14th WHO/UNICEF Consultation with OPV & IPV Manufacturers and National Regulatory Authorities

October 29, 2015
Note for the record
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# Agenda

14th WHO/UNICEF Consultation  
with OPV/IPV Manufacturers and National Regulatory Authorities  
29 October 2015, Geneva, WHO/HQ, EB room

**FINAL AGENDA**  
Chairman: Dr Hamid Jafari  
Rapporteurs: Dr Carolyn Sein & Dr Jacqueline Fournier-Caruana

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<td>09:00</td>
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<td>Introduction</td>
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<td>09:00</td>
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<td>Polio Eradication &amp; Endgame Strategy 2013-2018: update on progress and last recommendations made by SAGE</td>
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<td>Progress with readiness criteria for the removal of type 2 OPV</td>
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<td>Last mile towards implementing the switch from tOPV to bOPV in 2016</td>
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Overview

On October 20 2015, the Strategic Advisory Group of Experts (SAGE) on Immunization confirmed that the globally synchronised withdrawal of the type 2 component in the trivalent oral poliomyelitis vaccine (tOPV) will occur during a 2 week window between 17 April to 1 May 2016 during which all tOPV using countries will “switch” from tOPV to bivalent OPV1&3 (bOPV). Heralding the switch, tOPV using countries will introduce 1 dose of inactivated poliomyelitis vaccine (IPV) into their routine immunisation (RI) schedules.

Given the importance of strong collaborations between key stakeholders involved in the global switch and IPV introduction, joint consultations between WHO, UNICEF, National Regulatory Authorities (NRAs) and OPV and IPV manufacturers were held on 2 occasions in 2015, on May 6 and October 29.

The consultation provided an opportunity to emphasize the importance of establishing relevant regulatory pathways and prequalification process to ensure timely licensing of bOPV and IPV in all countries of use. In addition key issues concerning OPV and IPV demand and supply were discussed. The consultation also emphasized that the implications and importance of ensuring timely preparations for containment were in place.

The key objective of the consultation was to strengthen collaboration between key stakeholders, ensuring greater awareness of the implications for their work in production, regulation, prequalification and containment, in order to continue working closely as partners in the Global Polio Eradication Initiative. The key outcome of the meeting was the alignment of interests and coordination of activities in preparation for the switch between key stakeholders in order to achieve this historic step in polio eradication.
Session 1: Introduction

Polio Eradication and Endgame Strategy 2013-2018, and

Vaccine Requirements: OPV and IPV Demand

Hamid Jafari (Director, Polio Operations and Research, WHO)

The attendees of the consultation were welcomed and thanked for their participation and continuous contribution to the global effort. The importance of the ongoing close collaboration between the manufacturers, NRAs, UNICEF and WHO as partners in the Global Polio Eradication Initiative (GPEI) was emphasized. It was highlighted that for an unprecedented time, not one but two consultations were held in 2015, which reflected the importance of the complex interaction between the key stakeholders to achieving global tOPV withdrawal, bOPV and IPV introduction.

The significant progress achieved by the GPEI between 1988 and today was highlighted, including three key milestones recently achieved: the removal of Nigeria from the list of polio endemic countries in September 2015; the detection of wild poliovirus (WPV1) from only 2 countries during the last 6 months (Afghanistan and Pakistan); and the declaration by the Global Commission for the Certification (GCC) of poliomyelitis eradication on 20 September 2015, that WPV2 has been eradicated. However the emergence of circulating vaccine derived poliovirus (cVDPV) cases was also presented (type 1 in Ukraine, Madagascar and Laos; and type 2 in Guinea, Nigeria and South Sudan), which highlighted the need for the global withdrawal of OPV.

The outcomes of the World Health Assembly (WHA) in May 2015 and SAGE in October 2015 were emphasized including implications for vaccine projections from 2015-2018: tOPV for supplementary immunization activities (SIAs) in Q3 2015 to Q1 2016; bOPV from 2015 onwards; and mOPV for outbreak response activities.

Discussion points

Forecasting OPV and IPV supply beyond 2018:

It was clarified that OPV (including bOPV and mOPV) and IPV will be required for routine immunization (RI) as well as outbreak response activities until 2020/2021. It was also clarified that in January 2016 the SAGE will initiate discussions to determine the new global immunization policy for IPV in RI as well as the use of other polio vaccines, leading into and
in the post eradication era. This will entail the removal of all oral Sabin poliomyelitis vaccines after the global certification of poliomyelitis eradication.

**Session 2: Interrupting Poliovirus Transmission**

**IPV and OPV Supply: Current Status and Looking Forward**

Monica Pereira (Specialist, Revolving Fund Management, PAHO) & Ann Ottosen (Lead, Polio Supply, UNICEF Supply Division)

PAHO highlighted the very limited global supply of IPV and clarified that 63% of countries in PAHO plan to introduce IPV into their routine immunization schedules by Q4 2015. The PAHO licencing pathway was presented, which included licensure of WHO prequalified vaccine, or vaccine registered by one NRA of WHO reference, with subsequent procurement by the revolving fund. Exceptions to this pathway were Peru and Chile which have a fast track process in pace, and Brazil which is self-procuring. The significant progress made in preparation for the global switch was highlighted including that no further purchase orders for tOPV would be made in 2016 as they had already been issued; furthermore bOPV demand has already been submitted with long term agreement expected in November 2015 and purchase order anticipated to be issued in 2015.

UNICEF presented on the changing supply requirements during the Polio Endgame and the complexities in managing the global supply through to the switch due to multiple factors: there will be increased tOPV demand until Q1 of 2016 for supplementary immunization activities (SIAs) to boost type 2 immunity before the global withdrawal; and an anticipated surge in bOPV demand in Q4 2015 and Q1 2016 due to more than 70 countries requiring to receive supplies for introduction into their routine programmes through UNICEF of which around 40 countries have placed purchase orders to date. Given the planned surge requiring shipment of around 600 mds of OPV to many countries between Q4 2015 and Q1 2016, the potential need for additional support for shipping and logistics functions was highlighted to the manufacturers. UNICEF informed that a new tender for OPV will be issued in the second half of 2016. The extremely tight global IPV supply situation was highlighted and despite many actions taken to mitigate the implications it has been necessary to apply prioritization criteria for allocation of available IPV supply to meet the programmatic objectives; currently 20 countries will be required to delay IPV introduction into their RI until after the switch. UNICEF informed that any further reductions in IPV would result in stock outs for RI or
further delays; a similar situation would occur in case there is an increase in demand for outbreak response activities. Lastly, UNICEF informed that the next IPV tender will be issued in 2017.

Discussion points

bOPV licensure:

The importance of monitoring and mapping countries which have a protracted course for bOPV regulatory pathway was emphasised and it was clarified that these countries have been encouraged to accept WHO prequalification with approval bOPV for use in their own country while their licensing pathway is ongoing.

Regarding the delay of IPV introduction in 20 countries, it was emphasized that the critical piece to proceeding with the switch is the availability of bOPV, of which there is no global shortage.

Future IPV dosing schedule:

It was clarified that the projection of IPV is based on one dose of IPV in the RI schedule and that the new global immunization policy for number of doses of IPV in RI is yet to be determined.

Session 3: IPV Introduction, Routine Immunization Strengthening & OPV2 Withdrawal

Michel Zaffran (Coordinator, Expanded Programme on Immunization/EPI, WHO)

The five readiness criteria for implementing the switch were presented. Regarding global IPV introduction it was highlighted that 46/126 countries have already introduced IPV with another 45 anticipated by Q4 2015. A risk assessment to determine the countries with highest risk for cVDPV2 emergence was conducted, stratifying countries into one of 4 Tiers, Tiers 1-4, with Tiers 1 and 2 having the greatest risk. Given the shortage in global IPV supply (for 5 and 10 dose vials, stand-alone and combination vaccine) this will result in delaying IPV introduction into the RI schedule of 19 Tier 3 and 4 countries, with IPV anticipated to be received in-country by July 2016 as a 5 or 10 dose presentation.

Regarding the bOPV regulatory pathway, it was emphasised that all 6 bOPV products have been licensed for RI use by their respective NRAs. Currently 125/148 countries are
proceeding in a timely manner with regards to the regulatory process with an additional 23 pending and anticipated to be on track. Countries requiring attention were mentioned including China, Brazil and Mexico due to local production of bOPV; Russia due to long review cycle (and hence Belarus and Kazakhstan which procure from Russia), as well as few countries which currently have no planned registration of bOPV (e.g. Qatar, Rwanda). The importance of sensitizing countries to the implications of stockpiling mOPV was emphasized, including the requirements to meet containment criteria and the need to obtain authorization from the Director General of WHO prior to any use of mOPV2.

The need for NRAs and manufacturers to alert WHO with regards to self procuring countries and countries undertaking mOPV2 stockpile initiatives was emphasised.

**Last Mile Towards Implementing the Switch from tOPV to bOPV in 2016**

Alejandro Ramirez Gonzalez (Technical Officer, EPI, WHO)

With the global switch window set for 17 April-1 May 2016, the 5 stages of the switch were presented which include: planning, preparation, implementation, switch day and validation. To date, activities conducted to facilitate the switch include support in developing national switch plans for each country, conducting “dry runs” (simulation exercises) and switch planning orientation workshops, webinar for key programmatic stakeholders as well as providing training for consultants to support the planning and implementation of the switch. Each step was further detailed as were the lessons learned from the dry run simulations.

Great progress has been achieved in regards to the planning at country level; 135 countries have already developed or are in final stages of endorsement of a switch plan. Remaining countries are identified with follow up and support provided to finalize the planning in all concerned countries.

Key lessons, learned during the dry runs included the need to minimize the risk of remaining large stocks of tOPV, highlighted in particular the importance of obtaining accurate balances, the need of conducting regular inventories and adjusting the purchase orders accordingly. The role of the Interagency Coordinating Committee (ICC) was highlighted: to endorse all national switch plans and ensure national switch dates fall within the 2 week window and operational details regarding inventories, supply distribution, budget and waste management plan align and meet the standards required to perform the switch.
Lastly it was highlighted that technical assistance would be made available to countries and that financial support would also be available for some countries, in particular low and low-middle income countries in Tiers 1, 2, 3 facing funding gaps. However it was also clarified that countries receiving a high level of polio assets would receive less financial assistance.

**GAP III: Containment Certification Scheme**

Jeffrey Partridge (Consultant, Surveillance, Monitoring and Information, WHO)

The principles of containment and its importance given the eradication of WPV2 were outlined. It was reminded that all member states had agreed at the WHA to implement GAP (Global Action Plan) III. GAP III is currently being finalized and its key objective was presented, to prevent the transmission of poliovirus from facilities by reducing the likelihood of release, and reducing the consequence of release in the event it occurred. The three phases of containment were detailed: phase 1 (destruction or transfer to poliovirus-essential facilities of WPV2 containing materials by end of 2015 and the destruction or transfer of Sabin 2 containing materials to poliovirus-essential facilities by July 2016); phase 2 (ensure containment of poliovirus type 2 in essential facilities in alignment with specifically defined safeguards); phase 3 (final poliovirus containment of all WPV and all OPV/Sabin polioviruses, when global WPV transmission has not been detected for three years, just prior to the certification of global WPV eradication).

It was highlighted that GAP III will likely reduce the number of facilities containing WPV2 to 42 poliovirus-essential facilities worldwide which will include Salk IPV, Sabin IPV producers as well as surveillance and research facilities. The key actors for containment and their roles were detailed, including the facilities themselves, the National Authorities for Containment (NACs), WHO and GCC. Specific challenges to achieving containment were also highlighted, in particular the lack of established NACs, the gap between GAP III and existing NRA requirements as well as reluctance by some facilities to implement GAP III.

The next steps in containment were presented, including countries hosting IPV producers to nominate their NAC, engaging Sabin IPV producers in training on containment which is anticipated to take place in January 2016, initiating dialogue between NACs, IPV producers and WHO, and revising the WHO TRS 926.
Discussion points

mOPV stockpile:
It was clarified that the global mOPV2 stockpile will be stored by the manufacturer and monitored by WHO based on stability data supplied by the manufacturer. Should annual additional testing need to be conducted in the event that the stockpile went beyond its expiry date, this would involve the respective NRA or an outside party (yet to be identified) to test the vaccine. It was highlighted that WHO encourages countries to use the global mOPV2 stockpile in preference to developing their own national stockpile. However should countries seek to develop their own mOPV2 stockpile, WHO should be notified and the country be aware of the ramifications of containment and the caveats for mOV2 use.

Containment:
It was clarified that containment training planned for January 2016 would incorporate NACs, NRAs and manufacturers.

It was clarified that steps to minimize the handling and manipulation of poliovirus type 2 materials would have to be determined on a country-by-country, and also manufacturer-by-manufacturer basis.

IPV introduction:
It was clarified that WHO, UNICEF and Gavi, the Vaccine Alliance, are working together to monitor the negative impact of IPV introduction on the introduction of other vaccines and that while this is unlikely, should this occur, the introduction of other vaccines would be delayed only by a few months.

It was requested that a list of countries where IPV introduction be delayed be made public however it was clarified that this list was currently still being determined.

Regulatory pathway for bOPV:
It was clarified that the label change for bOPV use for RI and SIAs is anticipated and is being expedited especially given that the shipment of bOPV to countries will commence in November 2015. It was also clarified that recommendations are for countries to hold and store bOPV at the central level until the switch date.
Specifically ANVISA (Agência Nacional de Vigilância Sanitária) from Brazil recommended that their Ministry of Health (MoH) communicate directly with manufacturer regarding bOPV licensure. It was clarified that communication had already been made to all the MoH of member states including Brazil, through formal correspondance which was co-signed by the DG at WHO and the CEO at UNICEF, regarding the switch and preparations to ensure its implementation.

Session 4: Research and Product Development for the Endgame
Securing a Polio-Free World – Priorities for Product Development
Roland Sutter (Coordinator, Polio Research and Product Development, WHO)

The 5 key priorities of the Global Polio Eradication were emphasized, including the interruption of poliovirus transmission, preparations for the global transition from OPV to IPV, maintenance of outbreak response capacity in the post-OPV era, ensuring affordable IPV, and maintaining long-term eradication. Scientific progress and developments to achieve these priorities were detailed, including updates on Sabin-IPV technology, application of IPV open-vial policy, 5-dose vial presentation, intradermal fractional IPV dose studies, use of adjuvants, development of higher potency monovalent IPV2, and novel delivery methods such as micro-needle patch, intradermal adaptors and jet injectors to facilitate house-to-house IPV campaigns. An update was also provided on the development of monoclonal antibodies and antivirals to treat immunodeficient individuals, although availability of these products is not anticipated until after 2017.

It was emphasized that although tOPV would not be used in any country after April 2016, it would remain important to maintain an emergency contingency plan which would ensure that tOPV production could be re-started. The resulting implications for tOPV manufacturers were emphasized; specifically keeping master and working seeds, maintaining tOPV license for 5 years after the switch, and the need to maintain reference standard for testing at the manufacturer and National Control Laboratory level; in addition production facilities will be required to be compliant with GAP III storage criteria.
The future of vaccine development and technology was presented, including non infectious production processes using virus like particle technology, and adjuvant for IPV which induces mucosal immunity without the need for exposure to live virus.

Discussion points
Maintaining tOPV license beyond 2016:
It was clarified that not all, but some tOPV manufacturers should maintain their license; furthermore that in some countries the license does not need to be withdrawn, but can be kept indefinitely. It was also clarified that in the EU although a sunset clause exists the manufacturer may apply to waive the clause in certain scenarios through valid and existing legislation, and that maintaining tOPV license would qualify for this process.

The role of mIPV2:
It was clarified that clinical trials continue to be conducted to evaluate higher potency mIPV2, in order to determine its role in the future for outbreak response.

Demand for IPV in the long term:
It was clarified that although Gavi’s commitment to provide country support for eligible countries extends for 5 years, the demand for IPV will extend well beyond the 5 year timeframe likely for decades to come, due to the need to maintain population immunity and also because of the risk of bioterrorism.

sIPV use in Japan: Seroprevalence Data
Susumu Ochiai (BIKEN, Japan)

Japan was the first country to license sabin-IPV (sIPV) combination vaccine in 2012 and this is currently available through 2 manufacturers. Results from the Phase 3 trial were presented; DTaP-siPV group and DTaP control group, which received either DTaP-siPV and OPV placebo, or DTaP and OPV, respectively. DTaP-siPV or DTaP was subcutaneously administered at a dose of 0.5 mL four times: a series of 3 doses given at intervals of 3-8 weeks for primary immunization, and one dose for booster immunization 6 to 18 months after the primary vaccination. OPV placebo or OPV at a dose of 0.05 mL was orally administered twice at an interval of at least 6 weeks. It was highlighted that although neutralizing titers were lower for wild strains, especially type 1, they were well above
protective levels. Interchangeability in different poliovaccine was demonstrated. Group A and B were DTaP-sIPV or conventional IPV group, OPV was used in both groups for first immunization of primary immunization. In group C and D, two kinds of IPV were mixed through immunization schedule. Seroprotective levels in each group were maintained at 2 years after receiving fourth dose. The age distribution and positivity rate of neutralizing antibody to poliovirus types 1, 2 and 3 was presented, demonstrating more rapid and higher rates after sIPV was introduced in 2012, particularly for type 3. Furthermore, national enterovirus surveillance data in Japan demonstrated that poliovirus has not been detected between April 2013 and August 2014.

**Discussion point**

It was highlighted that the oldest age cohort had the highest seropositivity rates likely due to their exposure to wild poliovirus 50 years ago in Japan.

**Freeze/Thaw Study and Collaborative Study for sIPV**

Jessica White (PATH), Ed Maes (CDC) & Kosty Chumakov (FDA)

Given the paucity in data on freeze-thaw effect on IPV, PATH, CDC and WHO are currently collaborating to undertake a study on the effect of freeze-thaw cycles on IPV whereby 4 field scenarios where freezing of IPV could occur are simulated. 100 vials of IPV as well as details on any unpublished data on this topic were solicited from the manufacturers who were present. The paradox of the IPV label was highlighted; the label has clear instructions not to freeze IPV; however it was pointed out that the reference standard is stored frozen. The previous study undertaken involved 5 cycles of freezing; the D antigen ELISA test was used and percent activity loss of D antigen content calculated, which demonstrated that freezing slightly lowers potency of type 1 with less effect on types 2 and 3; these findings were validated with 2 other laboratories. Both rat potency testing as well as aforementioned collaborative study will be undertaken, the latter of which will provide proof of concept. It was highlighted that manufacturers will need to undertake testing for their own product if they wish to submit a variation to the licensing dossier.

**Discussion point**

Impact of freezing on IPV:
It was clarified that the freezing of IPV may be tolerated as the reference standard is frozen. However currently there is no clinical data which tests the impact on immunogenicity.

**Collaborative Study for Harmonization of sIPV Testing**

Rahnuma Wahid (PATH)

Potency testing is based on D antigen content, and this is currently non-uniform between products due to absence of uniform reagents and differences in the ELISA methods used by the various manufacturers. Even for the same product there can be a significant variation in the results of potency testing due to the lack of standardization. Currently there are 3 licenced sIPV products (2 in Japan and 1 in China). There will be additional manufacturers coming online by the technology transfer through Intravacc which facilitates sIPV production in other companies in China, India, South Korea and Mexico.

In September 2014 a workshop was held to discuss how to harmonize sIPV testing between products. This resulted in a collaboration between manufacturers, National Institute for Biological Standards and Control (NIBSC) and PATH whereby the manufacturers would supply vaccine bulks, NIBSC would put together a test kit (using the sIPV bulks supplied; all samples will be blinded so the sources of products will not be known), develop a test protocol and within a consortium of laboratories conduct all testing, while PATH would investigate the development of new reagents that could be used if the current reagents are not suitable for harmonization of the potency method for sIPV. The main objective will be to assess whether reagents currently used, as well as the international standard for Salk IPV are suitable to measure D antigen content in sIPV. The bulk vaccines were received by NIBSC in September 2015 and testing kits will be shipped to the laboratories in November 2015. The study is expected to be completed in January 2016 and all results provided by the consortium to NIBSC for compilation and analysis.

The current antibody reagents may be relevant for sIPV D antigen assay, however should it be demonstrated that this is not the case, new reagents will need to be developed for the potency assay. The role of the Lankenau Institute was also
detailed, including developing a bank of human monoclonal antibodies specific to siPV. The human monoclonals are isolated from patients vaccinated with OPV; the monoclonals will be characterized to identify antibodies that are strain specific, which would be subsequently screened for specific binding to D antigen content, and used to develop complementary pairs of monoclonal antibodies for ELISA testing. It is also possible that the current international Salk IPV standard may not be suitable for measuring siPV potency and a new international standard may have to be developed. The use of these reagents and a new international reference standard would mean that there would need to be considerable development work conducted to develop the D antigen potency ELISA.

**Discussion point**

*Access to the results of harmonization study:*

It was clarified that the results from the ongoing and subsequent studies, including reagents and standardized protocols will be made available to the manufacturers in a series of workshops and relevant publications.

**Closing remarks**

Margaret Chan (Director General, WHO)

The DG of WHO encouraged the ongoing close communication and collaboration between key stakeholders to ensure full preparations are in order for the switch, including ensuring IPV supply, containment measures, mOPV2 stockpile and bOPV licensure for routine use.

She emphasized that the switch is not only a significant historical event, but more importantly one which will leave a positive legacy and “a perpetual gift for the generation of children to come.”