Note for the Record

WHO-UNICEF Consultation with OPV/IPV Manufacturers, National Authorities for Containment and National Regulatory Authorities

Geneva – 15 October 2019

POLIO GLOBAL ERADICATION INITIATIVE

Overview

The *18th WHO-UNICEF consultation with OPV/IPV manufacturers, National Authorities for Containment (NACs) and National Regulatory Authorities (NRAs)* of polio-vaccine producing countries took place on the 15th of October 2019 in Geneva.

The Consultation had the overarching goal of enabling polio vaccine manufacturers to optimally plan their production over the span of the poliovirus eradication strategy. In doing so, the Consultation had the following key objectives:

- Appraise manufacturers of the Polio Eradication, Integration and Certification Endgame Strategy: 2019-23.
- Develop a shared understanding of the wider polio epidemiological context, the status of the programme, and the projected demand for polio vaccines over the span of the new strategy.
- Bring manufacturers up-to-date on new vaccine technologies and the regulatory pathways for the licensing of poliovirus vaccines.

Executive summary

The new Endgame Strategy outlines innovative approaches, and targets wider collaboration with health sectors, to achieve the eradication goal. The strategy is based on three pillars: eradication, integration, and certification and containment. This meeting was a first opportunity to brief the manufacturers on these new developments and the evolving epidemiology.

To enable polio vaccine manufacturers to optimally plan their production over the span of the poliovirus eradication strategy, the sessions were designed in such a way as to ensure that the manufacturers were appraised of the new strategy by subject-matter experts. In complement to this, the Consultation included sessions that served to develop a shared understanding of the wider polio epidemiological context, the current status of the programme, and the projected demand for polio vaccines over the span of the new strategy.

The Consultation aimed to bring manufacturers up-to-date on new vaccine technologies and the regulatory pathways for the licensing of poliovirus vaccines. In this connection, the ongoing work in developing the Novel mOPV2 vaccine, including the Emergency Use Listing procedure, was particularly notable. The development of this new vaccine, and its successful rollout in the coming 1-2 years, is of fundamental importance achieving the goal of stopping outbreaks of cVDPV2.

WHO's Director of Polio Eradication, Michel Zaffran, thanked all participants for contributing to the Consultation and for their continued dedication, commitment and engagement in the polio eradication programme. Mr. Zaffran also emphasised that the world cannot eradicate poliovirus without the full support of industry, NRAs, NACs and Ministries of Health.

The GPEI welcomes feedback on how the meetings may evolve in the future, and aims to ensure that future Consultations are interactive and dynamic. To do so, the organisers will be reaching out to the attendees seeking their feedback on how to optimise the upcoming Consultation.

The polio eradication effort finds itself at a challenging juncture. The engagement of industry, NACs and NRAs – and the spirit of collaboration that they have shown – is crucial to our shared success. In this

sense, the GPEI is grateful for the engagement of these parties and looks forward to ongoing collaboration over the coming years.

SESSION 1: Interrupting poliovirus transmission

PRESENTATION: Update on new strategy: *Polio Eradication, Integration and Certification Endgame Strategy 2019-23*

Michel Zaffran (WHO)

The Global Polio Eradication Initiative's (GPEI) *Polio Eradication, Integration and Certification Endgame Strategy: 2019-23* lays out the roadmap to achieving and sustaining a world free of all polioviruses. It comprises three key pillars:

1. Eradication: Stopping transmission of the wild poliovirus and preventing, detecting, and responding to outbreaks.
2. Integration: Collaborating with immunization and emergency partners to eradicate polio and to protect populations.
3. Certification: Certify eradication and Containment of all wild polioviruses (WPVs) and ensure long-term polio security.

The new strategy also includes critical enabling factors such as gender, research and preparing for Post-Certification Strategy (PCS) implementation. It builds on and optimises use of the proven lessons and tools of the GPEI's *Polio Eradication and Endgame Strategic Plan 2013-2018*, which has brought the world to the threshold of being polio-free and outlines new innovations to help ensure we cross the finish line.

PRESENTATION: Update on progress towards eradication and stopping outbreaks

Arshad Quddus (WHO)

An update was provided on the status of the polio eradication programme. There has been no WPV3 detected globally since November 2012, and no WPV of any serotype detected in Africa since September 2016.

There has been an increase in the number of WPV1 paralytic cases in Pakistan and Afghanistan, from 33 cases in 2018 to 89 cases so far in 2019 (data as 15 October 2019). In Pakistan, the programme has been off-track, facing political disruption and increased community resistance. In Afghanistan, the ban on house-to-house campaigns has severely affected the ability of the programme to reach children.

The programme is currently battling many outbreaks of circulating vaccine-derived poliovirus type 2 (cVDPV2) in sub-Saharan Africa and the risk of re-established poliovirus type 2 endemicity in this region. In 2019, there has also been detection of cVDPV2 outbreaks in Asia (China, Pakistan, the Philippines). The limited supply of the monovalent OPV2 (mOPV2) vaccine, which is the only currently available tool to control these outbreaks, presents a serious concern.

PRESENTATION: SIA calendar: Latest changes and demand forecast

William Mbabazi (WHO)

This presentation gave an overview of considerations used in development of the multi-year and annual supplementary immunisation campaigns (SIA) calendars. Notably, SIAs are the key intervention for interruption of WPV transmission and prevention/control of cVDPV outbreaks in the eradication goal. The multi-year calendar of SIAs reflects the medium term forecast of SIAs planned as part of the GPEI's 2019-2023 strategy. The multi-year SIA calendar fits within the GPEI budget and is the reference point for the development of risk-based annual implementation calendars. The objective of the multi-year SIA calendar is to provide (i) vaccination requirements for interrupting endemic circulation of WPVs; (ii) vaccination activities for mitigating risks of WPV importations or VDPV 1 and 3 emergence; and (iii) resource requirements for vaccine, human and financial resources. Subject to annual adjustments as the global polio risk assessments will prescribe, the presentation estimated that about one billion OPV doses will be needed annually to meet the SIAs demands for the planning period 2020-2023.

PRESENTATION: Supply of IPV and OPV: Current status and looking forward

Ann Ottosen (UNICEF)

After several years of supply shortages, IPV supply is improving to an extent that, in 2019, all 126 countries which used OPV only in 2013 have introduced at least one dose of IPV into the routine immunisation schedule. In addition, catch-up vaccination has started for the estimated 42 million children who were missed since April 2016 due to supply constraints. The IPV demand for 2020-2023 is projected to continue to increase, assuming a gradual introduction of a second dose of IPV into routine immunisation schedules as supplies become available prior to the cessation of OPV use.

The current assumption of the timeline for the withdrawal of bOPV is four years after the last notification of a WPV. It is essential to secure sufficient bOPV to be able to achieve eradication and OPV cessation but also to be able to adjust to changing requirements of the Programme. UNICEF have awarded an additional 2.3 billion doses, on top of what was already awarded, to secure supply until 2022, with a need to make award beyond 2022 during 2nd half of 2020.

There is a need to secure large volumes of mOPV2 immediately to be able to respond to cVDPV2 outbreaks or events, with high-quality campaigns to interrupt transmission. It is essential to secure and fill all available mOPV2 bulks which are not yet under UNICEF contracts for the stockpile.

Discussion:

- The forecasted IPV supply assumes that countries currently using fractional IPV (such as India) continue to do so.

PRESENTATION: Gavi board decisions: IPV support post-2020, in-principle decision on the whole-cell pertussis Hexavalent product

Stephen Sosler (Gavi, the Vaccine Alliance)

In June 2019, Gavi approved to support IPV with core funding resources for the 2021-25 period. The scope of this support is for the 70 currently IPV-supported countries, for a duration of ten years following global bOPV cessation. Gavi has additionally decided in-principle on support for a whole-cell pertussis Hexavalent vaccine.

PRESENTATION: Update on the global mOPV2 stockpile

David Woods (WHO)

Between April 2016 and October 2019, a total of 341 million doses (mds) of mOPV2 have been released. Out of these 341 mds, the majority have been used in Nigeria (59%) and DRC (15%). The current level of the mOPV2 stockpile, as of 15 October 2019, is 21.2 mds.

The mOPV2 stockpile plan for 2020-23 has been developed based on two principles:

1. Supply of both Sabin and Novel OPV2 should enable full-scale responses necessary to stop type 2 outbreaks.
2. Transition from Sabin to Novel OPV2 should be effected as soon as Novel OPV2 supply allows.

It is expected that during 2020-23 on-going cVDPV2 outbreaks will spread further within the regions already affected and the programme will require large-scale responses in WHO's African, Southeast Asian and Eastern Mediterranean regions. Based on this assumption, an estimated at 471 million children (under 5 years) will require vaccination and 5.8 billion doses of OPV2 (both Sabin and Novel) is forecasted as needing to be produced from now until the end of 2023.

SESSION 2: Regulatory pathways for scaling-up polio vaccine production

PRESENTATION: Prequalification and Emergency Use Listing of a polio vaccine

Carmen Rodriguez Hernandez (WHO)

The Prequalification (PQ) procedure was overviewed with details on the purpose, the routes and steps for PQ, and monitoring of performance of PQ-ed vaccines. As a risk-based assessment pathway, the Emergency Use Listing procedure (EUL) defines the steps that WHO will follow to establish the eligibility of products, the minimum information required and the process to conduct the assessment to make a product available under a time-limited listing status, while further data is being gathered and evaluated with PQ as the final aim. This involves a pre-emergency phase to concentrate most of the assessment activities and therefore to allow a rapid decision when the emergency is declared and a post-deployment monitoring phase.

SESSION 3: New product developments and innovations with potential to impact supply

PRESENTATION: nOPV2 scale-up

John Modlin (Bill & Melinda Gates Foundation)

The objective of the Novel OPV (nOPV) project is to develop new, genetically stable OPV strains to reduce the risk of generating cVDPV and vaccine-associated paralytic poliomyelitis (VAPP). Two nOPV2 candidate strains (C1 and C2) have completed pre-clinical development and nearing completion of Phase II studies in adults, toddlers and infants. Two nOPV1 and nOPV3 candidate strains are in late stage pre-clinical development.

The Phase I nOPV2 first-in-human study was conducted in IPV-immunised adults in Antwerp, Belgium, under Containment settings. The results of this study have been published in The Lancet (Van Damme P, 2019) and concluded that both the nOPV2 candidates are safe and immunogenic. Preliminary results from the Phase II clinical trials (in Panama and Belgium) indicate that both candidates are safe, immunogenic, replicate in the human gut. The results of neurovirulence and deep sequencing studies on shed stool specimens assessing genetic stability from these studies are anticipated between Q4 2019 and Q3 2020.

An overview of nOPV2 regulatory matters, manufacturing and supply planning were provided:

- Containment
    - The WHO Containment Advisory Group confirmed that both candidates may be used outside the containment requirements of GAPIII.
- Candidate selection
    - There has been an accelerated selection of Candidate 1 for EUL submission and commercial scale manufacturing.
- Emergency Use Listing
    - The process to include nOPV2 in EUL has been accepted by WHO Regulation of Medicines and other Health Technologies/Prequalification Team (but the dossier has not yet been submitted).
- Manufacturing and Supply Planning
    - The manufacturing capacity is constrained.
    - The nOPV2 supply has been incorporated into mOPV2 supply forecasting.
    - Bulk production started at Bio Farma Q3 2019.
    - A major effort underway to accelerate nOPV commercial production with a goal of producing more than 200 million doses by end of 2020.

Discussion:

- Under Containment guidelines, nOPV2 does not need to be stored in a Polio Essential Facility (PEF); however, any national guidelines or legislation for storing a genetically-modified organism must be followed.

PRESENTATION: GPEI's research and product development priorities

Roland Sutter (WHO)

The profile of GPEI research and product development priorities and projects was presented. This comprises research in the areas of: vaccine development; laboratory assays; primary immune deficiency surveillance and point-of-contact diagnostics; antiviral therapies; devices for vaccine administration; and programme evaluation and support.

SESSION 4: Containment and Certification

PRESENTATION: Global poliovirus Containment update

Arlene King (Global Certification Commission, Containment Working Group)

Currently, 25 countries plan to indicate poliovirus type 2 (PV2) materials in 70 PEFs. Out of these 25 countries, 24 have established NACs. All certificates of participation (CP) applications for facilities retaining PV2 should be submitted to relevant NACs by December 2019, with the CP expiration date on April 2021.

Discussion:

- There were questions regarding the Containment requirements following the certification of WPV3. Currently, there is no plan to withdraw OPV3 after certification. The Strategic Advisory Group of Experts on Immunization's (SAGE) Polio Working Group has reviewed this and recommended against the withdrawal of OPV3. Regarding Containment, it is expected that facilities using WPV3 will come into Containment, but there is no timeline established.

PRESENTATION: Containment Advisory Group recommendations and GAPIII amendments

Harpal Singh (WHO and Containment Advisory Group Secretariat)

The Containment Advisory Group (CAG) was established in March 2017 for a tenure of three years. The CAG acts as an advisory body to the Director-General of WHO and makes recommendations to WHO based on their terms of references (Annex B), The CAG has met at least four times and continues to meet and has had numerous teleconference to deliberate on these important issues. It has also established two working group of the CAG: the expert group on Novel poliovirus strains and the working group on the shower.

SESSION 5: Updates from vaccine manufacturers

PRESENTATION: LG's Sabin-IPV development

Hyung-Shin (Helen) Kim (LG Chem)

LG Chem established a Sabin-IPV Technology Transfer with Intravac in 2011. Results were presented from the phase III randomised control trial conducted in Thailand and Philippines, which compared LG sIPV and Sanofi Pasteur IPV. Infants were randomised to receive three doses of IPV at 6, 10 and 14 weeks of age. The LG sIPV was demonstrated to be equivalent and non-inferior to Sanofi Pasteur IPV. LG Chem are aiming to obtain WHO Prequalification in 2020 and have an annual production capacity of 50 mds.

PRESENTATION: Progress of GAPIII project in the Wuhan Institute of Biological Products

Li Li (Sinofarm)

This presentation provided information on the development of Sabin-IPV and combination vaccines including Sabin-IPV by Wuhan Institute of Biological Products Co. Ltd (WIBP). Through Phase I to Phase III clinical trials, the safety and effectiveness of Sabin-IPV were demonstrated. Meanwhile, combination vaccines including Sabin-IPV, like DTaP-sIPV, DTaP-sIPV-Hib, were being developed at WIBP. Supply of Sabin IPV will be available in 2020 in the domestic market, with an annual production capacity of 20 mds.

Annex A: Agenda

18th WHO-UNICEF Consultation with OPV/IPV Manufacturers and National Authorities for Containment and National Regulatory Authorities

Tuesday, 15 October 2019
Starling Hotel & Conference Centre (Room: *Geneva I*), Geneva

Chair	Michel Zaffran (Director of Polio Eradication, WHO; and Chair, GPEI Strategy Committee)
Goal	Enable polio vaccine manufacturers to optimally plan their production over the span of the poliovirus eradication strategy.
Objectives	Appraise manufacturers of the *Polio Eradication, Integration and Certification Endgame Strategy: 2019-23*. Develop a shared understanding of the wider polio epidemiological context, the status of the programme, and the projected demand for polio vaccines over the span of the new strategy. Bring manufacturers up-to-date on new vaccine technologies and the regulatory pathways for the licensing of poliovirus vaccines.

08.30 – 08.45	Registration	
Introduction		
08.45 – 09.00	Welcome, opening remarks	Michel Zaffran (WHO)
SESSION 1: Interrupting poliovirus transmission		
09.00 – 09.30	Update on new strategy: *Polio Eradication, Integration and Certification Endgame Strategy: 2019-23* *Objective: Update all on the new strategy*	Michel Zaffran (WHO)
09.30 – 10.00	Update on progress towards eradication and stopping outbreaks *Objective: Develop a shared understanding of the status of the programme*	Arshad Quddus (WHO)
10.00 – 10.20	SIA calendar: Latest changes and demand forecast *Objective: Update on the current calendar and how it was developed*	William Mbabazi (WHO)

10.20 – 10.40	Tea / coffee	
10.40 – 11.10	Supply of IPV and OPV: Current status and looking forward *Objective: Update on the current supply and future projections*	Ann Ottosen (UNICEF)
11.10 – 11.40	Gavi board decisions: IPV support post-2020, in-principle decision on the whole-cell pertussis Hexavalent product *Objective: Brief on the current status of Gavi's support for polio vaccines and its plans for the future*	Stephen Sosler (Gavi, the Vaccine Alliance)
11.40 – 12.00	Update on global mOPV2 stockpile *Objective: Develop a shared understanding of the status of the stockpile and the trends*	David Woods (WHO)
SESSION 2: Regulatory pathways for scaling-up polio vaccine production		
12.00 – 12.30	Prequalification and Emergency Use Listing of a polio vaccine *Objective: Update all on regulatory pathways to the use of polio vaccines*	Carmen Rodriguez Hernandez & Mathias Janssen (both WHO)
12.30 – 14.00	Lunch	
SESSION 3: New product developments and innovations with potential to impact supply		
14.00 – 14.30	nOPV2 scale-up *Objective: Brief on the status of the scale-up*	John Modlin (Bill & Melinda Gates Foundation)
14.30 – 15.00	GPEI's research and product development priorities *Objective: Update on the latest research and products undergoing development*	Roland Sutter (WHO)
15.00 – 15.20	Tea / coffee	
SESSION 4: Containment and Certification		
15.20 – 15.50	Global poliovirus Containment update *Objective: Given the outbreak situation, update on status of Containment and challenges to OPV production*	Arlene King (Global Certification Commission, Containment Working Group)
15.50 – 16.20	Containment Advisory Group recommendations and GAPIII amendments *Objective: Update on the recent and relevant outcomes of CAG and status/amendments of GAP III*	David Heymann (Containment Advisory Group)

SESSION 5: Updates from vaccine manufacturers		
16.20 – 16.40	LG's Sabin-IPV development *Objective: Update on development of the Sabin-IPV product*	Hyung-Shin (Helen) Kim (LG Chem)
16.40 – 17.00	Progress of GAPIII project in the Wuhan Institute of Biological Products *Objective: Progress update on the GAPIII project*	Li Li (Sinofarm)
Wrap-up		
17.00 – 17.20	Summary comments and wrap-up *Objective: Summarise outcomes and outline next-steps*	Michel Zaffran (WHO)

Annex B: Containment Advisory Group's Terms of Reference

Terms of References			
Technical issues associated with the Implementation of GAPIII* specifically the biorisk management requirements for facility holding WPV or those holding OPV/Sabin (no wild)- as currently described in Annexes 2 and 3 of GAPIII (Primary Safeguards)			
Major outputs to date	Alignment between industrial challenges with implementation of GAPIII and WHO Technical Report Series (TRS) 1016: Annex 4 Guidelines for the safe production and quality control of poliomyelitis vaccines (Replacement of Annex 2 of WHO Technical Report Series, No. 926).	Note, if any	Although these appears to be production based, the general intent is for more risk-based approaches than prescription requirements with limited evidence. These would be applicable to all facilities.
Guidance on handling of poliovirus-related materials for diagnosis, research and vaccine production (including production of VLPs, pseudoviruses, new OPV, etc.)			
Major outputs to date	Criteria for the evaluation of improved 'safety' of novel poliovirus strains to determine the containment requirements for their storage and handling *(cf. 1 after the table)* Exemption of the following from GAPIII requirements (other regional, institutional, national guidelines may apply). 1. nOPV2 candidate vaccines (S2/cre5/S15domV/rec1/hifi3 and S2/S15domV/CpG40) for Clinical trials, stockpile, outbreak response, production of nOPV2 and for quality control testing using both candidate vaccines' strains. 2. Series of genetic cassettes of S19 with the capsid protein encoding P1-region of polioviruses (Sabin and Wild, all serotypes) and the parallel series with the mutation (substitution) of an asparagine by a serine at amino acid 18 in the non-structural protein 2A to allow better growth in Vero for IPV production, rat neutralization IPV potency assays, human serum neutralization test and potency testing for immunoglobulin (human) lot control and release	Note, if any	CAG recommendations are strain-specific, and the approvals are conditional by specific terms of usage. When approved they may not subject to Annex 2 or Annex 3 of GAPIII and the CCS. But these materials should still be part of the survey and inventory phase as these materials fulfil the definition of poliovirus.
Guidance on the identification and categorization of poliovirus potentially infectious materials, their destruction, or handling and storage			
Major outputs to date	The exclusion of OPV/Sabin potentially infectious materials from the requirements of Annex 3 of GAPII but subject to the risk mitigation strategies described in the Guidance to minimize risks for facilities collecting, handling or storing materials potentially infectious for polioviruses (PIM guidance) *(cf. 2 after the table)*	Note, if any	The development of the PIM Guidance was adopted by CAG in November 2017

Guidance on the identification of acceptable alternative containment solutions in the interim period, before full eradication			
Major outputs to date	An operational example of collaboration between CAG had occurred in the past which was timely and useful in CWG deliberation of the CP application.	Note, if any	This is expected to increase with the implemented of the CCS.

The revision process of GAPIII is expected to more risk-based in approach, neutrality with period of public consultation and consolidation before endorsement of CAG informing the WHO GBS.

[1.] Criteria for the evaluation of improved 'safety' of novel poliovirus strains to determine the containment requirements for their storage and handling. Available at: http://polioeradication.org/wp-content/uploads/2017/08/criteria-evaluation-novel-pv-june-2019-eng.pdf

[2.] Guidance to minimize risks for facilities collecting, handling or storing materials potentially infectious for polioviruses (PIM Guidance). Available at: Guidance to minimize risks for facilities collecting, handling or storing materials potentially infectious for polioviruses (PIM Guidance).