15th WHO/UNICEF Consultation with OPV & IPV Manufacturers and National Regulatory Authorities

July 28, 2016
Note for the record
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Agenda

World Health Organization

15th WHO/UNICEF Consultation with
OPV/IPV Manufacturers and National Regulatory Authorities
28 July 2016, Geneva, WHO/HQ, Salle C

FINAL AGENDA
Chairman: Mr Michel Zaffran
Rapporteurs: Dr Carolyn Sein & Ms. Daniela Decina

08:30 - 09:00
Session 1
Registration

09:00 – 09:30
Session 2
Introduction
Update on Polio Eradication & Endgame Strategy:
Michel Zaffran

09:30 – 09:45
Interrupting poliovirus transmission
Vaccine requirements: OPV & IPV demand
Arshad Quddus

09:45 – 10:15
IPV & OPV supply: current status and looking forward
Anne Ottosen, Monica Pereira

10:15 – 10:30
Discussion
All

10:30 – 11:00
Coffee Break

Session 3
Lessons from the Switch & Planning for OPV Withdrawal

11:00– 11:30
Report on OPV Switch Execution and Validation
Lisa Menning & Daniela Decina

11:30– 12:00
Industry and NRA feedback
Christophe Saillez (GSK), Rajesh Jain (DCVMN), Mathias Jansen (Belgian NRA), Stephane Maisonneuve (ANSM)

12:00 – 12:30
GAPIII Implementation: Progress and Obstacles
Nicoletta Previsani

12:30 – 13:00
Discussion
All

13:00 – 14:00
Lunch

Session 4
Research, Policy & Product Development for the Endgame

14:00 – 14:30
Polio Immunization Policy Post-Eradication
Roland Sutter

14:30 – 14:45
Fractional IPV: A Public Health Perspective to Address IPV Supply Constraints
Harish Verma

15:00 – 15:15
Progress on Development of New Delivery Devices
Hiromasa Okayasu

15:15 – 15:30
Collaborative study for harmonization of sIPV testing
Javier Martin

15:30 – 15:45
Discussion
All

15:45 – 16:15
Tea break

16:15 – 16:30
Closing remarks
Chairman
Overview

An important milestone took place in the path towards polio eradication; the 2 week period from 17 April to 1 May 2016 saw the globally synchronised withdrawal of the type 2 component in the trivalent oral poliomyelitis vaccine (tOPV), whereby all tOPV-using countries “switched” from tOPV to bivalent OPV1&3 (bOPV). This historical achievement was in alignment with the Polio Eradication and Endgame Strategic Plan 2013-2018, and a recommendation made in October 2015, by the Strategic Advisory Group of Experts (SAGE) on Immunization.

Heralding the switch, the SAGE also recommended that at least 1 dose of inactivated poliomyelitis vaccine (IPV) be introduced into the routine immunisation (RI) schedules of all tOPV-only using countries. This has led to a significant increase in the demand for IPV in a short space of time. However the need to rapidly scale-up IPV production to meet global demand has faced ongoing challenges resulting in significant constraints in global IPV supply.

Given the importance of planning and preparations related to future polio immunization policy including vaccine forecast, and the importance of continued strong collaborations between key stakeholders including WHO, UNICEF, National Regulatory Authorities (NRAs) and OPV and IPV manufacturers, a joint consultation was held on 28th July, 2016. The consultation provided an opportunity discuss key issues concerning OPV and IPV demand and supply and also emphasized the implications and importance of ensuring timely preparations for containment are in place.

The key objective of the consultation was to strengthen collaboration between key stakeholders, and ensure greater awareness of the implications for their work in production, regulation, prequalification and containment, in order to continue collaborating as partners in the Global Polio Eradication Initiative. The key outcome of the meeting was to promote and align interests and better coordinate activities in preparations leading into the post-eradication era.
Session 1: Introduction
Update on Polio Eradication and Endgame Strategy
Michel Zaffran (Director, Polio Eradication, WHO)

An overview of the Global Polio Eradication programme was provided, with emphasis on the status, progress and challenges in the 2 remaining endemic countries facing ongoing transmission of type 1 wild poliovirus (WPV1); the last cases of WPV1 were reported in May 2016 in Afghanistan, and June 2016 in Pakistan. With enforced programmatic efforts including improved quality in supplementary immunization activities (SIAs) and enhanced environmental surveillance, interruption to endemic transmission in Pakistan and Afghanistan is anticipated in 2017. In the context of the recent withdrawal of type 2 component from tOPV, an update was also provided on type 2 circulating vaccine derived poliovirus (cVDPV) outbreaks (Myanmar, Guinea, Nigeria), and events (DRC), as well as the ensuing response by the GPEI.

The programme’s priorities for the next 6 months were outlined, and include: 1) ongoing political advocacy and resource mobilization; 2) ongoing support to Afghanistan and Pakistan; 3) strengthening of outbreak response capacity at global and regional levels; 4) documentation of the switch in preparation for OPV withdrawal in 2019; and 5) acceleration of efforts for containment and transition planning.

Discussion points: cVDPV1 outbreaks: it was clarified that in the last 12 months, cVDPV1 outbreaks had occurred (in Ukraine, Laos and Madagascar), however these were not specifically covered in the presentation which focused on cVDPV2.

Session 2: Interrupting Poliovirus Transmission
Vaccine Requirements: OPV & IPV Demand for 2017-2019
Arshad Quddus (Team Lead, Polio Eradication, WHO)

GPEI implemented intense SIAs during 2015 and in first quarter of 2016 with aim to interrupt WPV1 circulation in Afghanistan-Pakistan and to boost population immunity to minimize risk of emergence of vaccine derived poliovirus of type 2 (VDPV2) after the global switch from tOPV to bOPV. The requirements for OPV (bOPV and mOPV2) forecast for 2017-2019 were
presented, with calculations based on 3 key assumptions: interruption of WPV1 transmission in Afghanistan and Pakistan in 2017; certification of AFRO as polio free in 2017; and the immediate cessation of OPV use following global polio free certification in 2020.

The requirements for OPV for routine immunization (RI) and SIAs forecast for 2016-2020 were outlined. Regarding OPV forecast, requirements are anticipated to decrease gradually from 2500M doses (of bOPV and tOPV) in 2016, to almost 900M doses of bOPV in 2020. However, it was highlighted that cessation campaigns using bOPV will be planned in 2021 to maintain high population immunity to emergence of VDPV1 and VDPV3 following complete OPV cessation. Regarding mOPV2 forecast it is anticipated that with passage of time likelihood of VDPV2 events/outbreaks goes down and so will be the requirements of mOPV2. The mOPV2 requirements will decrease from 106M doses in the first year after OPV2 withdrawal, to 7M doses 4 years after OPV2 withdrawal.

Given the current constraints in IPV supply, the introduction of IPV has been prioritized to meet the requirements of all Tier 1 and nearly all Tier 2 countries. The forecast for IPV for RI from 2015-2018 was also outlined, with requirements anticipated to increase from 58M doses of IPV in 2015 to 98M in 2018.

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

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

UNICEF presented on the current status of OPV and IPV supply. Notable achievements included the roll out of bOPV supply for introduction into 155 countries globally, and timeliness in meeting tOPV and bOPV requirements for all unplanned campaigns and outbreak response activities. However a key challenge faced was the underestimation of demand projections for OPV in the tender covering 2013-2017, requiring 10 sequential awards to meet demand increasing from 5.2B doses to 7.3B doses (42%). Key milestones, timelines and objectives for the next procurement round for bOPV were outlined, aiming to secure sufficient supply starting from January 2018 through to cessation. It was also highlighted that bOPV demand remains dynamic and uncertain primarily due to the challenges of interruption WPV transmission and outbreak response activities, but that a close partnership will continue to be required between GPEI and vaccine manufacturers to achieve the eradication goal.
The tenuous global supply of IPV was highlighted, which will continue despite the implementation of specific mitigation strategies. The overall delay in scaling up vaccine production has reduced the available supply to UNICEF by 40% compared to original awards in 2014. While annual supply to UNICEF continues to increase, the rate of increase projected for 2016 and 2017 are low, and considerably below what will be required to achieve the awarded quantities of 70Mds in 2018. The situation has necessitated the implementation of an allocation process overseen by the Polio Oversight Board, ensuring that available supply is allocated to countries considered at high risk for a type 2 outbreak after the switch. The shortfall is expected to continue until Q4 of 2017, with the impact that 22% of the global birth cohort in 43 countries considered at lower risk for type 2 polio, will not be offered IPV vaccination until later. Key timelines were outlined, including tender issuance for IPV in Q1 2017 to solicit supply offers for 2019 and onwards.

The PAHO Revolving Fund supplies IPV to 34 countries and territories, and has faced significant challenges due to ongoing constraints in global IPV supply. The Technical Advisory Group (TAG) for PAHO currently recommends a sequential RI schedule, preferably 2 doses of IPV + 2 or 3 doses of OPV; or, 1 dose of IPV + 3 or 4 doses of OPV. However, given the ongoing shortage in IPV, the latter schedule is being implemented. An extraordinary meeting was held by the TAG in May 2016, to specifically address this situation with the outcome that should the supply situation deteriorate further, fractional dose IPV may be considered and recommended in lieu of full dose IPV. PAHO highlighted that there had been a 50% reduction in IPV doses committed from the sole supplier of IPV in 2016, from 13.2M to 6.6M. PAHO also emphasized that stocks will be closely monitored with prudent supply allocation to try to avoid stock outs.

Three manufacturers have agreements with the PAHO Revolving Fund to supply bOPV to 33 countries. PAHO highlighted that bOPV supply is not constrained, and that overall, the regulatory pathway for bOPV introduction proceeded smoothly. PAHO also highlighted one specific challenge noted in Argentina and Peru, where less than 20 doses of bOPV were obtained per vial, resulting in an increased demand for bOPV in 2017.

**Discussion points:** The WHO position on national stockpile of mOPV was clarified as per the WHA resolution passed in 2015, the establishment of a national stockpile of mOPV2 is not
recommended. However should one be established, the use of mOPV2 should only implemented after authorization by the DG of WHO.

Report on OPV Switch Execution and Validation
Lisa Menning (Technical Officer, EPI, WHO) & Daniela Decina (Technical Officer, EMP, WHO)

An update was provided on the implementation of the switch from tOPV to bOPV, including the introduction of one dose of IPV into RI schedules of all countries using tOPV. As of 28 July 2016, 103/126 countries previously using OPV-only have introduced IPV into their RI schedules. However due to significant ongoing constraints in supply, 22% of the global birth cohort will face delays in IPV introduction or re-supply until Q4 of 2017. Specific risk mitigation measures to manage the IPV supply constraints were highlighted.

Indicators tracking the successful implementation of the switch were outlined and specific approaches to switch implementation were highlighted. Key strategies contributing to the success of the switch were emphasized, including strong partnership; clear distribution of roles; ownership at the country and regional level; defined timeframe; timely dissemination of guidance and updates; dedicated funding to facilitate country efforts.

The regulatory aspects of the switch were presented. It was highlighted that one year before the switch, less than 10% of countries had an approval in place for the use of bOPV in RI schedules; in addition, 126 countries needed to introduce IPV into their RI schedules. The three regulatory pathways by which countries established an approval for use were outlined: special authorization including waiver; marketing authorization; and acceptance of prequalified bOPV; with the majority (66%) of countries implementing the approach to accept prequalified vaccines. Regarding IPV regulatory status, it was highlighted that only 3 countries remain to obtain approval for use. Important lessons learned were shared and included: the importance of tracking progress, identifying and engaging key stakeholders, and sharing information. It was emphasized that maintaining and updating the regulatory lessons learned will be invaluable to future vaccine introduction.

Discussion points: The importance of establishing regulatory pathways in as timely a manner as possible was emphasized, in order to avoid delay in the introduction of new vaccines. In
addition specific initiatives such as the regional harmonization initiative in AFRO were highlighted, as a way to simplify the means to register necessary products more efficiently.

Industry and NRA Feedback
Christophe Saille (GSK), Rajesh Jain (DCVMN), Mathias Jansen (Belgian NRA), Stephane Maisonneuve (ANSM)

Feedback on the switch from the perspective of industry and NRAs was provided. Three key observations were noted: 1) registration of bOPV remains ongoing, with many countries viewing the process as registration of a new vaccine, as opposed to capitalising on available evidence on tOPV 2) ongoing communication gaps between Ministries of Health/National Immunization Programmes, and WHO/Expanded Programme on Immunization, and the NRAs 3) the importance of harmonization of regulatory requirements to reduce lead times as well as redundacies in requirements for additional reviews.

With the restriction in the usage of Sabin poliovirus type 2 due to implementation of GAP III, Panacea raised a concern that it will hamper the testing in conventional QC laboratories. In addition, its impact on R & D activities to develop Sabin IPV was also highlighted, given the requirements to build and commission bio-contained poliovirus essential facility, for the storage and handling of Sabin Poliovirus type 2.

The Belgian NRA provided an update on the implementation of phase I and II of GAP III. It was highlighted a royal decree was instituted in order to help health minister to designate poliovirus essential facilities. An update on specific challenges facing Belgian NCL was also raised, including the status of their current facility which is not GAP III compliant.

Feedback on the implementation of GAP III was also provided by ANSM, with specific challenges highlighted, including the lack of an accredited organization to oversee the process, and the absence of a designated and qualified inspectorate. However, actions have been taken in ANSM laboratory in charge of OPV controls to implement GAP III recommendations.

GAP III Implementation: Progress and Obstacles
Nicoletta Previsani (Team Lead, Polio Eradication, WHO)
The principles of containment and the importance of meeting GAP III requirements was emphasized, particularly in the context of formal declaration of the eradication of WPV2 in 2015. In addition, the commitment by all member states to implement GAP III, during the WHA in May 2016, was highlighted. An overview of the two phases of GAP III were detailed: the objective of phase I to reduce the number of facilities designated to handling poliovirus type 2; the objective of phase II to reduce the risk of release of poliovirus type 2 from the designated poliovirus-essential facilities (PEFs) and subsequent transmission to people. Currently 20 countries reported hosting 55 designated poliovirus-essential facilities.

Specific supporting activities to achieve implementation of GAP III were detailed, including the finalization of the Containment Certification Scheme (CCS) to assist countries with containment certification; the establishment of a formal Containment Advisory Group (CAG) to address technical concerns, the development of a pool of GAP III auditors to support national containment certification activities; and the work in progress to align the Technical Report Series 926 on the safe production of poliovirus vaccines to GAP III. In terms of next steps, the publication of CCS will require for countries to finalize the establishment of their National Authority for Containment (NAC) in order to engage with the PEFs in the containment certification process; and for the Global Commission for the Certification of Poliomyelitis Eradication (GCC) to take on their new global containment oversight role.

**Discussion points:** It was emphasized that in countries planning to retain type 2 poliovirus, NACs should be established as soon as possible.

Regarding type 2 poliovirus containment certification, it was clarified that it is a national endeavour, and that it is not the primary responsibility of WHO to issue waivers for GAP III compliance.

**Session 4: Research, Policy and Product Development for the Endgame**

*Polio Immunization Policy Post-Eradication*

Roland Sutter (Coordinator, Polio Eradication, WHO)

The future immunization policy in the post-eradication era was discussed. It was highlighted that OPV withdrawal is anticipated in 2020 or 2021. Specific remaining questions were
outlined, including whether immune response following immunization with one dose of IPV is sufficient to induce population immunity and provide protection from paralysis; the risk of re-introduction of poliovirus from immunodeficient individuals; and the options of future IPV supply (Salk-IPV or Sabin IPV, and single or combination vaccines).

The uncertainties of IPV supply and the importance of IPV affordability were highlighted. Multiple routine immunization schedules using either fractional or full doses were presented as lowest-cost, medium-cost or high-cost options for countries. Regarding IPV affordability, it was highlighted that Gavi funding is ensured until 2018, with gap in financing mechanism from 2019 and onwards, to ensure one dose of IPV in RI schedules.

It was emphasized that the achievement of certification of a polio free world is anticipated by 2019-2020, with the decision to continue immunizing with IPV until 2030 or longer, currently under consideration. The GPEI objective regarding cost per dose of standalone IPV is $0.50. Considerations for IPV future routine immunization schedule were outlined, specifically the number and timing of doses, the interval between doses, and formulation (i.e. fraction-dose or full dose: stand-alone or combination IPV).

The timeline for future immunization policy decision making was presented, including the Strategic Advisory Group of Experts decision which is anticipated in October 2017. The future direction of research to address existing knowledge gaps was also outlined, including whether mucosal immunity is induced after full-dose of fractional-dose IPV; priming induced by a single dose of IPV; and interference of IPV with measles-rubella vaccine.

**Fractional IPV: A Public Health Perspective to Address IPV Supply Constraints**

Harish Verma (Technical Officer, Polio Eradication, WHO)

The available scientific evidence for the use of fractional-dose IPV was discussed. It was highlighted that fractional-dose IPV as a strategy has been reviewed and encouraged by SAGE as far back as 2012, again in 2015 and 2016, with endorsement by the Strategy Committee in 2016 for use in all OBRA for 12 months until after the switch. The implementation of fractional-dose IPV was further emphasized in the WHO position paper in 2016: specifically, 2 fractional-doses of IPV in RI demonstrated greater immunogenicity than one full-dose; in addition the use of fractional-dose IPV may be appropriate for OBRA if IPV
supplies are limited. Results from recent studies were presented demonstrating higher seroconversion rates and antibody titers after 2 fractional-doses, compared to after 1 full dose.

Given the impact of the constraints of global IPV supply on the Indian national immunization programme, a national decision was made to implement a 2 fractional-dose RI schedule in 8 states of the country, administered at 6, 14 weeks as “off label” use. In addition, Sri Lanka has confirmed it will adopt this approach. Specific programmatic initiatives implemented in India to operationalise this decision were presented, including changes to existing immunization cards, appropriate training of health workers and monitoring of wastage.

Furthermore the recent OBRA in Telangana state of India following the detection of VDPV2 in environmental sample demonstrated the feasibility of implementing fractional-dose IPV administration in a campaign setting. Programmatic observations were shared: over 300,000 children were vaccinated in Hyderabad over 7 days, using 10 dose vials and BCG needle and syringe. Over 90% of injections that were monitored observed bleb formation, and 41-50 fractional-doses of IPV were obtained per 10 dose vial. In addition no leakage or damage to the vaccine vial septum due to multiple punctures was observed.

Future studies to assess immunogenicity and feasibility of fractional-dose IPV in RI and OBR settings in multiple countries are planned, using both, BCG needle and syringe as well as devices to deliver fractional-dose IPV.

**Progress on Development of New Delivery Devices**

Hiromasa Okayasu (Team Lead, Polio Eradication, WHO)

The development of intradermal delivery of fractional-dose IPV as a strategy was outlined, including the context of ongoing constraints in IPV supply, recent SAGE recommendations and the implementation of fractional-dose IPV in RI, OBR and SIAs to accelerate eradication in Pakistan and Afghanistan. The operational challenges in administration of intradermal injection were highlighted, emphasizing the need to develop novel ways to improve the ease of administration of intradermal injections.
Intradermal devices to delivery fractional-dose IPV include adapters and needle free injectors, both of which are currently available, as well as microarray patch technology which will be available in the future. Examples of specific devices were presented and it was emphasized that the GPEI Strategy Committee recently endorsed the use of intradermal devices and approved the budget to procure the devices for cVDPV2 OBRA.

Lastly, it was highlighted that the strategy of fractional-dose IPV was originally developed as an option to ensure IPV affordability, however its scope to potentially stretch limited IPV supply has become pertinent in the context of significant constraints in global IPV supply. As a result WHO and GPEI partners are actively facilitating the development and evaluation of these devices.

**Discussion point:** 1. Data on intradermal administration of Sabin-IPV is not yet available. 2. It was clarified that additional countries cannot be supplied with IPV as IPV supplies are limited and prioritized to Tier 1 and 2 countries; however should Tier 1 and 2 countries consider fractional-dose IPV as a strategy for RI, this would free up doses to be available to Tier 3 and 4 countries. 3. It was emphasized that countries which have received IPV, are encouraged to consider fractional-dose IPV for their RI programme. 4. The wastage rates related to the fractional-dose IPV campaign in India were lower than expected, with the majority of vials used within 2 days after opening.

**Collaborative Study for Harmonization of sIPV Testing**

**Javier Martin (NIBSC)**

The importance of harmonizing Sabin-IPV was emphasized. Potency testing is based on D antigen content, which is currently non-uniform between Sabin-IPV products. The absence of international standards is due to differences in reagents and ELISA methods used by different manufacturers. This contrasts with conventional IPV where international references are available with <10% laboratory variation.

Specific challenges in analysing available data pertaining to assay validity were presented, emphasizing that assay validity improved significantly when using Sabin-IPV standard. The solution to improve assay validity and reduce between-laboratory variability is to use common methods and/or to establish an International Standard for Sabin-IPV.
During a workshop recently held in Seattle in May 2016, the importance of harmonization of Sabin IPV testing was evident, with 20/20 of participants surveyed from manufacturing sector, expressing agreement on the importance of establishing an International Standard for Sabin-IPV, ideally by June 2018; in addition 19/20 indicated that they would incorporate this standard into their laboratories.

**Closing remarks**

Michel Zaffran (Director Polio Eradication, WHO)

The attendees of the consultation were thanked for their participation and continuing contribution towards polio eradication. The importance of ongoing close collaboration between vaccine manufacturers, NRAs, UNICEF and WHO leading into the post-eradication era was emphasized, particularily given the significant and ongoing constraints in global IPV supply and the anticipated changes in future immunization policy in the post eradication era.