The introduction of IPV, the OPV switch, and risk mitigation

Information Note
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In the context of the current supply constraints for Inactivated Polio Vaccine (IPV), this document provides a summary of the rationale for the introduction of IPV, in relation to the switch in Oral Polio Vaccines (OPV) that is scheduled for April 2016.

This document also outlines the implications of the delays on all product presentations that are procured through UNICEF and the PAHO Revolving Fund, including actions being taken to proactively manage and minimize the consequences.

Importantly, for countries affected by the supply constraints, there is an overview of the risk management rationale and mitigating strategies, as endorsed by the Strategic Advisory Group of Experts on immunization (SAGE) to WHO.

Contents

1. Background and rationale for IPV ................................................................. 2
2. The position of SAGE on IPV and the OPV switch in April 2016 ......................... 3
3. Overview of the supply constraints for IPV ...................................................... 4
4. Risk management rationale and mitigating strategies ......................................... 6
1. Background and rationale for IPV

As part of the Polio Eradication and Endgame Strategic Plan (the Polio Endgame) 2013-2018, and as recommended by WHO, all 126 countries which, at the start of 2013 were only using OPV, were required to introduce at least 1 dose of the IPV into routine immunization schedules as part of preparations for the global withdrawal of the type 2 containing OPV now confirmed for April 2016.

The level of commitment from countries to meet this timeline has been exceptional. Almost all countries using only OPV at the start of 2013 had committed to introduce IPV before the end of 2015 and 94\(^2\) (out of a total of 126) have already introduced IPV as of 1 April 2016. Unfortunately the rapid scale-up of IPV production required has encountered multiple challenges, leading to a global shortage.

Based on the assessment of scenarios at 6 April 2016 following additional reductions in supply, current constraints mean that approximately 20 countries that have not already received their first IPV shipment through UNICEF and are considered at low risk for circulating vaccine-derived poliovirus (cVDPV) type 2 outbreaks will not be able to introduce IPV in 2016. These countries are expected to receive their first IPV shipments in the fourth quarter of 2017.

In addition, shipments to approximately 25 countries that have already introduced IPV and considered at low risk for type 2 outbreaks will not receive additional supply before the fourth quarter of 2017. These delays, while unfortunate and leading to stock-outs, are unavoidable. As soon as a decision is made on supply allocation, affected countries will be immediately notified by WHO and UNICEF.

Regardless of a country’s IPV introduction date, it was confirmed by SAGE at its October meeting\(^2\) that all countries must implement the globally synchronized switch from trivalent OPV (tOPV) to bivalent OPV (bOPV) in April 2016.

What is the role of IPV in the Endgame Strategy?

IPV’s primary value is in minimising the occurrence of paralytic disease from any type 2 VDPV after the OPV switch in April 2016.

The short term risk of a cVDPV2 outbreak after the switch is higher in countries with low routine immunization coverage or a history of cVDPV2 or wild polio virus outbreaks, as well as in countries sharing borders with higher risk countries. This risk has being reduced by boosting population immunity through ongoing high quality tOPV campaigns before the switch to bOPV.

In tier 1 and 2 countries at risk of cVDPV2, should an outbreak of cVDPV2 occur after the switch, having IPV already introduced will enable a more effective and rapid outbreak response, due to IPV’s role in priming the immune system for a more rapid and robust response to OPV. IPV will also help to protect against paralytic polio and to boost immunity to polio infection.

In the event of a VDPV2 being detected in any country after the switch, a global stockpile of monovalent type 2 OPV (mOPV2) and IPV will be available for outbreak response\(^3\).

One dose of IPV will therefore induce an immunity base to poliovirus type 2 and overall serve as a risk mitigation tool.

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3. In this case, mOPV and IPV will be used per the Type 2 Outbreak Protocol, to be published April 2016: [http://www.polioeradication.org/](http://www.polioeradication.org/)
2. The position of SAGE on IPV and the OPV switch in April 2016

**SAGE has confirmed the global OPV switch date from 17 April to 1 May 2016**

On 20-22 October 2015 the Strategic Advisory Group of Experts on immunization (SAGE) to WHO met and reviewed type 2 Vaccine Derived Poliovirus (VDPV2) epidemiology and all readiness criteria for the switch. SAGE reaffirmed April 2016 for the globally coordinated withdrawal of type 2 containing Oral Polio Vaccine (OPV2), by switching from use of trivalent OPV (tOPV) to bivalent OPV (bOPV).

SAGE confirmed that every country should stop using tOPV and introduce bOPV on a single day of its choosing between 17 April and 1 May 2016, then remove all stocks of tOPV within two weeks of that date and confirm its removal from service delivery points to WHO.

SAGE’s landmark decision follows the endorsement by the World Health Assembly (WHA) in May 2015, when Ministers of Health from 194 Member States adopted a resolution on the global effort to eradicate polio.

In a milestone towards the switch, wild poliovirus (WPV) type 2 was declared as eradicated worldwide in September 2015. WPV type 3 has not been detected globally since November 2012, and the only remaining endemic WPV type 1 strains are now restricted to Pakistan and Afghanistan.

The withdrawal of type 2 containing OPV will ultimately eliminate the risk of the emergence of new cVDPV2 in the future, and will prevent upwards of 200 cases of vaccine associated paralytic poliomyelitis that currently occur each year as a result of the type 2 component in trivalent OPV. The globally synchronised switch will therefore be of great significance for the polio eradication programme with tremendous public health benefits.

**At its meeting in October 2015, SAGE confirmed a number of key points, summarized below.**

- **The two-week window for switch implementation:**
  - The globally synchronized switch will take place from **17 April to 1 May 2016**
  - All countries must implement the OPV switch in April 2016, regardless of IPV introduction date
  - Even in the event of further changes in IPV supply, the switch date will not be changed
  - Risks of continued tOPV use is greater than the risks of switching to bOPV at this stage

- **The allocation process for the available supply of IPV** (for further details, see page 5)

- **The risk management rationale** (for further details, see page 6)

The conclusions and recommendations of the SAGE meeting in October 2015 are published in the *Weekly Epidemiological Record, 90* (December 2015). [http://www.who.int/wer/2015/wer9050.pdf]
3. Overview of the supply constraints for IPV

Who are the manufacturers involved? Why are there supply constraints?

In March 2014, UNICEF issued awards to two manufacturers (Sanofi Pasteur and Bilthoven Biologicals) for the supply of IPV in 1, 5 and 10 dose vials, and long term supply agreements were established through to 2018. These were the only two manufacturers which offered substantive quantities from the start of the programme in response to UNICEF’s tender and agreed to provide IPV to the UNICEF market. Only Bilthoven Biologicals is supplying the PAHO Revolving Fund.

Both manufacturers have reported reduced availability due to technical challenges in scaling up IPV bulk production and the associated quality control testing and releases.

The constrained situation is projected to remain through 2017 for all IPV product presentations procured through UNICEF, the PAHO Revolving Fund, and national Governments. This is a global situation, all markets are affected, and manufacturers have reaffirmed to WHO that IPV is not being redistributed to more profitable markets.

Regular updates will be shared with WHO and UNICEF regional staff, country offices, governments and partners as soon as new information becomes available.

Why has the allocation of IPV supply to countries frequently changed?

In the third quarter of 2014, IPV manufacturers informed UNICEF and PAHO that they would not be able to meet their commitments to supplying IPV in 2015. In 2015, manufacturers also advised of further delays on IPV supply in 2016.

In February and March 2016, manufacturers announced added substantial decreases in availability for 2016 and 2017, as well as delays to the timing of deliveries. These reductions—which result in approximately 40% less IPV than the original commitments—mean that not all countries will be able to introduce IPV by the time of the OPV switch in April 2016.

Vaccine manufacturers had initially been confident that the scale-up of IPV production would ensure sufficient capacity to meet the global demand for IPV. However, over the past two years, manufacturers have repeatedly reported issues with their scale-up, resulting in diminished supply. The reporting has been incremental, and resulted in a progressive deterioration of the supply situation.

This series of changes has also meant that some countries have regretfully been informed of changes to their IPV shipment at last minute and on more than one occasion. In a few cases, delays have also occurred in order to allow time for the programme to evaluate how the use of existing stocks can meet the global public health need most effectively.

Frequent discussions have taken place between WHO, UNICEF and manufacturers to identify any steps to manage the reductions. WHO, UNICEF and partners are also taking all actions to limit the number of countries impacted by the delays and minimise the consequences of this changing situation.

Was there an assessment of risks related to the rapid scale up of IPV at the start of the Endgame Plan and at the time of tendering manufacturers?

Prior to the tender, analysis conducted confirmed that the capacity of manufacturers was sufficient to produce enough vaccine to enable the introduction of one full dose of IPV into all routine immunization systems (around 80 million doses annually). The offers originally received exceeded this demand.
Price has frequently been cited as the main hurdle against IPV introduction, but it now seems supply is the primary obstacle. Was there insufficient focus on adequate supply?

When the switch was being planned, price was seen as the largest obstacle to global roll-out of one-dose of IPV in the 126 OPV-only using countries, most of whom are low and middle income countries (it was around 15 times more expensive per dose than tOPV). The large volume made it possible to achieve a price which allowed the programme to proceed with the recommendation to introduce 1 dose of IPV (documented in the WHO Position Paper on polio, published in February 2014).

However, due to the large volume of IPV needed, only two manufacturers were in the process of scaling up their production capacity to meet the increase in the global requirements, and therefore offered to supply the required vaccine to the UNICEF and PAHO markets. This was also confirmed through independent assessments. In early 2014, these manufacturers confirmed that enough IPV could be made available to meet the needs of the Endgame Plan, at an affordable price.

In March 2016, the largest IPV supplier to the GPEI announced an approximately 40% reduction in supply for 2016 and 2017. This reduction is related to production scale up issues and not to pricing.

How is the available supply being allocated?

The available IPV supply is being managed globally, prioritizing delivery of IPV to countries at highest risk.

When the Polio Endgame Strategy was launched, countries were divided into four tiers, primarily for purposes of planning and prioritization. These tiers represent each country’s level of risk (tier 1 being at highest risk) for a cVDPV2 outbreak after the switch from tOPV to bOPV.

There are four criteria used to determine the classification of each country, and therefore their prioritization for the allocation of IPV supply. Countries are considered to be in a higher risk tier if:

- The transmission of wild poliovirus has not yet been interrupted
- The country has a history of cVDPV outbreaks
- There are consistently low levels of routine immunization coverage (and therefore population immunity to type 2)
- The country shares borders with higher risk countries

In the current context of the constraints, this grouping of countries into tiers is a primary consideration for supply allocation, and countries at higher risk of cVDPV2 outbreaks are being prioritized.

In October 2015, SAGE emphasized that even in the event of further changes in IPV supply, the switch date will not be changed. At this time, SAGE also requested its Polio Working Group to provide urgent guidance on the optimal management of IPV supply if it is again reduced.

In early April, following the substantial decreases to supply availability, the Polio Oversight Board (POB) reviewed the overall global situation, including the needs of endemic countries, outbreak response, and routine IPV immunization. The POB decision on the allocation of IPV supply builds on SAGE recommendations, with the final approach agreed as follows:

- First ensuring the introduction and sustained use of IPV for routine immunization in tier 1 and 2 countries;
- Making stocks available for SIAs in endemic countries and for outbreak response after the switch;
- Minimizing delays in introduction in routine immunization and stock-outs in tier 3 and 4 countries.
What is the impact on national immunization programmes?

Based on the latest information from manufacturers on supply availability and the most optimum scenarios, at least 90 countries out of 126 – including almost all tier 1 and 2 countries – have received their first IPV shipment in time to introduce the vaccine before the end of 2015.

For countries that have not yet introduced IPV:
Of the low risk countries, approximately 20 countries will experience delays in deliveries. The majority of these countries will be delayed until the fourth quarter of 2017.

For countries that will experience delays to their resupply for routine immunization:
Approximately 25 countries (that have already introduced IPV) will not receive additional supply until the fourth quarter of 2017. This group of countries is considered at low risk for type 2 outbreaks.

The above information is based on the assessment of scenarios as of 4 April 2016, and is expected to fluctuate over coming months. All efforts are being made to minimize the number of countries delayed. WHO and UNICEF will coordinate closely with countries affected on the related implications.

All countries affected are receiving direct communications from UNICEF Supply Division and WHO about the timing of their shipment. This will allow for planning of the IPV introduction or restart of IPV vaccination for eligible infants as soon as possible after the receipt of vaccines. Once available supply is confirmed, WHO and UNICEF regional and country offices will facilitate discussions with countries to identify new launch dates and support any adjustments to programmes.

4. Risk management rationale and mitigating strategies

What is the level of risk for the countries without IPV?

The SAGE considered the following as a compelling risk management rationale:

- IPV has a limited role in preventing VDPV2 emergence, however is very effective in preventing paralytic disease in any outbreak. This value will increase with time after the switch, as the birth cohorts that have not received OPV2 begin to accumulate;
- The majority of countries affected by the delay are in low risk tiers 3 and 4. Population immunity against type 2 is high in these countries (due to consistently high routine immunisation coverage) so the risk of VDPV2 emergence and spread is minimal;
- The risk of VDPV2 emergence is principally reduced by ensuring high coverage, and may include high quality tOPV SIAs before the switch in countries/communities with immunity gaps;
- In addition to tOPV SIAs, almost all highest risk (tier 1 and tier 2) countries will have introduced IPV in routine immunization before the switch;
- A global stockpile of mOPV2 (which is WHO prequalified) and IPV is available for outbreak response in the event of VDPV2 detection after the switch. Countries should have a mechanism in place for emergency authorization of mOPV2 use in an outbreak.

The SAGE concluded that the public health risks associated with the continued use of tOPV far outweigh the risk of new VDPV2 emergence after use of tOPV is stopped, even in countries where IPV introduction is delayed4.

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The IPV supply situation remains dynamic and is being closely monitored. Should anything change from current projections, regions and countries will be contacted promptly.

If affected by the delays, what can a country do to mitigate risks?

All countries affected by delays in the receipt of IPV for national introduction should:

- **Make all efforts to optimize type 2 population immunity prior to the switch** with effective use of remaining tOPV stocks. Global supply is available for countries to conduct tOPV campaigns before the switch. The higher the type 2 population immunity is at the time of the switch, the longer that immunity will protect against type 2 poliovirus.

- **Coordinate implementation of the switch in a highly effective and timely manner**, to make sure that strictly no tOPV is used after the global switch window from 17 April to 1 May.

- **Ensure that preparations for IPV introduction are completed well in advance**, so that IPV roll out can start as soon as the vaccine becomes available.

- **Document, where possible, a missed dose of IPV (to facilitate any later tracking and follow up) for infants eligible for IPV after the OPV switch**, e.g. came for DTP3 after switch, but IPV was not available. (Further guidance on recording the missed dose is to come.)

- **Enhance surveillance systems** through both Acute Flaccid Paralysis (AFP) surveillance and environmental sampling, where it has been established, to help identify and confirm any type 2 poliovirus infections as soon as possible after the switch.

- **Prepare a response plan** so that in the unlikely situation that a type 2 cVDPV outbreak occurs, it can be addressed and ended as soon as possible.

Countries that experience delays to the resupply of IPV for their routine programme may also:

- **Closely monitor IPV stocks at all levels, to prioritize available supply to at-risk populations, and to** balance stocks effectively to help delay any stock-outs, e.g. smaller and more frequent deliveries to lower levels to help with effective distribution of available supply.

- **Ensure strict adherence to vaccinating children only in the target group**, e.g. at 14 weeks of age or the nearest immunization visit.

- **Apply the multi-dose vial policy**, to enable use of IPV with the vaccine vial monitor on the label up to 28 days after opening, to help minimize wastage.

- **Use vaccination cards and registers effectively** to, where possible, record a missed dose of IPV, to facilitate any later tracking and follow up. (Further guidance on recording to come.)

Finally, as an alternative to the intramuscular injection of a full IPV dose, **countries in any situation may choose the implementation of a two-dose fractional dose schedule** (using 1/5 of a full dose), via the intradermal (ID) route. Programmatic implications should be carefully considered.

The option of a fractional dose schedule as endorsed by SAGE is reflected in the WHO Position Paper on polio vaccines.

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What factors should countries consider in relation to the two-dose fractional dose schedule for IPV?

While the option of a fractional dose of IPV administered via the intradermal (ID) route has been studied for many years, it has been considered a more complex option for rapid roll-out due to the operational challenges of administering ID IPV. These studies have shown that two fractional doses administered at 6 and 14 weeks are superior at conferring immunity compared to one full dose administered intramuscularly.

Should a country be interested in exploring the two-dose fractional dose schedule, the following factors warrant close consideration:

- Syringes and devices: 0.1ml syringe is required (not the 0.05ml syringe used for BCG)
- Timing in the schedule: starting at or after 6 weeks, with a minimum interval of 4 weeks, e.g. at 6 and 14 weeks building on the “prime-boost” model for protection
- Administration: the ID administration is programmatically more demanding, therefore requires added quality training and supervision
- Data recording: may involve adjustments to registers and home-based records, to support tracking and follow up of infants for the complete schedule
- Communications: as with any new practice, advance planning and careful messaging will be critical, to reassure caregivers and community members

Is IPV licensed for use as a fractional dose administered via ID injection?

It should be noted that IPV is not currently licensed by the manufacturers for ID use, although both companies are being requested to fast-track their efforts to file for a license revision to include a provision for ID use.

There is a wealth of evidence demonstrating the safety and improved efficacy of a 2-dose schedule with fractional IPV administered via the ID route. WHO has independently assessed all available information and concluded that this new method of administration would lead to better public health outcomes, while reducing the number of doses needed and the cost of each dose.

Furthermore, having reviewed the existing scientific evidence, SAGE has reaffirmed that a two-dose ID fractional dose schedule provides better protection than a single full dose administered at 14 weeks.

The final decision, however, on the use of IPV ID will need to be made by each country and its respective regulatory agencies.

Additional programmatic guidance on strategies related vaccination of eligible infants who may have missed a scheduled dose of IPV after the OPV switch in April 2016 will be issued in coming weeks.

As WHO and UNICEF our organizations remain at your disposal for further information or support.

For more information on IPV introduction and the switch, please visit: http://www.who.int/immunization/diseases/poliomyelitis/endgame_objective2/en/

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