

# Proposed policy for a global switch from 'tOPV to bOPV' for routine immunization

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*SAGE Polio Working Group*

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## 1 Executive summary

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The SAGE Polio Working Group (WG) has taken on the responsibility in 2011 to review the evidence for a potential policy switch from tOPV to bOPV for routine vaccination. During a >12 months process, and using 2 face-to-face meetings and 2 conference calls, the WG reviewed the scientific evidence and debated the merits and preconditions for such a switch, and formulated recommendations for review by the full SAGE, including: to introduce at least one dose of IPV (whether fractional or full-dose IPV at DTP3 visit) universally at least 6 months (by September 2013) prior to a switch date from tOPV to bOPV (earliest date would be April 2014). This policy would cover the period starting with universal IPV introduction (September 2013) until discontinuation of all Sabin strains (anticipated in 2018) after wild poliovirus eradication, during which time the post-OPV options will be further reviewed.

## 2 Background

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SAGE, at their November 2010 meeting, had requested the Polio Working Group (WG) to assess the utility and feasibility of the cessation of type 2 oral poliovirus vaccine use, i.e. of a global 'switch' from tOPV to bOPV for routine immunization, in the pre-eradication era. The WG had initiated work on this additional term of reference at their March 2011 meeting.

In November 2011, SAGE had endorsed this goal, stating that a phased rather than simultaneous removal of SABIN serotypes was desirable, and agreeing that a pre-eradication switch from tOPV to bOPV was advantageous because of: a) the type 2 risks (vaccine-derived poliovirus type 2 [VDPV2] and vaccine-associated paralytic poliomyelitis [VAPP]); b) bOPV availability and its superior immunogenicity over tOPV; and c) low cost IPV options.

In January 2012, the WHO Executive Board (EB) passed a resolution in which WHO was requested to develop a comprehensive eradication and endgame strategy, and to inform Member States of the potential timing of a switch from tOPV to bOPV for all routine immunization programmes.

## 3 Context for the tOPV-bOPV switch

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This background paper outlines the scientific evidence that guides decision-making regarding a proposed switch from tOPV to bOPV. This switch, and the discontinuation of the Sabin type 2 strain in tOPV, is considered as a pivotal part of the "polio endgame re-thinking" because:

- 1) although indigenous wild poliovirus type 2 transmission has been eradicated in 1999 [1], 483 and >1500 individuals (mostly children) are estimated to have become paralyzed in the past decade due to VDPV2 or type 2 VAPP, respectively (a burden that is becoming increasingly unacceptable to parents and countries) [2];
- 2) vaccine-derived poliovirus type 2 (VDPV2) has been causing an outbreak that is still ongoing in Nigeria since 2005 (377 cases in this country alone) [3-6];
- 3) bOPV is more efficacious than tOPV for types 1 and 3, respectively, and could accelerate eradication [7]; and

- 4) as part of risk mitigation broader use of inactivated poliovirus vaccine (IPV) is envisioned (either universal or selective use), which could boost type 1 and 3 immunity levels, and potentially accelerate eradication.

The SAGE Polio WG was asked in the February 2012 meeting to address the following four key questions in the context of a tOPV-bOPV switch:

- 1) Should IPV be universally or selectively introduced into routine immunization?
- 2) Should one or more than one dose of IPV be used?
- 3) For the purposes of the switch, could fractional-dose be considered equivalent to full-dose IPV? and
- 4) What would be the earliest timing for such a switch?

#### 4 Prerequisites for a tOPV-bOPV switch

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The WG will continue to review evidence related to several key pre-requisites which will need to be satisfied or in place before a global tOPV-bOPV switch.

The most critical pre-requisite is that, prior to OPV2 cessation, **all ongoing cVDPV2 outbreaks will need to have been stopped**, with sufficiently sensitive surveillance to detect rapidly any new outbreaks. This will be particularly important for cVDPV2 outbreaks persisting for more than 12 months, such as the Nigeria outbreak, where cVDPV2 emerged first in 2005 and transmission has not yet been interrupted. Also, all countries, particularly those in areas at higher risk of cVDPV emergence, should have the capacity to timely detect and interrupt cVDPV outbreaks within < 6 months.

Work is ongoing to **adapt the Global Action Plan for Laboratory Containment** of polioviruses to reflect additional issues related to OPV2 cessation.

Another key prerequisite will be the availability of **sufficient vaccine supplies** to allow a globally coordinated synchronized tOPV-bOPV switch, including the availability of sufficient bOPV and of **sufficient quantities of 'affordable' IPV** to introduce, in all countries deciding to do so, at least 1 supplementary IPV dose, 6 months before the bOPV-tOPV switch. In this context, there will also need to be international consensus on stopping the delivery of tOPV formulations globally, parallel to discontinuing tOPV.

Lastly, the tOPV-bOPV switch will require the availability of **stockpiles of OPV2-containing vaccine** (monovalent OPV 2 [mOPV2; and possibly tOPV]) to respond to possible post-switch cVDPV2 emergences and outbreaks).

#### 5 Selective vs. universal use of IPV

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##### a) Evidence

The main objectives that support the introduction of IPV (universally or selectively) are the following:

- to boost type 2 immunity in advance of the tOPV-bOPV switch; and
- to accelerate eradication by boosting the population immunity to poliovirus types 1 and 3, respectively, with routine IPV, in children with a history of multiple doses of OPV.

Countries that use IPV in routine immunization programs: currently, >72 countries have introduced IPV in routine immunization programs, either using a sequential (usually 1-2 doses of

IPV followed by multiple doses of OPV) or an IPV-only schedule [8]. This includes all OECD countries that use IPV-only schedules, except for Japan (currently using only OPV but on the verge of introducing IPV). Furthermore, Argentina, Brazil and Uruguay have announced the introduction of IPV in 2012. On the other hand, none of the GAVI-eligible countries is using IPV routinely.

Risk of VDPV: all countries using OPV are at risk for VDPV emergence and spread, and the risk appears to be primarily dependent on actual vaccination coverage with polio vaccine. Even in countries with high coverage in the general population, there may be high-risk pockets containing groups objecting to vaccination (religious or other groups) that could support poliovirus transmission [9-12]. There is no reason to assume that VDPV cannot be introduced in these populations, circulate and cause paralytic disease. This was documented among the Amish in the United States in 1993 for poliovirus type 2, an introduction which fortunately didn't result in paralytic cases [13].

Schedule of IPV administration: To harvest optimal immunity gains (seroconversion and antibody titer) and because IPV performance is negatively affected by levels of maternally-derived antibody [14-15], the timing of IPV administration should be delayed to minimize the interference effect, but before infants lose the protective effect of maternally-derived antibody, and become susceptible to poliovirus. Thus, the DTP3 visit (14 weeks in the EPI schedule) may offer the best compromise in terms of timing. For countries using other schedules with later onset and longer intervals between doses, they may want to administer a dose of IPV with DTP2 (if given at age 4 months).

Timing of IPV introduction: IPV should be introduced in routine programs at least 6 months before an anticipated switch from tOPV to bOPV, to boost population immunity against all poliovirus serotypes, decrease the risk of VDPV emergence (and control ongoing outbreaks of VDPV) and spread, and in polio-endemic areas accelerate eradication of wild poliovirus types 1 and 3.

Cost: The key consideration is to have an affordable IPV option available to countries (either fractional-dose or low cost full-dose IPV). Currently, the UNICEF price is ~\$3.00 per full-dose IPV. It is anticipated that the price will decrease by at least 50% with volume pricing based on estimated decreases in cost-of-good (CoGs). Most promising, the intradermal administration of fractional-dose IPV could potentially result in nearly proportional decreases in cost per dose (i.e., <\$0.50 per dose).

## **b) WG conclusions and recommendations for vaccination policy**

In view of the available evidence, the WG concludes and recommends the following as basis for vaccination policy recommendations:

- Contingent on the availability of a low-cost IPV option, the introduction of IPV should be universal
  - all countries currently using tOPV exclusively or as part of a combined IPV/OPV schedule should switch to bOPV and introduce a supplementary dose of IPV during an immunization contact at or after age 14 weeks;
  - IPV will boost immunity to all serotypes in children with prior immunity and prime naïve children. Should there be an emergence of VDPV2, as part of outbreak control, mOPV2 will be needed. In addition, to boost immunity in areas of risk but not infected, IPV could reduce the risk of an outbreak.

This approach will reduce the risk of cVDPV2 emergence and the number of cases and provide a base for boosting immunity if needed. The evidence from the literature suggests that IPV and OPV can be used inter-changeably [16].

## **6 Should one or two doses of supplementary IPV be recommended?**

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### **a) Evidence**

If the question of universal or selective use of IPV has been decided, the next question would be whether one or more doses IPV would be indicated in the context of the “new polio endgame”. The main consideration would be what would be the incremental benefit of a second dose of IPV (over a single dose) in infants that have received multiple doses of OPV.

Humoral immunity: a number of trials have addressed this question: 1) Hanlon et al. in the Gambia [17]; 2) Morinière et al. in Côte d’Ivoire [18]; 3) Sutter et al. in Oman [19]; and 4) Estivariz et al. in India [20].

These studies provide important scientific evidence, including:

- one dose of IPV after multiple doses of OPV effectively closes the remaining immunity gaps (~90% of seronegative cases will seroconvert);
- in seropositive individuals, a dramatic boosting of antibody titers is seen (~70-90%); after boosting, the antibody persist and then decline to a new baseline that is higher than before the IPV booster dose;
- this effect is most pronounced against poliovirus type 2. In Cote d’Ivoire and India studies [18, 20], one IPV dose in seronegative infants closed the immunity gaps against type 2 completely.

Mucosal immunity: In general, IPV-only induced immunity results in shorter periods of excretion (~50%), decrease in titer of virus (0.5-1 log10), but not in substantial decrease in the proportion of individuals that excrete after challenge [7, 21]. Modlin et al. suggest that two doses of OPV are needed for optimal mucosal immunity (but this may not be true if one controls for “serotype take”) [22]. In the schedule proposed for the switch, 3 doses of bOPV (birth, 6, and 10 weeks) would be administered prior to simultaneous bOPV/IPV administration (at 14 weeks), so the mucosal immunity against type 1 and 3, respectively, should be strengthened further. However, a single dose of IPV (or indeed 3 doses of IPV) in naïve infants would not be expected to reduce the prevalence of excretion (but should result in shorter duration and titer). Grassly et al. suggest that mucosal immunity is relatively short-lived (~6 months) [23], but can be boosted with subsequent doses of OPV or IPV. Data from the Netherlands suggest that mucosal priming with live virus is necessary to obtain an IgA response after IPV booster vaccination. In subjects that were naturally immune, a single dose of IPV booster dose resulted in strong increases of IgA levels within a week in 93%, 94% and 83% against poliovirus types 1, 2, and 3, respectively [24]. Furthermore, they observed that a booster vaccination with IPV in previously mucosally exposed subjects led to a strong induction of poliovirus-specific IgA in the saliva, but the presence of IgA in saliva was, in most cases, of limited duration [25]. In Oman, IPV was administered at age 9 months in infants with a history of 5 doses of OPV [19]. Infants were then challenged with monovalent type 3 poliovirus vaccine (mOPV3) 6 months later. In the IPV group, 12.7% subjects excreted virus compared with 17.0% and 16.4% in the two tOPV groups, respectively. If shorter excretion (with lower viral titer) equates with lower secondary transmission (as would be expected), then one dose of IPV should have an effect on population transmission at the time of the tOPV-bOPV switch.

### Efficacy:

- *Against wild poliovirus:* The efficacy of a supplemental dose of IPV following multiple doses of OPV has not been assessed. However, there are data of a one-dose efficacy case-control study in Senegal that reported 36% (95% confidence interval 0-67%) in preventing paralysis [26, 27]. In addition, the original Francis Field trial in the United States in 1954 reported also one-dose estimates, but they are less relevant because the potency of the IPV used at that time was substantially lower [27].
- *Against vaccine-associated paralytic poliomyelitis:* The most convincing data come from countries introducing one or more doses of IPV followed by OPV to prevent vaccine-associated paralytic poliomyelitis (VAPP). WHO is aware of a single case of VAPP in a child that had received a single dose of IPV [WHO unpublished data]. Similarly, in the United States, after introduction of a sequential schedule of IPV followed by OPV, no case of VAPP was reported in infants that had received at least a single dose of IPV [28]. The most convincing data, however, come from Hungary, the country that has traditionally reported the highest rate of VAPP [29-32]; not a single case of VAPP was reported following the introduction of a single dose of IPV in 1990-91, suggesting that a dose of IPV is efficacious in preventing VAPP, and by analogy wild poliovirus-associated paralytic disease [WHO unpublished data].

In addition, in terms of type 2, the currently formulated IPV vaccines are most efficacious against type 2 poliovirus, probably because during the formulation trials, IPV had to overcome maternally-derived antibody levels against type 2, which are typically higher (seroprevalence and antibody titer) than those against types 1 and 3, respectively.

Program consideration: In previously vaccinated children (multiple doses of OPV), a single dose of IPV seems effective in closing the immunity gaps, and boost antibody titers to very high levels. In naïve children, a single dose of IPV would prime and seroconvert infants (study provided a dose of IPV at age 4 months in Cuba) [33].

### **b) WG conclusions and recommendations for vaccination policy**

In view of the available evidence, the WG considers the following to be main conclusions and recommendations for vaccination policy:

- Given a low-cost IPV, all countries should introduce one IPV dose at least 6 months prior to a tOPV - bOPV switch, as part of the routine schedule at DPT3 contact

Further work will examine the potential value of offering a 2<sup>nd</sup> IPV opportunity for high-risk areas, including the development of clear criteria for defining high-risk areas.

## **7 Is intradermal, fractional (1/5th) IPV dose an acceptable alternative to whole-dose IPV?**

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### **a) Evidence base**

The question here is whether fractional-dose IPV could be considered equivalent to full dose IPV in the context of the anticipated switch from tOPV to bOPV, in conjunction with simultaneous administration of IPV.

Humoral immunity: There are a number of studies which examined the use of fractional-dose IPV in routine schedules: 1) Resik et al. in Cuba [33, 34]; 2) Mohammed et al. in Oman [35]; 3) Cadorna-Carlos et al. in the Philippines [36]. These studies basically confirmed that 1/5 (0.1 ml) of IPV, can induce high seroprevalence (>95% to all three serotypes and solid antibody titers against all three poliovirus serotypes).

Although there have been discussions regarding the difference in antibody titers between fractional- and full dose IPV, we have to keep in mind that any detectable antibody titer (reciprocal titer  $\geq 8$ ) would be considered protective [37], and that in the Oman study the titers were  $>200$  for each serotype in the fractional-dose IPV arm.

In the Cuba study, one dose of IPV induced a priming immune response in 96.8% versus 99.4% of infants vaccinated against type 2 poliovirus with fractional- and full-dose IPV, respectively [32].

In a single study where fractional-dose IPV was administered to 6-9 months old infants with a history of multiple doses of OPV, the IPV was administered with an experimental needle-free device that generated a lot “wet injections”, meaning that a high proportion of infants received a lower dose than was intended. Despite this, boosting was evident in ~60% of infants receiving a fractional-dose IPV [20].

Mucosal immunity: in the Oman trial, infants were challenged with monovalent type 1 oral poliovirus vaccine (mOPV1) at age 7 months, and excretion prior to, and 7 days after the challenge was assessed. The findings suggest that there was a difference (74.8% in the fractional-dose arm excreted versus 63.1% in the full-dose arm) [35].

Efficacy: No data are available.

Programmatic consideration: in virtually all developing countries, BCG is administered intradermally shortly after birth or at first contact with the health system. Therefore, health systems in these countries are familiar with intradermal administration of vaccine in routine immunization programs. If IPV is given in campaigns, intradermal needle-free devices may be needed to facilitate house-to-house vaccination.

Cost: The fractional-dose IPV (1/5 of a full-dose) would result in major cost-savings, which could facilitate introduction.

IPV production capacity: The fractional-dose approach would not necessitate major investments in augmenting the IPV production capacity.

## **b) WG conclusions and recommendations for vaccination policy**

Intradermal (ID) fractional (1/5th dose) IPV offers important potential advantages over intramuscular (IM) whole dose IPV in the context of a tOPV-bOPV switch:

- for the purposes of boosting immunity following OPV, ID IPV appears equivalent to IM IPV;
- for the purposes of providing priming or protection against type 2 polio in the context of a tOPV-bOPV switch, ID IPV appears to provide an acceptable alternative to IM use.
- lower production costs should lead to a substantially lower price than whole dose IPV, and represents the current leading opportunity to offer a low-cost, universal IPV option; and
- sufficient quantities should be available with current global IPV capacity, although use requires may fast-tracking of regulatory approval (or off-label use).

## **8 Key target dates for a tOPV-bOPV switch timeline**

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The WG considered possible timelines for scheduling a global tOPV-bOPV switch, taking into account key 'milestones' that would need to be met. As previously noted, the most critical pre-requisite for a switch will be to stop the persisting cVDPV2 outbreak in Nigeria.

Assuming that the Nigeria outbreak can be controlled by the end of 2012, and that sufficient quantities of IPV for fractional-dose ID application becomes available (see below), the introduction of 1 dose of supplementary IPV in all OPV-using countries could begin latest by

September 2013, to enable a global tOPV-bOPV switch by April 2014, possibly linked to the 'global immunization week'.

- **by end-2012:** cessation of the ongoing cVDPV2 in Nigeria
- **by September 2013 (latest):** introduction of one supplementary IPV dose at an immunization contact (at or above age 14 weeks) in all OPV-using countries
- **by April 2014:** replacement of tOPV with bOPV for routine & supplementary immunization globally (possibly linked to a Global Immunization Week)

## **9 Proposed recommendations for SAGE**

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Based on its review of available evidence and data, the SAGE Polio Working Group proposes the following programmatic and immunization policy to SAGE:

### **a) Programmatic recommendations (as per February 2012 extraordinary SAGE meeting)**

- The ongoing cVDPV2 in Nigeria must be treated as a public health emergency & stopped as rapidly as possible
- Intradermal, fractional (1/5th dose) IPV should be submitted for regulatory review as rapidly as possible

### **b) Policy recommendations**

- By April 2014, tOPV should be replaced with bOPV for all routine & supplementary immunization in a globally synchronized manner
- 6 months in advance (i.e., September 2013) of a global tOPV-bOPV switch, all OPV-using countries should have introduced 1 supplementary dose of IPV (e.g., at an immunization contact at or above age 14 weeks), given the availability of a low-cost IPV option
- For the purpose of a tOPV-bOPV switch, IPV could be given either as full dose (IM) or fractional (1/5th) ID dose

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