Background and Technical Rationale for Introduction of One dose of Inactivated Polio Vaccine (IPV) in Routine Immunization Schedule

A handbook for training regional consultants and briefing NITAG members on technical aspects related to introduction of IPV as it relates to the Polio Eradication and Endgame Strategic Plan

Version date: February 14, 2014

NOTE: This is a working draft that will be revised based on ongoing feedback and availability of new IPV related information.

For the most up-to-date information please visit: http://tinyurl.com/ipv-intro

Ce document est aussi disponible en Francais. Consultez http://tinyurl.com/ipv-intro pour info:
Background and Technical Rationale for Introduction of One dose of Inactivated Polio Vaccine (IPV) in Routine Immunization Schedule

ABBREVIATIONS & GLOSSARY OF TERMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AFP</td>
<td>Acute Flaccid Paralysis</td>
</tr>
<tr>
<td>bOPV</td>
<td>Bivalent Oral Polio Vaccine containing serotypes 1 and 3</td>
</tr>
<tr>
<td>cVDPV</td>
<td>Circulating vaccine-derived poliovirus</td>
</tr>
<tr>
<td></td>
<td>· cVDPV1 (type 1)</td>
</tr>
<tr>
<td></td>
<td>· cVDPV2 (type 2)</td>
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<tr>
<td></td>
<td>· cVDPV3 (type 3)</td>
</tr>
<tr>
<td>EPI</td>
<td>Expanded Programme on Immunization</td>
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<td>GAVI</td>
<td>Global Alliance for Vaccines and Immunisation</td>
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<td></td>
<td>· GAVI Countries</td>
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<td></td>
<td>· NON-GAVI Countries</td>
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<td>GPEI</td>
<td>Global Polio Eradication Initiative</td>
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<td>IPV</td>
<td>Inactivated Polio Vaccine</td>
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<tr>
<td>iVDPV</td>
<td>Immunodeficiency-associated vaccine-derived poliovirus</td>
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<tr>
<td>mOPV</td>
<td>Monovalent Oral Polio Vaccine</td>
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<tr>
<td>OPV</td>
<td>Oral Polio Vaccine</td>
</tr>
<tr>
<td>PIE</td>
<td>Post-Introduction Evaluation</td>
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<tr>
<td>PPS</td>
<td>Post-Polio Syndrome</td>
</tr>
<tr>
<td>PV1</td>
<td>Poliovirus type 1</td>
</tr>
<tr>
<td>RI</td>
<td>Routine Immunization</td>
</tr>
<tr>
<td>SAGE</td>
<td>Strategic Advisory Group of Experts on Immunization</td>
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<tr>
<td>tOPV</td>
<td>Trivalent Oral Polio Vaccine</td>
</tr>
<tr>
<td>VAPP</td>
<td>Vaccine-associated paralytic poliomyelitis</td>
</tr>
<tr>
<td>VDPV</td>
<td>Vaccine-derived poliovirus</td>
</tr>
<tr>
<td>VPD</td>
<td>Vaccine-preventable disease</td>
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<tr>
<td>WHA</td>
<td>World Health Assembly</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WPV</td>
<td>Wild poliovirus</td>
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<td>WPV</td>
<td>Wild poliovirus</td>
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ABBREVIATIONS & GLOSSARY OF TERMS • 2
Version: February 14, 2014
EXECUTIVE SUMMARY

The Polio Eradication and Endgame Strategic Plan 2013-2018 was drawn up in response to the May 2012 World Health Assembly declaring the completion of poliovirus eradication to be a programmatic emergency for global public health. Under this endgame plan to achieve and sustain a polio-free world, the use of oral polio vaccine (OPV) must eventually be stopped worldwide, starting with OPV that contains type 2 poliovirus (OPV type 2). At least one dose of inactivated polio vaccine (IPV) must be introduced as a risk mitigation measure before the withdrawal of type 2 OPV.

The steps involved are:

1. **By end 2015, introduce at least 1 dose of IPV into all routine immunization systems**, at least 6 months before the switch from trivalent oral polio vaccine (tOPV) to bivalent oral polio vaccine (bOPV, containing types 1 and 3 poliovirus).
2. **During 2016, switch from tOPV to bOPV, which does not contain type 2 virus, in routine immunization and polio campaigns.**
3. **Plan for the eventual withdrawal of all OPV.**

This manual will provide key technical information and up-to-date references to decision-makers and programme managers and to train consultants who subsequently will be available to support country planning activities and training sessions for the introduction of IPV.

The key messages of this document include:

- SAGE has recommended that **all countries introduce at least one dose of IPV into the routine immunization schedule** before the end of 2015 and that all priority countries develop an introduction plan by June 2014 and all remaining OPV only countries develop a plan by end-2014.
- Because OPV in rare cases can cause paralysis, **OPV cessation must occur for the world to be polio free.**
- OPV cessation will occur globally in 2 phases, with **removal of type 2 component in 2016 (global switch from trivalent OPV to bivalent OPV, containing types 1&3)** followed by bOPV withdrawal in 2018-2019.
- Introducing **IPV before the tOPV-bOPV switch** in 2016 will ensure that a substantial proportion of the population is protected against type 2 polio after the withdrawal of type 2 OPV.
- Introducing IPV will **mitigate risks of type 2 reintroduction** in association with the withdrawal of type 2 OPV and will **facilitate polio eradication** by boosting immunity to types 1 & 3.
- IPV introduction will happen through the routine immunization programme. There is currently no plan to use IPV in mass immunization campaigns for catch up or other purposes. It is however possible that, in a few limited geographic areas of endemic countries, IPV could be used in combination with OPV for accelerating the eradication of the wild polio virus.
- IPV is given in **addition to the OPV routine schedule doses** and does not replace any OPV doses.
INTRODUCTION

The eradication of polio is a top global health priority. Since the World Health Assembly (WHA) announced a goal to eradicate polio in 1988, thereby creating the Global Polio Eradication Initiative (GPEI), the number of polio cases has drastically declined (Figure 1) from ~350,000 cases per year in 1988 to only 341 cases in 2013 (as of 20 Nov 2013).(1)

Figure 1: Clinical cases of polio related to wild polio virus globally (1988-2013, as of 20 Nov 2013)

To complete the final milestone, the WHA and countries endorsed GPEI’s Polio Eradication and Endgame Strategic Plan in May 2013 which provides a detailed approach and concrete timeline for complete eradication of polio.(2) This plan is different from previous eradication plans because it deals with the eradication and containment of polio caused not just by wild viruses but also paralytic cases associated with oral polio vaccine (OPV). To address risks associated with OPV use, the Plan calls for a phased withdrawal of OPV globally. This phased withdrawal would begin with removal of the type 2 component of OPV through a switch globally from trivalent OPV (tOPV) to bivalent OPV (bOPV, containing only types 1 and 3) in 2016. To manage risks associated with removal of the type 2 component of OPV, such as the emergence of circulating vaccine-derived poliovirus (cVDPV) or the reintroduction of the wild type 2 poliovirus, the World Health Organization’s (WHO) Strategic Advisory Group of Experts (SAGE) has recommended that all OPV-using countries introduce at least one dose of IPV in their routine immunization programs before the end of 2015, prior to the tOPV-bOPV switch.(3-7)
The need to introduce IPV into all OPV-only using countries globally in a relatively short time represents a major and unprecedented challenge. However, it is also a timely opportunity to improve collaborations between global immunization partners and make efficient use of GPEI resources to strengthen routine immunization services, particularly in countries with the highest risk target populations and weak immunization systems.

The complete Endgame Plan and other resources related to GPEI can be found at http://www.polioeradication.org/resourcelibrary/strategyandwork.aspx

1. **GPEI’s Polio Eradication & Endgame Strategic Plan (the Plan)**

1.1. **Overview of the Plan and timeline**

In May 2013, the WHA endorsed *The Polio Eradication & Endgame Strategic Plan 2013-2018* (the Plan), developed by GPEI to complete the eradication and containment of all wild, vaccine-derived, and Sabin polioviruses. It is important to note that this plan differs from previous plans to eradicate polio in that it comprehensively addresses strategies for both endemic and vaccine-related polio. The Plan also incorporates a strategy to contribute to the strengthening of Routine Immunization (RI) and to deliver other health services to the world’s most vulnerable children in 10 focus countries (footnote countries).

The Plan outlines four objectives (Figure 2). This manual provides the technical rationale for **Objective 2** which addresses the Endgame component of the Plan and calls for:

- strengthening routine immunization in 10 focus countries
- introducing at least one dose of IPV into the routine immunization schedule, and
- then replacing tOPV with bOPV (tOPV-bOPV switch) in 2016 in all **OPV using countries** – setting the stage for eventually ending bOPV use in 2019-2020.

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Focus countries have been identified by GPEI as representing areas still at considerable risk where GPEI has committed significant field assets. They include: Afghanistan, Angola, Chad, Democratic Republic of Congo (DRC), Ethiopia, India, Nigeria, Pakistan, Somalia, South Sudan.

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Key elements of the Plan
- End all types of polio disease
- Improve immunization systems
- Introduce IPV & withdraw OPV
- Mitigate risks of further outbreaks
- Establish a concrete timeline
Figure 2: Polio Eradication and Endgame Strategic Plan (This figure shows that with full funding, the objectives can be pursued in parallel, with working target dates established for the completion of each.)

2. SAGE recommendations
This manual relates to **Objective 2 of the Plan**, specifically the introduction of IPV into infant immunization schedules of all OPV using countries worldwide.

SAGE has recommended a global, coordinated withdrawal of the type 2 component of tOPV from immunization programmes by April 2016. For countries which use only tOPV in their routine infant immunization programmes, this will require switching from tOPV to bOPV (containing only types 1 and 3) for that purpose.\(^{3-5, 8}\)

Prior to the tOPV-bOPV switch, SAGE recommends that all countries introduce at least one dose of IPV into their infant immunization schedules as a risk mitigation measure by
providing immunity in case a type 2 poliovirus re-emerges or is reintroduced (8).

SAGE provided recommendations to address the wild polio virus risks and IPV introduction globally in the context of the polio endgame, including (8):

- countries introducing 1 dose of IPV into the routine immunization schedule should administer the dose at or after 14 weeks of age, in addition to the 3-4 doses of oral polio vaccine (OPV) already given in the primary vaccination series;
- countries have flexibility to consider alternative schedules (e.g. earlier IPV administration) based on local conditions (e.g. documented risk of vaccine-associated paralytic poliomyelitis or VAPP prior to 4 months of age); and
- to help accelerate eradication and reduce vulnerability, all endemic and other high risk countries should develop a plan for IPV introduction by mid-2014; all other OPV-only using countries should develop such a plan by end-2014.

**Note:**

- IPV introduction will happen through the routine immunization programme. There is currently no plan to use IPV in mass immunization campaigns for catch up or other purposes. It is however possible that, in a few limited geographic areas of endemic countries, IPV could be used in combination with OPV for accelerating the eradication of the wild polio virus.

- IPV is given in addition to the existing OPV doses and **does not replace any OPV doses.**

**Figure 3.** Potential schedules of incorporating single dose of IPV with DTP/Penta and OPV vaccination schedule, SAGE recommendation, November 2013

<table>
<thead>
<tr>
<th>DTP/Penta dosing schedule</th>
<th>Timing of single dose of IPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>6,10,14 weeks</td>
<td>• Single dose of IPV at <strong>14 weeks of age</strong> with DTP3-OPV3.</td>
</tr>
<tr>
<td>2,3,4 months</td>
<td>• Single dose of IPV with DTP3-OPV3 at <strong>4 months</strong></td>
</tr>
<tr>
<td>2,4,6 months</td>
<td>• Single dose of IPV with DTP3 and OPV3 at <strong>6 months</strong>, though DTP2-OPV2 can also be considered</td>
</tr>
</tbody>
</table>
A catch-up strategy, where children born before the vaccine introduction date are immunized, is not recommended for IPV because these children will have been vaccinated with tOPV, and thus immunized against all three types of polio, particularly type 2. It is also important to note that IPV should be administered at the first immunization contact after 14 weeks of age, but waiting until 9 months of age is not recommended. Waiting until 9 months to administer IPV would mean leaving a large pool of susceptible hosts (all children aged 0-8 months) to be infected by or to transmit type 2 vaccine derived polioviruses.

SAGE RECOMMENDATIONS (excerpt from reference 8)
SAGE reviewed evidence on IPV immunogenicity by age, and recommended that countries introducing 1 dose of IPV into the routine immunization schedule should administer that dose >14 weeks of age, in addition to the 3 to 4 doses of OPV in the primary series. As IPV immunogenicity is highest after 14 weeks of age due to reduction in maternal antibodies that otherwise interfere with immunogenicity, IPV administration at 14 weeks maximizes the benefit of IPV in protecting children against type 2 poliovirus after OPV2 cessation, while helping to close immunity gaps to types 1 and 3 virus. In countries with primary immunization contacts at 6, 10 and 14 weeks of age or 2, 3, and 4 months of age, the IPV dose should be added at the DPT3-OPV3 contact; for countries with a 2, 4, and 6 months schedule, the IPV dose could be added at the DPT3-OPV3 contact, though DPT2-OPV2 can also be considered. For children vaccinated with bivalent OPV but who did not receive IPV at 14 weeks of age, the IPV doses can be given at any subsequent immunization contact. Those starting the routine immunization schedule late (age >3 months) should receive IPV at the first immunization contact. SAGE recommended that countries should have flexibility to consider alternative schedules (e.g. IPV administration earlier than 14 weeks) based on local conditions (e.g. documented risk of VAPP prior to 4 months of age).

3. Poliovirus vaccines: Role of IPV and OPV in The Endgame and Eradication Strategic Plan

The development of effective vaccines to prevent paralytic polio was one of the major medical breakthroughs of the 20th century. With the development and evaluation of bivalent oral polio vaccine in 2009, the Global Polio Eradication Initiative now has an armory of six different vaccines to stop polio transmission (Table 1). (9-12)
Table 1: Overview of available polio vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Wild Poliovirus (WPV) targeted</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>tOPV</td>
<td>All three types</td>
<td>Historically, the most common form of OPV used in the routine and supplementary immunization activities in low and middle-income countries globally, because of cost, ease of administration, and excellent oral and intestinal immunity</td>
</tr>
<tr>
<td>bOPV</td>
<td>Types 1 &amp; 3</td>
<td>Licensed in 2009 after a clinical trial showed non-inferior immunogenicity to use of monovalent types 1 or 3</td>
</tr>
<tr>
<td>mOPV1, mOPV2, mOPV3</td>
<td>Either types 1, 2, or 3</td>
<td>mOPV1 and mOPV3 were introduced by GPEI in 2005 to improve OPV effectiveness in the last WPV reservoirs in Africa and Asia.</td>
</tr>
<tr>
<td>IPV</td>
<td>All three types</td>
<td>Currently used in most high-income countries due to its excellent safety profile and high efficacy; SAGE recommends introducing at least one dose in routine immunization schedules of all countries before beginning OPV2 cessation in 2016</td>
</tr>
</tbody>
</table>

3.1. **Inactivated Polio Vaccine (IPV)**

Key messages on IPV introduction

- The primary role of introducing one dose of IPV into routine immunization programs is to mitigate risks associated with OPV withdrawal and the potential reintroduction of polioviruses
- IPV will maintain type 2 poliovirus immunity during the tOPV-bOPV switch (removal of type 2 component of OPV) in 2016
- SAGE recommends that at least IPV should be administered **at or after 14 weeks of age, in addition to 3-4 doses of OPV in the primary vaccination series**
- Unlike OPV, IPV is not a “live” vaccine and thus carries no risk of vaccine-associated polio paralysis
- IPV induces humoral and oral immunity to polioviruses and boosts intestinal immunity in children previously vaccinated with OPV

3.1.1. **Summary of IPV**

IPV was developed in 1955 by Dr. Jonas Salk. Also called the “Salk vaccine,” currently available IPV consists of inactivated (killed) wild-type poliovirus strains of all three poliovirus types. (12) The Salk IPV
should be distinguished from the Sabin IPV that is still currently under development and is based on
the Sabin OPV strains rather than wild virus strains. More information on Sabin OPV stains, OPV
immunogenicity and rationale for OPV use can be found in Annex 3.

Because IPV is an inactivated vaccine and not a “live” attenuated vaccine, it carries no risk of vaccine-
associated polio paralysis. However, in contrast to OPV, since it does not replicate in the gut, IPV
induces substantially lower levels of intestinal immunity and does not confer protection to others
through secondary spread. IPV is also less effective than OPV in reducing fecal-oral transmission. IPV
is as effective as OPV in inducing oral immunity so it will be equivalent to OPV in preventing oral-oral
transmission. Using both vaccines together provides the best form of protection.

The immune response to intramuscularly administered IPV varies based on the number of
administered doses (higher with more doses) and the age at vaccination (higher with delayed
immunization) (Table 2). Unlike OPV, immune response does not vary substantially between
industrialized and tropical developing country settings.

In the event of infection, the antibodies induced by IPV prevent the spread of the virus to the central
nervous system and protect against paralysis.

**Note:** Due to interference from higher levels of circulating maternal antibodies, particularly during
the first 3 months of life, IPV immunogenicity is higher if given after 3 months of age. Delaying
vaccination until at or after 14 weeks gives time for those maternally derived antibodies to decline
thereby decreasing the potential that they will interfere with the immune response to IPV. This is
the rationale for the SAGE recommendation to administer IPV *at or after 14 weeks of age, in
addition to 3-4 doses of OPV in the primary vaccination series.*
Overview of IPV formulations: Currently licensed IPV formulations are given by intramuscular injection and administration requires sterile injection equipment and procedures by trained health workers. IPV is available as a:

- **stand-alone vaccine**, and
- **combination products** with diphtheria, tetanus, acellular pertussis, hepatitis B, or Hib antigens in tetravalent, pentavalent, or hexavalent formulations. Note that a combination product with whole-cell pertussis is not currently available.

The combination products currently available are offered at a substantially higher cost than stand-alone IPV (at least $20-$40 per dose) as they use acellular pertussis, which is significantly more expensive to produce than whole cell pertussis.\(^{15}\)

**Note:** Currently, only the stand-alone IPV is prequalified by WHO.

- It is available in fully liquid 1-dose and 10-dose presentations.
- UNICEF expects a 5-dose presentation to be available and WHO prequalified in the second half of 2014.
- A 2-dose presentation is prequalified but is not currently available through UNICEF.

Stand-alone IPV is sensitive to heat and freezing and must be handled appropriately (see Operational Field Manual for additional information).\(^{16}\) IPV has a shelf life of 24-36 months (depending on the brand) when stored in a refrigerator at 2°C - 8°C and protected from light. IPV is freeze sensitive and **should not be frozen**.

**Note:** Stand-alone IPV is preserved with 2 phenoxy-ethanol. This preservative does not meet WHO requirements for enabling the application of the Multi-dose vial policy. Hence all open multidose vials of this vaccine must be discarded at the end of the immunization session or within 6 hours after opening, whichever comes first.
### Background and Technical Rationale for Introduction of One dose of Inactivated Polio Vaccine (IPV) in Routine Immunization Schedule

Table 2: Comparison of characteristics of OPV and IPV

<table>
<thead>
<tr>
<th></th>
<th>Oral Polio Vaccines (OPV)</th>
<th>Inactivated Polio Vaccines (IPV)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Types</strong></td>
<td>• Trivalent (tOPV): 1, 2, &amp; 3</td>
<td>Trivalent</td>
</tr>
<tr>
<td></td>
<td>• Bivalent (bOPV): 1 &amp; 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Monovalent (mOPV): 1, 2, or 3</td>
<td></td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td>• Oral</td>
<td>Intramuscular (and sub cutaneous for some brands)</td>
</tr>
<tr>
<td><strong>Immune response</strong></td>
<td>• In industrialized settings, seroconversion is ~ 50% to all 3 serotypes for one dose, and &gt; 95% after 3 doses with lifelong immunity</td>
<td>• Immune response similar between industrialized and tropical developing settings</td>
</tr>
<tr>
<td></td>
<td>• In tropical developing countries, lower immune response necessitates more than 3 doses and additional booster doses. After 3 doses of tOPV seroconversion rates vary from:</td>
<td>o <strong>3 doses</strong>: nearly 100% seroconversion rates to all 3 serotypes</td>
</tr>
<tr>
<td></td>
<td>o 73% (range 36%-99%) for type 1</td>
<td>o <strong>2 doses</strong>: 40%-93% against the 3 serotypes, but exceeds 90% when vaccination is initiated after 8 weeks of age.</td>
</tr>
<tr>
<td></td>
<td>o 90% (range 71%-100%) for type 2</td>
<td>o <strong>1 dose</strong>: 19%-46% against Type 1, 32%-63% against Type 2, and 28%-54% against Type 3 poliovirus.</td>
</tr>
<tr>
<td></td>
<td>o 70% (range 40%-99%) for type 3</td>
<td>• It is important to note that immune response to one dose is substantially higher, particularly against Type 2 poliovirus when administered at 4 months of age compared to 6 weeks to 2 months of age.</td>
</tr>
<tr>
<td></td>
<td>• Interference from type 2 vaccine virus is one reason for lower immune response to types 1 and 3</td>
<td></td>
</tr>
<tr>
<td><strong>Pros</strong></td>
<td>• Cheap</td>
<td>• No risk of VAPP</td>
</tr>
<tr>
<td></td>
<td>• Easy to administer</td>
<td>• Highly effective</td>
</tr>
<tr>
<td></td>
<td>• Good oral and intestinal immunity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Confers transmission to contacts and secondary vaccination</td>
<td></td>
</tr>
<tr>
<td><strong>Cons</strong></td>
<td>• Causes paralysis in very rare cases (VAPP &amp; cVDPVs)</td>
<td>• More costly than OPV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cannot be administered by volunteers as it requires and injection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Does not confer transmission to contacts and thus provide secondary vaccination</td>
</tr>
</tbody>
</table>

The remainder of the section focuses on the technical rationale for the SAGE recommendation on withdrawing OPV and introducing one dose of IPV into routine immunization schedules. (17)
3.1.2. **Rationale for phased withdrawal of OPV**

Although OPV is the appropriate vaccine until polio transmission is interrupted, with ongoing use of OPV and control of polio disease related to wild virus globally, the estimated number of polio cases related to OPV has exceeded those related to wild virus (Figure 4).

Because of this **very low but real risk of polio associated with OPV**, if the world is to remain free of polioviruses following eradication, then use of OPV ultimately will need to be stopped. To curtail the risk of polio associated with OPV (cVDPV and VAPP), the Endgame calls for a withdrawal of vaccine in two phases:

- **Phase 1**: removal of type 2 component of OPV, through a global switch from tOPV to bOPV
- **Phase 2**: withdrawal of bOPV after the certification of eradication of wild polioviruses

The phased withdrawal of OPV related to the epidemiology of WPV and vaccine-related cases of polio occurring globally in the past decade (Table 1). Removal of the type 2 component first is justified because:

- Type 2 WPV has not been circulating naturally since the last case was detected in 1999 in Aligarh, India thus obviating the need for the type 2 component of the vaccine
- Since 2009, 97% of all VDPVs have been due to Type 2 virus
- 40% of all VAPP cases are related to Type 2 component of OPV
- Presence of type 2 component in the vaccine impairs the immune response to types 1 and 3 poliovirus requiring more doses of tOPV to reach herd immunity thresholds for those types compared to the number of doses of bOPV to reach those same immunity thresholds.

Note that all cases of polio related to wild virus are now due to type 1 virus. Type 3 was last detected in November 2012, although absence of virus detection for one year is not sufficient for certifying eradication.
3.1.3. **Role of one dose of IPV in polio eradication and control**

The primary role of introducing **one dose of IPV into routine immunization programs** is to mitigate risks associated with OPV withdrawal and possible reintroduction of polioviruses (Figure 5). The initial phase of OPV withdrawal – switch from tOPV to bOPV-- would lead to a gradual increase in the number of persons susceptible to type 2 poliovirus resulting in three main risks to the population.(6)

1. Immediate time-limited risk of cVDPV2 emergence;
2. Medium and long-term risks of type 2 poliovirus re-introduction from a vaccine manufacturing site, research facility, diagnostic laboratory, or a bioterrorism event.
3. Spread of virus from rare immune deficient individuals who are chronically infected with OPV2.

A reintroduction of poliovirus or cVDPV2 emergence could potentially result in a substantial polio outbreak or even re-establishment of global transmission.
There is precedent for type 2 wild polioviruses to be reintroduced into the population. During 2002-2003, a laboratory strain of type 2 wild poliovirus was introduced in India. Fortunately, this outbreak was controlled, but it highlights the potential risk if the population is 100% susceptible, as would occur if all polio vaccination against type 2 viruses was stopped.

The introduction of at least one dose of IPV has an important supporting role in assuring complete global eradication of all polioviruses. SAGE has recommended the introduction of IPV in all OPV using countries worldwide by the end of 2015. The primary role for IPV introduction in 2015 is to maintain type 2 poliovirus immunity during the tOPV-bOPV switch (removal of type 2 component) in 2016. IPV introduction will also help interrupt transmission if an outbreak occurs and hasten the eradication of all polio diseases.

Figure 5: Schematic of rationale for introducing at least one dose of IPV

It is important to note that SAGE recommends IPV be introduced into the routine immunization programmes. As indicated before and described in the subsequent sections, IPV is primarily intended to maintain type 2 poliovirus immunity while OPV2 cessation occurs globally. Thus, infants have to be vaccinated with at least one dose of IPV in addition to OPV during their routine EPI visit.

3.1.4. Reducing risks: individual protection from one dose of IPV

Evidence indicates that one dose of IPV may reduce risk by protecting individuals against paralytic polio should they be exposed to cVDPV2 or WPV2 or by enhancing the population immunity that can be achieved through use of mOPV2 in the setting of an outbreak of type 2 poliovirus post OPV2 cessation (Figure 6). Because a proportion of the population will already be immune as a result of having received IPV, the immunity levels reached after a dose of mOPV2 will be higher than the immunity levels reached with a single dose of mOPV2 in a completely susceptible population.
Prevention of paralytic polio

Three lines of evidence support the notion that one dose of IPV will prevent paralytic polio in those exposed to cVDPV2 or WPV2.

1. **Clinical protection**: A case control study from Senegal demonstrated that one dose of IPV was \( \sim 36\% \) (0-67\%) effective against paralytic polio caused by WPV1.\(^{(19)}\)

2. **Immunogenicity**: One dose of IPV induces seroconversion of \( \sim 32\%\text{-}63\% \) against type 2 poliovirus. Most notably, seroconversion was higher when IPV was administered at 4 months of age (63\%) in a recent study from Cuba compared to older studies where IPV was given at 6-8 weeks of age (32\%-39\%).\(^{(14, 20)}\) The higher seroconversion at 4 months of age is likely related to lower circulating maternal antibodies and hence reduced interference with immune response compared to that observed at younger ages. More importantly, in this study from Cuba, among those who did not seroconvert (37\%), 98\% had a priming response to a subsequent dose of OPV—that is, they developed significant antibody responses within 7 days of subsequent exposure to OPV.\(^{(20)}\) All those who seroconvert should be protected against polio. In addition, there is some information to suggest that many of those who do not seroconvert may also be protected because they are primed and can mount an accelerated immune response. However, the data are conflicting as to whether primed persons are protected. Nevertheless, the proportion of the population protected by seroconversion alone is high and if primed persons are protected then protection against paralytic polio will be even higher.

3. **Protection against VAPP**: The last line of evidence supporting efficacy against paralysis relates to data demonstrating elimination of VAPP from Sabin strains in countries that introduced IPV at 3 months of age before the first dose of OPV.\(^{(10, 21)}\) The hypothesis was that IPV induced sufficient humoral immunity thus preventing paralysis from Sabin strains that revert to a neurovirulent form.

   - The epidemiology of VAPP differs in developing countries compared to developed countries. In developed countries, VAPP typically occurs after the first dose of OPV, which is most immunogenic; however in tropical developing countries, VAPP can occur after the second and third doses due to greater vaccine take (possibly due to lower maternal antibodies at that age). Thus the protection from one dose of IPV given at DTP3/OPV3 or at 14 weeks as recommended by SAGE may have different benefits against prevention of VAPP depending on the epidemiology of the adverse event in the country.

Immunologic response to mOPV2 after one dose of IPV

In the event that an outbreak of type 2 poliovirus does occur post OPV2 cessation, evidence indicates that the humoral and intestinal immunological response to mOPV2 or additional doses of IPV in individuals vaccinated with one dose of IPV would be substantially superior to those without prior IPV exposure.
1. **IPV closes the immunity gap against type 2 poliovirus:** A study from Cote d'Ivore demonstrated that in previously tOPV vaccinated infants who were seronegative had seroconversion rates against type 2 poliovirus of **100% after one dose of IPV versus 53% after tOPV.** (22) Similarly, in India, previously OPV vaccinated infants who were seronegative to type 2 poliovirus had seroconversion rates against **type 2 of 100% after IPV.** (23) Data from the US indicates immune response is similar in those receiving IPV followed by OPV compared to those who receive OPV followed by IPV. (24, 25)

2. **IPV and OPV result in additive immunity:** Studies in Baltimore and Buffalo in the United States showed that equivalent serologic responses were seen after two doses of IPV, two doses of OPV, and a dose of IPV followed by a dose of OPV. (24, 25)

3. **Boosting intestinal immunity:** A recent study from India demonstrated that giving IPV to children with multiple previous doses of OPV substantially boosts intestinal immunity and decreases excretion prevalence after challenge with bivalent OPV (see next section). (26)

### 3.1.5. Transmission Interruption

Transmission of polio can either be oral-oral (more commonly in developed settings) or fecal oral (more commonly in high density, low sanitation settings). IPV is equally effective against oropharyngeal shedding as OPV—that is, oral shedding of poliovirus is rare after vaccination with either IPV or OPV. (27) With regard to fecal shedding, OPV is superior at reducing the prevalence of fecal excretion of poliovirus.

However, IPV dose reduce the duration of shedding and the amount of virus in the stool. Thus, it is expected that prior receipt of IPV should contribute to curtailing transmission of poliovirus in the setting of an outbreak.

- A study from Cuba showed that viral titers after IPV versus unvaccinated controls were 0.5-1 log10 lower (3-10 fold decrease) at day 7 after OPV challenge and the excretion period was shortened by half (median of 10-12 days after 2 IPV doses versus >20 days with unvaccinated controls). (26, 28)

- More recently, in India, a single IPV dose in infants 6-11 months, 5 years, and 10 years of age who received multiple prior OPV doses reduced excretion prevalence by 54%-72% (type 1) and 51%-81% (type 3) after a challenge with bOPV. (26)

These findings are consistent with previous research demonstrating that mucosal exposure to OPV is needed after IPV to achieve an IgA response and that the resistance to excretion depends on the type-specific antibody levels induced by IPV. (29)

In summary, administration of one dose of IPV would induce immunity in a substantial proportion of the population and facilitate outbreak control with mOPV, should polioviruses be reintroduced. Faster outbreak control would be expected because the population immunity might already be close to herd
immunity thresholds. Thus, a single dose of mOPV would be much more likely to induce the immunity levels needed to interrupt transmission than in a completely unvaccinated population.

### 3.1.6. Accelerating polio eradication efforts

According to SAGE recommendations, IPV should be given along with OPV3 or OPV4 or at first immunization contact after 14 weeks of age, and as such, most infants will likely have received 1-3 doses of OPV prior to IPV. Thus, IPV could also play a role in the eradication efforts, in conjunction with bOPV, by boosting immunity against type 1 and 3 polioviruses in polio endemic countries and countries where poliovirus circulation has been reestablished.

Solid evidence exists supporting closing of immunity gaps and substantial boosting of antibody titers to types 1 and 3 (in addition to types 2 as described previously) when IPV is administered after OPV.

- In Cote d'Ivore, a study examined the immune response of a single dose of IPV at six months of age in seronegative children who received three prior doses of tOPV at 2,3, and 4 months of age. Seroconversion was 80% and 76% after IPV compared to 40% and 22% after OPV only, for types 1 and 3 poliovirus, respectively. (22)
- A similar study in Moradabad, India demonstrated that a single dose of IPV among children who had previously been immunized with tOPV but were seronegative substantially improved seropositivity rates against types 2 and 3 wild poliovirus (100%-and 91% seroconversion, respectively). (23)

Combined and sequential schedules of OPV and IPV have generated high seroconversion rates, and a number of studies have shown use of both vaccines simultaneously induces better immune responses than either vaccine alone. (12, 13) Sequential schedules have been successfully used for several decades in a number of countries.\(^b\)

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\(^b\) As of the end of 2010, routine sequential schedules have been recommended in Belarus, Bosnia-Herzegovina, Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates, Jordan, Lebanon, Russian Federation, Syria, South Africa, Turkey, Ukraine, and the West Bank and Gaza.
4. Alternative future "low cost" IPV options

SAGE has reviewed potential strategies for achieving a low cost IPV product for OPV type 2 withdrawal and identified two approaches that could potentially reduce the cost of IPV below US$1 per dose. While many of these approaches are promising, they are unlikely to be widely available in the near future. This means that while countries should be aware of these developments for future planning, they should also plan to introduce a full dose of IPV in the interim.

Some of the most promising options include:
• **Intradermal fractional IPV (1/5 of a full dose):** would reduce the volume of vaccine per dose to about 20% of the volume of a standard dose and result in cost savings of approximately 70% per immunized infant. Some logistics costs might also be reduced due to less space requirements in the cold chain. WHO has been collaborating with the manufacturers of needle-free injection devices for several years, which has resulted in the engineering of two new intradermal devices that are undergoing investigation in clinical trials. If successful, these devices could be used to administered fractional dose IPV intradermally. However, additional clinical trials, funding, and support from manufacturers and regulatory authorities are necessary to better understand the immunogenicity of fractional IPV with different schedules and devices, and to fast-track approval processes.

• **Adjuvanted intramuscular IPV:** Adjuvants, such as aluminum-based adjuvants, would potentially enhance the immune response to the IPV antigen thus allowing the IPV antigen content and cost to be reduced. Development of adjuvanted IPV lags behind fractional dose IPV and the estimated time for development of adjuvanted formulations is unlikely to have an impact on IPV demand from 2014-2020.

For the most up-to-date information please visit: [http://tinyurl.com/ipv-intro](http://tinyurl.com/ipv-intro)

Annex 1: Oral poliovirus vaccine (OPV)

A.3.1. Summary of OPV

OPV was developed in 1961 by Dr. Albert Sabin. OPV contains live-attenuated strains of poliovirus that are also referred to as the “Sabin strains.”(10) Three forms of OPV are currently available--tOPV, bOPV, and mOPVs--with tOPV being the most commonly used form in routine and supplementary immunization activities in low and middle-income countries globally (Table 1).(9)

Live attenuated polioviruses replicate in the oral cavity, intestinal mucosa and lymphoid cells and in lymph nodes that drain those organs. Vaccine viruses are excreted in the stool of the vaccinated person for up to 6 weeks after a dose, with maximum viral shedding occurs in the first 1–2 weeks after vaccination, particularly after the first dose.

OPV strains may spread from the recipient to contacts, who upon exposure may be infected with vaccine virus and thus protected.

Studies in temperate developed countries found that 3 doses of tOPV resulted in seroconversion of >95% of infants to all types and provided long-lasting immunity.(13) In developing countries, an average of 73%, 90%, and 70% of children seroconverted to poliovirus types 1, 2, and 3, respectively. Therefore, more than 3 doses and additional booster doses are required (through supplementary immunization activities) to improve seroconversion and achieve high levels of intestinal immunity.

The selection of the type of OPV for routine and supplementary immunization activities is evolving due to two factors:

1. Changing epidemiology of circulating polio strains: Since November 2012, all cases of polio related to wild virus have been Type 1. There has been no natural circulation of Type 2 WPV since 1999 when the last case was last detected in Aligarh, India. Type 3 WPV was last detected in November 2012, although absence of virus detection for one year is not sufficient for certifying eradication.

2. Cases associated with OPV: although OPV offers effective protection against polio, it is a live attenuated vaccine and in very rare cases can lead to paralysis. There are two ways this can occur:
   a. Vaccine Associated Paralytic Poliomyelitis (VAPP): refers to spontaneous reversion to neurovirulence of one of the attenuated Sabin viruses in OPV. For every 2.4 million doses of OPV administered, one vaccine recipient or a close contact is paralyzed.

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(c) http://www.polioeradication.org/Dataandmonitoring/Poliothisweek.aspx
(d) http://www.who.int/ith/vaccines/polio/en/
Background and Technical Rationale for Introduction of One dose of Inactivated Polio Vaccine (IPV) in Routine Immunization Schedule

There are an estimated 250 – 500 VAPP cases globally per year.(10, 31) Of these, about 40% are caused by tOPV’s type 2 component.(32)

b. Circulating Vaccine Derived Poliovirus (cVDPV) outbreaks: these rare outbreaks occur when a OPV strain is passed from person-to-person, mutating back to a neurovirulent and highly transmissible form.(33) Almost all cVDPV outbreaks (97%) in recent years have been caused by a type 2 OPV-derived virus. Circulating VDPVs are widely transmitted in a community and are not likely to be related to contact with a recent vaccine recipient in contrast to VAPP which occurs in OPV recipients or their close contacts. Other very rare forms include VDPVs in persons with a primary immunodeficiency syndrome (iVDPVs) and ambiguous VDPVs where the virus is genetically different than the Sabin strains implying prolonged circulation allowing those mutations to occur but is not known to be associated with an outbreak or immunodeficiency.

Note: For the world to be “polio-free,” we must achieve complete eradication and containment of all polio disease related to 1) wild polioviruses; 2) VDPVs; and 3) VAPP

A.3.2. Rationale for ongoing use of OPV

OPV have been the primary vaccines of choice in the eradication effort because(9):

- OPV is inexpensive
- OPV can be easily administered orally without requiring trained health workers
- OPV not only induces humoral immunity to prevent infection of the nervous system but also produces oral and intestinal mucosal immunity thus reducing the amount of virus excreted leading to decreased transmission
- OPV can spread to close contacts through secondary spread thus immunizing them or boosting their immunity

Two important aspects of the current global situation of polio warrant ongoing use of OPV until polio transmission is interrupted.

1. First, WPV is still endemic in three countries (Pakistan, Afghanistan, and Nigeria) that continue to be reservoirs for re-infecting other countries worldwide
2. Second, in 2013, polio cases were also detected in five additional countries (Somalia, Kenya, Ethiopia, Cameroon, and Syria) that were previously polio free.

Until polio transmission is interrupted in all of these high transmission settings, OPV will be a critical component of the Eradication Plan.

* http://www.polioeradication.org/Dataandmonitoring/Poliothisweek/Circulatingvaccinederivedpoliovirus.aspx
REFERENCES


