requirement for the IPV component in their schedule

\*\*\* Brunei Darussalam included here because it includes a dose of DTaPIPV in its schedule at 5 years.

\*\*\*\* South Africa also includes a birth dose of OPV in its schedule

**Table 5.**

Studies reporting cumulative seroconversion rates for oral poliovirus vaccine (adapted from Patriarca et al.<sup>(37)</sup>) and updated, only includes studies published in English between 1978 and 2012 with 20 subjects and 4 doses

Country <sup>(ref)</sup>	Study period <sup>d</sup>	Setting <sup>b</sup>	No. of subjects <sup>c</sup>	Vaccine formulation <sup>d</sup>	Schedule	Cut-off <sup>e</sup>	Fold rise in antibodies	Assumed half-life for maternal antibodies <sup>f</sup>	Cumulative seroconversion (%)			Grade <sup>g</sup>
									PV1	PV2	PV3	
<b>tOPV, 1 dose:</b>												
Bangladesh <sup>(56)</sup> <sup>h</sup>	1990-1992	Non-temperate	99;98;99	10:1:3	6-16 w	1:16	4	NR	33	41	27	3
Bangladesh <sup>(56)</sup> <sup>i</sup>	1990-1992	Non-temperate	211;209;212	10:1:3	6-16 w	1:16	4	NR	34	56	42	3
Brazil <sup>(57)</sup>	1986-1988	Non-temperate	27	10:1:5	2 m	1:5	4	30 d	63	96	22	2
Brazil <sup>(57)</sup>	1986-1988	Non-temperate	27	10:1:3	Birth	1:5	4	30 d	22	59	11	2
Brazil <sup>(58)</sup>	1988-1989	Non-temperate	195	20:1:6	Birth	1:8	4	28 d	30	51	14	2
Brazil <sup>(58)</sup>	1988-1989	Non-temperate	184	10:0.5:6	Birth	1:8	4	28 d	31	52	11	2
Brazil <sup>(58)</sup>	1988-1989	Non-temperate	175	10:1:6	Birth	1:8	4	28 d	30	59	13	1
Brazil <sup>(58)</sup>	1988-1989	Non-temperate	176	10:1:3	Birth	1:8	4	28 d	22	60	13	2
Egypt <sup>(59)</sup>	2005	Non-temperate	190	25:1:10	Birth	1:8	4	28 d	32	62	17	2
Ghana <sup>(60)</sup>	1977-1978	Non-temperate	158;131;161	10:1:3	3-8 m	1:8	2	NA	22	31	28	3
Ghana <sup>(61)</sup>	1990-1991	Non-temperate	200	10:1:3	Birth	1:8	4	28 d	34	60	35	2
Ghana <sup>(61)</sup>	1990-1991	Non-temperate	195	10:1:3	6 w	1:8	4	28 d	42	67	52	2
India <sup>(62)</sup>	<1993	Non-temperate	30	NR	3 d	NR	4	21-45 d	42	39	35	2
India <sup>(63)</sup>	<1997	Non-temperate	25	NR	Birth	1:10	4	NA	56	72	28	3
India <sup>(49)</sup>	<1997	Non-temperate	51	10:1:6	3 d	1:4	2	4 w	69	73	69	3
India <sup>(64)</sup> <sup>j</sup>	<1997	Non-temperate	~100	NR	3 d	1:4	4	3-4 w	72	82	64	2
India <sup>(65)</sup> <sup>k</sup>	2005-2008	Non-temperate	363	10:1:6	Birth	1:8	4	28 d	10	15	1	1
India <sup>(66)</sup>	2008	Non-temperate	168	10:1:6	Birth	1:8	4	28 d	15	25	4	1
Mexico <sup>(67)</sup> <sup>l</sup>	1992-1995	Non-temperate	96	10:1:4	2 m	1:8	4	28 d	67	92	40	2
Mexico <sup>(67)</sup> <sup>m</sup>	1992-1995	Non-temperate	85	10:1:4	6 w - 6 m	1:8	4	28 d	72	89	32	2

Country <sup>(ref)</sup>	Study period <sup>d</sup>	Setting <sup>b</sup>	No. of subjects <sup>c</sup>	Vaccine formulation <sup>d</sup>	Schedule	Cut-off <sup>e</sup>	Fold rise in antibodies	Assumed half-life for maternal antibodies <sup>f</sup>	Cumulative seroconversion (%)			Grade <sup>g</sup>
									PV1	PV2	PV3	
South Africa <sup>(68)</sup>	< 2012	Non-temperate	184	10:1:6	Birth	1:8	4	30 d	39	63	21	1
Thailand <sup>(69)</sup>	< 1994	Non-temperate	105;103;104	10:1:3	2 m	1:8	4	NA	25	81	35	3
Tunisia <sup>(70)</sup>	1993-1994	Non-temperate	109	10:1:6	3 m	1:8	4	NA	69	88	20	1
China <sup>(71)</sup>	1981-1982	Temperate	107	10:1:3	3 d	1:4	4	45 d	41	42	33	2
China <sup>(71)</sup>	1981-1982	Temperate	107	10:1:3	60 d	1:4	4	45 d	72	82	91	2
Croatia (now) <sup>(72)h</sup>	1984	Temperate	68;62	10:1:3	3 m	1:2	4	NA	62	NR	37	3
Italy <sup>(73)h</sup>	1984-1985	Temperate	~ 40	NR	~ 3 m	1:4	4	NA	78	NR	38	2
USA <sup>(42)</sup>	1980-1983	Temperate	287;303;295	8:1:5	2.2 m (on average)	1:4	4	28 d	39	84	71	2
USA <sup>(74)</sup>	1990-1991	Temperate	NR ( 55)	NR	2 m	1:8	4	28 d	43	95	25	2
<b>tOPV, 2 doses:</b>												
Brazil <sup>(57)</sup>	1986-1988	Non-temperate	27	10:1:5	2, 4 m	1:5	4	30 d	85	100	67	2
Brazil <sup>(57)</sup>	1986-1988	Non-temperate	27	10:1:3	Birth, 2 m	1:5	4	30 d	59	96	67	2
Brazil <sup>(58)</sup>	1988-1989	Non-temperate	195	20:1:6	Birth, 6 w	1:8	4	28 d	65	78	43	2
Brazil <sup>(58)</sup>	1988-1989	Non-temperate	184	10:0.5:6	Birth, 6 w	1:8	4	28 d	57	77	36	2
Brazil <sup>(58)</sup>	1988-1989	Non-temperate	175	10:1:6	Birth, 6 w	1:8	4	28 d	57	81	38	1
Brazil <sup>(58)</sup>	1988-1989	Non-temperate	176	10:1:3	Birth, 6 w	1:8	4	28 d	48	78	39	2
Gambia <sup>(58)</sup>	1988-1989	Non-temperate	161	20:1:6	< 6, ~ 8 w	1:8	4	28 d	61	76	45	2
Gambia <sup>(58)</sup>	1988-1989	Non-temperate	169	10:0.5:6	< 6, ~ 8 w	1:8	4	28 d	51	78	43	2
Gambia <sup>(58)</sup>	1988-1989	Non-temperate	190	10:1:6	< 6, ~ 8 w	1:8	4	28 d	54	74	46	1
Gambia <sup>(58)</sup>	1988-1989	Non-temperate	159	10:1:3	< 6, ~ 8 w	1:8	4	28 d	52	77	36	2
Ghana <sup>(60)</sup>	1977-1978	Non-temperate	51;47;52	10:1:3	3-8, 9-14 m	1:8	2	NA	24	60	52	3
Ghana <sup>(75)</sup>	1990-1991	Non-temperate	200	10:1:3	Birth, 6 w	1:8	4	28 d	59	79	67	2
Ghana <sup>(75)</sup>	1990-1991	Non-temperate	196	10:1:3	6, 10 w	1:8	4	28 d	64	80	67	2
India <sup>(65)</sup>	2005-2008	Non-temperate	143;133;159	10:1:6	Birth, 30 d	1:8	4	28 d	56	77	40	1
India <sup>(66)</sup>	2008	Non-temperate	168	10:1:6	Birth, 30 d	1:8	4	28 d	63	91	52	1



Country <sup>(ref)</sup>	Study period <sup>d</sup>	Setting <sup>b</sup>	No. of subjects <sup>c</sup>	Vaccine formulation <sup>d</sup>	Schedule	Cut-off <sup>e</sup>	Fold rise in antibodies	Assumed half-life for maternal antibodies <sup>f</sup>	Cumulative seroconversion (%)			Grade <sup>g</sup>
									PV1	PV2	PV3	
Mexico <sup>(67)</sup> <sup>f</sup>	1992-1995	Non-temperate	96	10:1:4	2, 4 m	1:8	4	28 d	83	99	59	2
Mexico <sup>(67)</sup> <sup>m</sup>	1992-1995	Non-temperate	85	10:1:4	6 w - 6 m (2 m apart)	1:8	4	28 d	91	95	65	2
China <sup>(71)</sup>	1981-1982	Temperate	107	10:1:3	3, 60 d	1:4	4	45 d	87	95	97	2
Italy <sup>(73)</sup> <sup>n</sup>	1984-1985	Temperate	~80	NR	~ 3 m, then at 6 w interval	1:4	4	NA	90	NR	80	2
USA <sup>(74)</sup>	1990-1991	Temperate	36;35;36	NR	2, 3 m	1:8	4	28 d	78	97	86	2
USA <sup>(74)</sup>	1990-1991	Temperate	27;26;27	NR	2, 4 m	1:8	4	28 d	89	100	93	2
<b>tOPV, 3 doses:</b>												
Bangladesh <sup>(56)</sup> <sup>h</sup>	1990-1992	Non-temperate	99;100;100	10:1:3	6-16 w, then at 4 w intervals	1:16	4	NR	69	77	67	3
Bangladesh <sup>(56)</sup> <sup>i</sup>	1990-1992	Non-temperate	213;210;214	10:1:3	6-16 w, then at 4 w intervals	1:16	4	NR	70	85	74	3
Brazil <sup>(57)</sup>	1986-1988	Non-temperate	27	10:1:5	2, 4, 6 m	1:5	4	30 d	96	100	74	2
Brazil <sup>(57)</sup>	1986-1988	Non-temperate	27	10:1:3	Birth, 2, 4 m	1:5	4	30 d	93	96	93	2
Brazil <sup>(58)</sup>	1988-1989	Non-temperate	195	20:1:6	Birth, 6, 10 w	1:8	4	28 d	82	87	56	2
Brazil <sup>(58)</sup>	1988-1989	Non-temperate	184	10:0.5:6	Birth, 6, 10 w	1:8	4	28 d	73	88	52	2
Brazil <sup>(58)</sup>	1988-1989	Non-temperate	175	10:1:6	Birth, 6, 10 w	1:8	4	28 d	75	88	55	1
Brazil <sup>(58)</sup>	1988-1989	Non-temperate	176	10:1:3	Birth, 6, 10 w	1:8	4	28 d	68	87	53	2
Ghana <sup>(60)</sup>	1977-1978	Non-temperate	75;64;74	10:1:3	3-8, 9-14, 15-20 m	1:8	2	NA	36	73	64	3
Ghana <sup>(75)</sup>	1990-1991	Non-temperate	200	10:1:3	Birth, 6, 10 w	1:8	4	28 d	73	90	78	2
Ghana <sup>(75)</sup>	1990-1991	Non-temperate	196	10:1:3	6, 10, 14 w	1:8	4	28 d	75	83	79	2
India <sup>(76)</sup>	1974	Non-temperate	78	10:1:3	1 m intervals between 3-36 m	1:10	NA <sup>o</sup>	NA	29	67	55	3
India <sup>(77)</sup>	< 1984	Non-temperate	139	10:1:3	7-42 d, then at 4 w intervals	1:8	4	~ 28 d	73	87	63	2
India <sup>(78)</sup>	1988-1989	Non-temperate	42	NR	6-12 w, then at 4-6 w intervals	1:20	4	NA	64	81	57	3
India <sup>(78)</sup> <sup>p</sup>	1988-1989	Non-temperate	35	NR	6-12 w, then at 4-6 w intervals	1:20	4	NA	77	80	60	3
India <sup>(62)</sup>	< 1993	Non-temperate	41	NR	6-8 w, then at 4-6 w intervals	NR	4	21-45 d	90	83	76	2
India <sup>(63)</sup>	< 1997	Non-temperate	30	NR	6, 10, 14 w	1:10	4	NA	57	77	47	3

Country <sup>(ref)</sup>	Study period <sup>d</sup>	Setting <sup>b</sup>	No. of subjects <sup>c</sup>	Vaccine formulation <sup>d</sup>	Schedule	Cut-off <sup>e</sup>	Fold rise in antibodies	Assumed half-life for maternal antibodies <sup>f</sup>	Cumulative seroconversion (%)			Grade <sup>g</sup>
									PV1	PV2	PV3	
India <sup>(79)</sup>	< 1999	Non-temperate	27	10:1:3	Birth, 6, 10 w	1:8	4	30 d	93	100	93	2
Indonesia <sup>(80)</sup> <sup>j</sup>	1992-1993	Non-temperate	304;353;347	10:1:6	6, 10, 14 w	1:2	NA <sup>f</sup>	4 w	99	100	100	3
Indonesia <sup>(81)</sup> <sup>f</sup>	< 1999	Non-temperate	478	NR	8, 12, 16 w	1:2	4	30 d	97	100	97	3
Morocco <sup>(82)</sup>	1987-1988	Non-temperate	42	10:1:3 (Vero)	Birth, 6, 10, 14 w	1:5	4	4 w	95	100	86	2
Morocco <sup>(82)</sup>	1987-1988	Non-temperate	42	10:1:3	Birth, 6, 10, 14 w	1:5	4	4 w	95	100	79	2
Nigeria <sup>(83)</sup>	< 1978	Non-temperate	56	10:1:3	2, 3, 5 m	1:8	NR	NR	43	88	48	3
Oman <sup>(50)</sup>	1990-1992	Non-temperate	150	10:1:3	Birth, 6, 10 w	1:8	4	28 d	81	97	73	2
Sri Lanka <sup>(84)</sup> <sup>s</sup>	1975	Non-temperate	68	10:1:2	3-6 m, then at 6-8 w intervals	1:16	4	NA	69	91	78	3
Sri Lanka <sup>(84)</sup> <sup>f</sup>	1975	Non-temperate	35	10:1:2	3-6 m, then at 6-8 w intervals	1:16	4	NA	6	49	34	3
Thailand <sup>(80)</sup>	1991-1992	Non-temperate	125	10:1:3	Birth, 6, 10 w	1:8	4	28 d	94	99	93	2
Thailand <sup>(69)</sup>	< 1994	Non-temperate	94	10:1:3	2, 4, 6 m	1:8	4	NA	67	93	80	3
Tunisia <sup>(70)</sup>	1993-1994	Non-temperate	114	10:1:6	3, 4, 5 m	1:8	4	NA	95	100	89	1
Australia <sup>(85)</sup> <sup>d</sup>	1995-1998	Temperate	198;197;198	10:1:3	2, 4, 6 m	1:8	4	30 d	94	100	98	2
Belgium <sup>(86)</sup> <sup>d</sup>	< 2005	Temperate	138	10:1:6 (MRC-5)	3, 4, 5 m	1:4	2	28 d	90	99	97	3
Belgium <sup>(86)</sup>	< 2005	Temperate	45;44;46	10:1:6	3, 4, 5 m	1:4	2	28 d	98	95	98	3
China <sup>(71)</sup>	1981-1982	Temperate	107	10:1:3	60, 90, 120 d	1:4	4	45 d	99	98	98	2
China <sup>(87)</sup>	2009-2010	Temperate	92	10:1:3	2, 4, 6 m	1:8	4	NA	100	100	100	2
Taiwan <sup>(88)</sup> <sup>d</sup>	< 1999	Temperate	~ 130	~10:1:2	2, 4, 6 m	1:4	4	21 d	98	98	98	2
USA <sup>(74)</sup>	1990-1991	Temperate	25	NR	2, 3, 4 m	1:8	4	28 d	96	100	100	2
USA <sup>(74)</sup>	1990-1991	Temperate	26;25;26	NR	2, 4, 6 m	1:8	4	28 d	100	100	96	2
<b>10PV, 4 doses:</b>												
Gambia <sup>(58)</sup>	1988-1989	Non-temperate	161	20:1:6	< 6 w, ~ 8, ~ 16, ~ 21 w	1:8	4	28 d	93	96	71	2
Gambia <sup>(58)</sup>	1988-1989	Non-temperate	169	10:0.5:6	< 6 w, ~ 8, ~ 16, ~ 21 w	1:8	4	28 d	85	97	73	2
Gambia <sup>(58)</sup>	1988-1989	Non-temperate	190	10:1:6	< 6 w, ~ 8, ~ 16, ~ 21 w	1:8	4	28 d	81	94	73	1

Country <sup>(ref)</sup>	Study period <sup>d</sup>	Setting <sup>b</sup>	No. of subjects <sup>c</sup>	Vaccine formulation <sup>d</sup>	Schedule	Cut-off <sup>e</sup>	Fold rise in antibodies	Assumed half-life for maternal antibodies <sup>f</sup>	Cumulative seroconversion (%)			Grade <sup>g</sup>
									PV1	PV2	PV3	
Gambia <sup>(58)</sup>	1988-1989	Non-temperate	159	10:1:3	< 6 w, ~ 8, ~ 16, ~ 21 w	1:8	4	28 d	78	95	70	2
Ghana <sup>(75)</sup>	1990-1991	Non-temperate	200	10:1:3	Birth, 6, 10, 14 w	1:8	4	28 d	84	91	83	2
India <sup>(62)</sup>	< 1993	Non-temperate	30	NR	3 d, 6 w, then at 4-6 w intervals	NR	4	21-45 d	87	90	87	2
India <sup>(63)</sup>	< 1997	Non-temperate	25	NR	Birth, 6, 10, 14 w	1:10	4	NA	92	88	72	3
India <sup>(49)</sup>	< 1997	Non-temperate	51	10:1:6	3 d, 6, 10, 14 w	1:4	2	4 w	92	94	90	3
Pakistan <sup>(89)</sup>	1996	Non-temperate	302	10:1:6	Birth, 6, 10, 14 w	1:8	4	28 d	89	96	95	1
Brazil <sup>(57)</sup>	1986-1988	Non-temperate	27	10:1:3	Birth, 2, 4, 6 m	1:5	4	30 d	100	100	96	2
Brazil <sup>(58)</sup>	1988-1989	Non-temperate	195	20:1:6	Birth, 6, 10, 14 w	1:8	4	28 d	92	95	64	2
Brazil <sup>(58)</sup>	1988-1989	Non-temperate	184	10:0.5:6	Birth, 6, 10, 14 w	1:8	4	28 d	86	93	64	2
Brazil <sup>(58)</sup>	1988-1989	Non-temperate	175	10:1:6	Birth, 6, 10, 14 w	1:8	4	28 d	85	91	66	1
Brazil <sup>(58)</sup>	1988-1989	Non-temperate	176	10:1:3	Birth, 6, 10, 14 w	1:8	4	28 d	84	91	63	2
Morocco <sup>(82)</sup>	1987-1988	Non-temperate	39	10:1:3 (Vero)	Birth, 6, 10, 14 w	1:5	4	4 w	95	100	90	2
Morocco <sup>(82)</sup>	1987-1988	Non-temperate	35	10:1:3	Birth, 6, 10, 14 w	1:5	4	4 w	86	100	89	2
Oman <sup>(50)</sup>	1990-1992	Non-temperate	150	10:1:3	Birth, 6, 10, 14 w	1:8	4	28 d	94	99	81	2
Thailand <sup>(69)</sup>	< 1994	Non-temperate	89	10:1:3	2, 4, 6, 9 m	1:8	4	NA	80	92	83	3
Thailand <sup>(50)</sup>	1991-1992	Non-temperate	125	10:1:3	Birth, 6, 10, 14 w	1:8	4	28 d	98	100	100	2
China <sup>(71)</sup>	1981-1982	Temperate	107	10:1:3	3, 60, 90, 120 d	1:4	4	45 d	98	99	99	2
<b>mOPV, 1 dose:</b>												
Egypt <sup>(59)</sup> (mOPV1)	2005	Non-temperate	231	10 <sup>6.8</sup>	Birth	1:8	4	28 d	55	-	-	1
India <sup>(65)</sup> <sup>W</sup> (mOPV1)	2005-2008	Non-temperate	778	10 <sup>6.0-6.8</sup>	Birth, 30 d	1:8	4	28 d	14	-	-	1
India <sup>(66)</sup> (mOPV1)	2008	Non-temperate	168	10 <sup>6</sup>	Birth	1:8	4	28 d	20	-	-	1
India <sup>(66)</sup> (mOPV2)	2008	Non-temperate	170	10 <sup>5</sup>	Birth	1:8	4	28 d	-	21	-	1
India <sup>(66)</sup> (mOPV3)	2008	Non-temperate	165	10 <sup>5.8</sup>	Birth	1:8	4	28 d	-	-	12	1
South Africa <sup>(68)y</sup> (mOPV1)	< 2012	Non-temperate	383	~10 <sup>6</sup>	Birth	1:8	4	30 d	75	-	-	1

Country <sup>(ref)</sup>	Study period <sup>d</sup>	Setting <sup>b</sup>	No. of subjects <sup>c</sup>	Vaccine formulation <sup>d</sup>	Schedule	Cut-off <sup>e</sup>	Fold rise in antibodies	Assumed half-life for maternal antibodies <sup>f</sup>	Cumulative seroconversion (%)			Grade <sup>g</sup>
									PV1	PV2	PV3	
South Africa <sup>(68)</sup> (mOPV3)	< 2012	Non-temperate	195	~10 <sup>5.8</sup>	Birth	1:8	4	30 d	-	-	58	1
<b>mOPV, 2 doses:</b>												
Egypt <sup>(59)</sup> (mOPV1)	2005	Non-temperate	231	10 <sup>6.8</sup>	Birth, 30 d	1:8	4	28 d	81	-	-	1
India <sup>(65)</sup> <sub>V</sub> (mOPV1)	2005-2008	Non-temperate	363	10 <sup>6.0-6.8</sup>	Birth, 30 d	1:8	4	28 d	87	-	-	1
India <sup>(66)</sup> <sub>V</sub> (mOPV1)	2008	Non-temperate	168	10 <sup>6</sup>	Birth, 30 d	1:8	4	28 d	90	-	-	1
India <sup>(66)</sup> <sub>V</sub> (mOPV2)	2008	Non-temperate	170	10 <sup>5</sup>	Birth, 30 d	1:8	4	28 d	-	90	-	1
India <sup>(66)</sup> <sub>V</sub> (mOPV3)	2008	Non-temperate	165	10 <sup>5.8</sup>	Birth, 30 d	1:8	4	28 d	-	-	84	1
<b>bOPV, 1 dose:</b>												
India <sup>(66)</sup>	2008	Non-temperate	159:159	10:6	Birth	1:8	4	28 d	20	-	7	1
<b>bOPV, 2 doses:</b>												
India <sup>(66)</sup>	2008	Non-temperate	159:159	10:6	Birth, 30 d	1:8	4	28 d	86	-	74	1

**Acronyms:** bOPV = bivalent oral poliovirus vaccine; CID50 = tissue- or culture-infective doses; d = days; m = months; ml= milliliter; mOPV(1,2,3) = monovalent oral poliovirus vaccine (types 1, 2, and 3, respectively); NA = not applicable; NR = not reported; PV(1,2,3) = poliovirus (types 1, 2, and 3, respectively); tOPV = trivalent oral poliovirus vaccine; w = weeks

Notes:

<sup>a</sup>If not reported, we list the upper bound as the year of publication

<sup>b</sup>Stratification by setting adopted from Cáceres and Sutter (2001)<sup>(39)</sup>

<sup>c</sup>If not equal for all serotype, then semicolon-separated values indicates numbers for each reported serotype (e.g., PV1;PV2;PV3)

<sup>d</sup>Ratio of CID50 virus content by type for tOPV and bOPV (as formulated) or absolute CID50 virus content for mOPV

<sup>e</sup>Minimum antibody titer used to define seropositivity; if not reported, we assume this equals the lowest dilution tested

<sup>f</sup>NA in this column indicates that the study did not account for maternal antibody decay; NR indicates that a study accounted for maternal antibody decay but did not state the assumed half-life.

<sup>g</sup>Grade 1: standard vaccine formulation (10:1:6 for tOPV, 10:6 for bOPV, any for mOPV) and standard serological methods; Grade 2: non-standard vaccine formulation (or not reported), but standard serological methods; Grade 3: non-standard serological methods (see methods). If the failure to account for maternal antibody decay represents the only reason for non-standard serological methods, then we still consider a 100% seroconversion rate consistent with serological standards, since the seroconversion rate would remain the same after accounting for maternal antibody decay.

<sup>h</sup>Study arm "diarrheal cohort"

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<sup>j</sup>Study arm “non-diarrheal cohort”

<sup>k</sup>Unweighted (if precise number of subjects by arm not provided) or weighted average of results for arms that received or did not receive Vitamin A supplement at time of tOPV immunization

<sup>l</sup>Weighted average of results for arms that received tOPV from different manufacturers in trials I and II

<sup>m</sup>Study arm that received tOPV through routine immunization

<sup>n</sup>Study arm that received tOPV through mass immunization campaign

<sup>o</sup>Weighted average of results for arms that received or did not receive various other vaccines at time of tOPV immunization

<sup>p</sup>“Seroconversion” numbers from this study reflect the difference of the percent seropositive before and after immunization

<sup>q</sup>This study arm received 0.2 ml instead of the conventional 0.1 ml of tOPV

<sup>r</sup>Seroconversion defined as an antibody titer of more than 1:2 “minus the calculated expected titer of passively acquired maternal antibody to poliovirus, assuming a half-life of immunoglobulin G to be 4 wk” (80, p. 2204)

<sup>s</sup>Weighted average of results for arms that received or did not receive oral iodine supplementation at time of tOPV immunization

<sup>t</sup>Study site Colombo

<sup>u</sup>Weighted average of results from Kandy and Jaffna study sites, outside Colombo. Seroconversion found decreasing seroconversion with distance from Colombo, suggesting cold chain problems for the study sites outside Colombo.

<sup>v</sup>Weighted average of results from different trial with different lots of the experimental tOPV vaccine produced on MRC-5 cells

<sup>w</sup>Weighted average of results for arms that received mOPV from different manufacturers and potency in trials I and II

<sup>x</sup>Weighted average of results for arms that received mOPV1 from different manufacturers

**Table 6.**

Studies reporting cumulative seroconversion rates for eIPV (adapted from Sutter et al.<sup>(38)</sup>) and updated, only includes studies published in English between 1978 and 2012 with 20 subjects and 4 doses)

Country <sup>(ref)</sup>	Study period <sup>d</sup>	Setting <sup>b</sup>	No. of subjects <sup>c</sup>	Vaccine formulation <sup>d</sup>	Schedule	Cut-off <sup>e</sup>	Fold rise in antibodies	Assumed half-life for maternal antibodies <sup>f</sup>	Cumulative seroconversion (%)			Grade <sup>g</sup>
									PV1	PV2	PV3	
<b>1 dose:</b>												
Cuba <sup>(44)</sup>	2006-2007	Non-temperate	177	40:8:32	6 w	1:8	4	28 d	29	38	43	1
Cuba <sup>(44),h</sup>	2006-2007	Non-temperate	187	5:1.6:6.4	6 w	1:8	4	28 d	10	20	8	2
India <sup>(63)</sup>	< 1997	Non-temperate	50	40:8:32	Birth	1:10	4	NA	48	64	30	3
Oman <sup>(45)</sup>	2007	Non-temperate	182;180;183	40:8:32	2 m	1:8	4	28 d	22	32	45	1
Oman <sup>(45),h</sup>	2007	Non-temperate	184;185;186	5:1.6:6.4	2 m	1:8	4	28 d	11	17	9	2
Thailand <sup>(69)</sup>	< 1994	Non-temperate	103	40:8:32	2 m	1:8	4	NA	25	39	28	3
USA <sup>(42),i</sup>	1980-1983	Temperate	618;622;612	Variable <sup>j</sup>	2.2 m (on average)	1:4	4	28 d	42	35	54	2
<b>2 doses:</b>												
Cuba <sup>(55)</sup>	2001	Non-temperate	72	40:8:32	8, 16 w	1:8	4	30 d	90	89	90	1
Cuba <sup>(44)</sup>	2006-2007	Non-temperate	177	40:8:32	6, 10 w	1:8	4	28 d	73	78	94	1
Cuba <sup>(44),h</sup>	2006-2007	Non-temperate	187	5:1.6:6.4	6, 10 w	1:8	4	28 d	33	57	44	2
India <sup>(98)</sup>	< 1985	Non-temperate	100	40:8:32	6-45 w, then at 4 w interval	1:8	4	4 w	96	80	96	1
India <sup>(98)</sup>	< 1985	Non-temperate	114	40:8:32	6-45 w, then at 8 w interval	1:8	4	4 w	96	88	97	1
India <sup>(99)</sup>	< 1992	Non-temperate	30	40:8:32	6-24 w, then at 4 w interval	1:10	4	4 w	93	93	87	1
India <sup>(99)</sup>	< 1992	Non-temperate	22	40:8:32	6-24 w, then at 8 w interval	1:10	4	4 w	91	91	86	1
India <sup>(43),h</sup>	< 1998	Non-temperate	30	5:1.6:6.4	6-8 w, then at 8 w interval	1:4	4	4 w	90	70	97	2
Oman <sup>(50)</sup>	1990-1992	Non-temperate	136	40:8:32	6, 10 w	1:8	4	28 d	71	83	81	1
Oman <sup>(45)</sup>	2007	Non-temperate	182;180;183	40:8:32	2, 4 m	1:8	4	28 d	91	91	96	1
Oman <sup>(45),h</sup>	2007	Non-temperate	184;185;186	5:1.6:6.4	2, 4 m	1:8	4	28 d	71	72	72	2
Thailand <sup>(50)</sup>	1991-1992	Non-temperate	141	40:8:32	6, 10 w	1:8	4	28 d	40	48	79	1

Country <sup>(re)</sup>	Study period <sup>d</sup>	Setting <sup>b</sup>	No. of subjects <sup>c</sup>	Vaccine formulation <sup>d</sup>	Schedule	Cut-off <sup>e</sup>	Fold rise in antibodies	Assumed half-life for maternal antibodies <sup>f</sup>	Cumulative seroconversion (%)			Grade <sup>g</sup>
									PV1	PV2	PV3	
<b>3 doses:</b>												
Cuba <sup>(55)</sup>	2001	Non-temperate	52	40:8:32	6, 10, 14 w	1:8	4	30 d	94	83	100	1
Cuba <sup>(44)</sup>	2006-2007	Non-temperate	177	40:8:32	6, 10, 14 w	1:8	4	28 d	89	95	99	1
Cuba <sup>(44)</sup> <sup>h</sup>	2006-2007	Non-temperate	187	5:1.6:6.4	6, 10, 14 w	1:8	4	28 d	53	85	69	2
India <sup>(63)</sup>	< 1997	Non-temperate	25	40:8:32	Birth, 6, 10 w	1:10	4	NA	88	88	100	3;3;2
India <sup>(43)</sup> <sup>h</sup>	< 1998	Non-temperate	39	5:1.6:6.4	6-8 w, then at 4 w intervals	1:4	4	4 w	90	79	97	2
Oman <sup>(50)</sup>	1990-1992	Non-temperate	136	40:8:32	6, 10, 14 w	1:8	4	28 d	90	96	95	1
Oman <sup>(45)</sup>	2007	Non-temperate	182;180;183	40:8:32	2, 4, 6 m	1:8	4	28 d	100	100	100	1
Oman <sup>(45)</sup> <sup>h</sup>	2007	Non-temperate	184;185;186	5:1.6:6.4	2, 4, 6 m	1:8	4	28 d	97	96	98	2
Philippines <sup>(100)</sup>	2008	Non-temperate	~ 115	40:8:32	6, 10, 14 w	1:8	4	28 d	98	98	100	1
Philippines <sup>(100)</sup> <sup>h</sup>	2008	Non-temperate	~ 115	5:1.6:6.4	6, 10, 14 w	1:8	4	28 d	99	95	95	2
Puerto Rico <sup>(101)</sup>	2003-2004	Non-temperate	225	40:8:32	6, 19, 14 w	1:8	4	28 d	86	86	97	1
Puerto Rico <sup>(101)</sup>	2003-2004	Non-temperate	230	40:8:32	8, 16, 24 w	1:8	4	28 d	100	100	99	1
Thailand <sup>(69)</sup>	< 1994	Non-temperate	92	40:8:32	2, 4, 6 m	1:8	4	NA	97	95	98	3
Thailand <sup>(60)</sup>	1991-1992	Non-temperate	141	40:8:32	6, 10, 14 w	1:8	4	28 d	67	65	94	1
China <sup>(87)</sup>	2009-2010	Temperate	91	40:8:32	2, 3, 4 m	1:8	4	NA	100	90	98	1;3;3
China <sup>(87)</sup> <sup>k</sup>	2009-2010	Temperate	266	Variable <sup>l</sup>	2, 3, 4 m	1:8	4	NA	98	91	97	3

**Acronyms:** d = days; eIPV = enhanced-potency inactivated poliovirus vaccine; NA = not applicable; NR = not reported; PV(1,2,3) = poliovirus (types 1, 2, and 3, respectively); w = weeks

Notes:

<sup>a</sup>If not reported, we list the upper bound as the year of publication

<sup>b</sup>Stratification by setting adopted from Cáceres and Sutter (2001)<sup>(39)</sup>

<sup>c</sup>If not equal for all serotype, then semicolon-separated values indicates numbers for each reported serotype (e.g., PV1;PV2;PV3)

<sup>d</sup>D<sub>D</sub>-antigen content by serotype

<sup>e</sup>Minimum antibody titer used to define seropositivity; if not reported, we assume this equals the minimal dilution tested

$f$  NA indicates that the study did not account for maternal antibody decay

$g$  Grade 1: standard vaccine formulation (40:8:32 of D-antigen content) and standard serological methods; Grade 2: non-standard vaccine formulation (or not reported), but standard serological methods;

Grade 3: non-standard serological methods (see methods); if failure to account for maternal antibody decay represents the only reason for non-standard serological methods, then we still consider a 100% seroconversion rate consistent with serological standards, since the seroconversion rate would remain the same after accounting for maternal antibody decay. If this leads to different grades by serotype, then we indicated serotype-specific grades separated by semicolons.

$h$  Study arm that received intradermally-administered fractional dose

$i$  Weighted average of results for arms that received eIPV from two different manufacturers

$j$  Potency testing found D-antigen contents of 24-38:3.6-6.5:28-36 (Merieux vaccine) or 20-25:3.7-9.2:26-30 (Connaught vaccine)

$k$  Weighted average of results for arms that received different formulations of IPV produced from Sabin seed strains

$l$  85 subjects had received high D-antigen content (45:64:67.5), 92 middle D-antigen content (30:32:45), and 89 low D-antigen content (15:16:22.5) Sabin IPV



**Table 7.**

Studies reporting cumulative seroconversion rates for tOPV and eIPV (includes studies published in English between 1978 and 2012 with 20 subjects)

Country <sup>(ref)</sup>	Study period <sup>d</sup>	Setting <sup>b</sup>	No. of subjects <sup>c</sup>	Vaccine formulation <sup>d</sup>	Schedule	Cut-off <sup>e</sup>	Fold rise in antibodies	Assumed half-life for maternal antibodies <sup>f</sup>	Cumulative seroconversion (%)			Grade <sup>g</sup>
									PV1	PV2	PV3	
<b>eIPV and tOPV, 4 doses:</b>												
India <sup>(63)</sup>	< 1997	Non-temperate	25	40:8:32 (eIPV) NR (tOPV)	Birth (eIPV), 6, 10, 14 w (tOPV)	1:10	4	NA	96	92	84	3
Thailand <sup>(69)</sup>	< 1994	Non-temperate	84	40:8:32 (eIPV) 10:1:3 (tOPV)	2, 4, 6 m (eIPV), 9 m (tOPV)	1:8	4	NA	90	94	94	3
<b>eIPV and tOPV, &gt; 4 doses:</b>												
Oman <sup>(50)</sup>	1990-1992	Non-temperate	138	40:8:32 (eIPV) 10:1:3 (tOPV)	Birth (tOPV), 6, 10 w (tOPV+eIPV)	1:8	4	28 d	81	99	91	1
Oman <sup>(50)</sup>	1990-1992	Non-temperate	138	40:8:32 (eIPV) 10:1:3 (tOPV)	Birth (tOPV), 6, 10, 14 w (tOPV+eIPV)	1:8	4	28 d	96	99	97	1
Pakistan <sup>(89)</sup>	1996	Non-temperate	304	40:8:32 (eIPV) 10:1:6 (tOPV)	Birth, 6, 10, 14 w (tOPV), 14 w (eIPV)	1:8	4	28 d	90	96	95	2
Pakistan <sup>(89)</sup>	1996	Non-temperate	304	40:8:32 (eIPV) 10:1:6 (tOPV)	Birth (tOPV), 6, 10, 14 w (tOPV+eIPV)	1:8	4	28 d	95	97	98	2
Oman <sup>(50)</sup>	1990-1992	Non-temperate	128	40:8:32 (eIPV) 10:1:3 (tOPV)	Birth (tOPV), 6, 10 w (tOPV+eIPV)	1:8	4	28 d	94	99	95	1
Oman <sup>(50)</sup>	1990-1992	Non-temperate	128	40:8:32 (eIPV) 10:1:3 (tOPV)	Birth (tOPV), 6, 10, 14 w (tOPV+eIPV)	1:8	4	28 d	99	99	99	1

**Acronyms:** d = days; eIPV = enhanced-potency inactivated poliovirus vaccine; NA = not applicable; NR = not reported; PV(1,2,3) = poliovirus (types 1, 2, and 3, respectively); w = weeks

Notes:

<sup>a</sup>If not reported, we list the upper bound as the year of publication

<sup>b</sup>Stratification by setting adopted from Cáceres and Sutter (2001)<sup>(32)</sup>

<sup>c</sup>If not equal for all serotype, then semicolon-separated values indicates numbers for each reported serotype (e.g., PV1;PV2;PV3)

<sup>d</sup>D-antigen content by serotype

<sup>e</sup>Minimum antibody titer used to define seropositivity; if not reported, we assume this equals the minimal dilution tested

<sup>f</sup>NA indicates that the study did not account for maternal antibody decay

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<sup>g</sup>Grade 1: standard vaccine formulation (40:8:32 of D-antigen content) and standard serological methods; Grade 2: non-standard vaccine formulation (or not reported), but standard serological methods;  
Grade 3: non-standard serological methods (see methods); if failure to account for maternal antibody decay represents the only reason for non-standard serological methods, then we still consider a 100% seroconversion rate consistent with serological standards, since the seroconversion rate would remain the same after accounting for maternal antibody decay. If this leads to different grades by serotype, then we indicated serotype-specific grades separated by semicolons.

**Table 8:**

Best estimates for cumulative and average per-dose seroconversion rates (%), showing number of data points (n), median;mean [minimum-maximum] based on studies and grades in Tables 5-7

Quantity	Setting	Age at first dose	Based on grade 1 only			Based on grades 1 or 2 only			Based on all studies					
			n	PV1	PV2	PV3	n	PV1	PV2	PV3	n	PV1	PV2	PV3
<b>Routine immunization:</b>														
Cumulative seroconversion rate, 3 tOPV	Non-temperate	7 days	1	94	100	89	5	90:86 [73-96]	87:91 [83-100]	76:76 [63-89]	18	70:67 [6-99]	84:84 [49-100]	71:69 [69-100]
	Temperate	7 days	0	ND	ND	ND	6	98:98 [94-100]	100:99 [98-100]	98:98 [96-100]	8	98:97 [90-100]	100:99 [95-100]	98:98 [96-100]
Cumulative seroconversion rate, 4 tOPV	Non-temperate	< 7 days	2	87:87 [85-89]	94:94 [91-96]	80:80 [66-95]	12	88:90 [84-100]	96:96 [90-100]	85:81 [63-100]	14	90:90 [84-100]	94:95 [88-100]	85:81 [63-100]
	Non-temperate	7 days	1	81	94	73	4	83:84 [78-93]	96:95 [94-97]	72:72 [70-73]	5	81:83 [78-93]	95:95 [92-97]	73:74 [70-83]
Cumulative seroconversion rate, 2 eIPV	Temperate	Any	0	ND <sup>a</sup>	ND <sup>a</sup>	ND <sup>a</sup>	1	98 <sup>a</sup>	99 <sup>a</sup>	99 <sup>a</sup>	1	98 <sup>a</sup>	99 <sup>a</sup>	99 <sup>a</sup>
	Non-temperate	6 weeks	3	71:61 [40-73]	78:70 [48-83]	81:84 [79-94]	4 <sup>b</sup>	55:54 [33-73]	67:66 [48-83]	80:74 [44-94]	4 <sup>b</sup>	55:54 [33-73]	67:66 [48-83]	80:74 [44-94]
Average per-dose seroconversion rate, 3 tOPV <sup>h</sup>	Non-temperate	> 6 weeks <sup>c</sup>	7	90:89 [90-96]	90:89 [80-93]	93:92 [86-97]	8 <sup>d</sup>	91:90 [71-96]	88:84 [70-93]	93:90 [72-97]	8 <sup>d</sup>	91:90 [71-96]	88:84 [70-93]	93:90 [72-97]
	Temperate	Any	0	ND <sup>e</sup>	ND <sup>e</sup>	ND <sup>e</sup>	0	ND <sup>e</sup>	ND <sup>e</sup>	ND <sup>e</sup>	0	ND <sup>e</sup>	ND <sup>e</sup>	ND <sup>e</sup>
Average per-dose seroconversion rate, mOPV <sup>i</sup>	Non-temperate	6 weeks	6	90:87 [67-98]	91:87 [65-98]	98:97 [94-100]	8 <sup>b</sup>	90:85 [53-99]	90:88 [65-98]	97-94 [69-100] <sup>f</sup>	9 <sup>b</sup>	89:85 [53-99]	88:88 [65-98]	97:94 [69-100]
	Non-temperate	> 6 weeks <sup>c</sup>	2	100:100 [100-100]	100:100 [100-100]	100:100 [99-100]	4 <sup>d</sup>	98:97 [90-100]	98:94 [79-100]	98:99 [97-99]	5 <sup>d</sup>	97:97 [90-100]	96:94 [79-100]	98:98 [97-99]
Average per-dose seroconversion rate, mOPV <sup>j</sup>	Temperate	Any	0	100 <sup>e,f</sup>	ND <sup>e</sup>	ND <sup>e</sup>	0	100 <sup>e,f</sup>	ND <sup>e</sup>	ND <sup>e</sup>	2 <sup>g</sup>	99:99 [98-100]	90:90 [90-91]	97:97 [97:98]
	Non-temperate	7 days	2	48:48 [34-63]	64:64 [50-78]	40:40 [28-55]	9	38:45 [32-67]	53:57 [45-78]	28:34 [26-53]	23	33:37 [2-76]	49:51 [20-84]	29:35 [13-86]
Average per-dose seroconversion rate, mOPV <sup>k</sup>	Temperate	7 days	0	ND	ND	ND	5	72:71 [61-79]	78:76 [72-78]	73:73 [66-78]	7	72:69 [53-79]	78:75 [64-81]	72:72 [66-78]
	Non-temperate	Any	3 <sup>j</sup>	64:63 [57-68]	68	60	3 <sup>j</sup>	64:63 [57-68]	68	60	3 <sup>j</sup>	64:63 [57-68]	68	60
Average per-dose seroconversion rate, mOPV <sup>k</sup>	Temperate	Any	0	ND <sup>k</sup>	ND <sup>k</sup>	ND <sup>k</sup>	0	ND <sup>k</sup>	ND <sup>k</sup>	ND <sup>k</sup>	0	ND <sup>k</sup>	ND <sup>k</sup>	ND <sup>k</sup>
	Non-temperate	Any	0	ND <sup>k</sup>	ND <sup>k</sup>	ND <sup>k</sup>	0	ND <sup>k</sup>	ND <sup>k</sup>	ND <sup>k</sup>	0	ND <sup>k</sup>	ND <sup>k</sup>	ND <sup>k</sup>

Quantity	Setting	Age at first dose	Based on grade 1 only			Based on grades 1 or 2 only			Based on all studies					
			n	PV1	PV2	PV3	n	PV1	PV2	PV3	n	PV1	PV2	PV3
Average per-dose seroconversion rate, bOPV <sup>g</sup>	Non-temperate	Any	1	62	NA	49	1	62	NA	49	1	62	NA	49
	Temperate	Any		ND	ND	ND		ND	ND	ND		ND	ND	ND

**Acronyms:** bOPV = bivalent (types 1&3) oral poliovirus vaccine; NA = not applicable; ND = no data; eIPV = enhanced-potency inactivated poliovirus vaccine; mOPV = monovalent oral poliovirus vaccine; PV(1,2,3) = poliovirus (types 1, 2, and 3, respectively); tOPV = trivalent oral poliovirus vaccine

Notes:

- <sup>a</sup> While we found only one seroconversion data point for this stratum, numerous studies suggest near 100% seropositivity after 3 or more tOPV doses in temperate countries<sup>(62)</sup>
- <sup>b</sup> Includes two data points for intradermally-administered fractional eIPV<sup>(44,100)</sup>
- <sup>c</sup> Includes data point from study arms that received the first dose at 6-8, <sup>(43)</sup> 6-24, <sup>(99)</sup> or 6-45 weeks<sup>(98)</sup>
- <sup>d</sup> Includes two data points for intradermally-administered fractional eIPV<sup>(43,45)</sup>
- <sup>e</sup> While we found no seroconversion data for this stratum, numerous studies suggest near 100% seropositivity after 2 or more eIPV doses in temperate countries<sup>(36)</sup>
- <sup>f</sup> One more data point for this serotype given inclusion of 100% seroconversion rate data point from a study that did not include maternal immunity decay (Table 6)
- <sup>g</sup> Includes one data point for IPV with variable potency based on Sabin seed strains<sup>(87)</sup>
- <sup>h</sup> Average per-dose seroconversion rate that gives the cumulative seroconversion rate measured after 3 or 4 tOPV doses administered in schedules without a birth dose, computed as  $1 - (1 - cum. serconv. rate \text{ after } d \text{ doses})^{1/d}$ . For studies that report 100% cumulative seroconversion, this formula would imply 100% seroconversion per dose, but to reflect the reality that not all subjects would seroconvert to each dose and that sufficiently large trial would detect some non-responders, we arbitrarily set the cumulative seroconversion rate at 99.9%. This translates into per-dose seroconversion rates of 78% (3-dose cumulative seroconversion of 99.9%) or 68% (4-dose cumulative seroconversion of 99.9%).
- <sup>i</sup> Average per-dose seroconversion rate that gives the cumulative seroconversion rate measured after 2 mOPV or bOPV doses, computed as  $1 - (1 - cum. serconv. rate \text{ after } d \text{ doses})^{1/d}$ . Given that all three available studies administered the first dose at birth, <sup>(59,65,66)</sup> we did not impose any restrictions in the age at first dose, although possibly administration of the first dose at older age may have resulted in different cumulative seroconversion rates.
- <sup>j</sup> Only one data point available for mOPV2 and mOPV3
- <sup>k</sup> While we found no recent seroconversion studies (i.e., published 1978 or later) for mOPV in temperate-climate countries, Cáceres and Sutter (2001)<sup>(39)</sup> reviewed earlier mOPV seroconversion studies and found per-dose seroconversion rates of 95 (range 90-100), 98 (range 83-100) and 94 (range 74-100) for types 1, 2, and 3, respectively.