17th WHO/UNICEF Consultation with OPV/IPV Manufacturers and National Authorities for Containment of Polio Vaccine Producing Countries

9 October 2018
Geneva, Switzerland

Note for the Record

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9 October 2018
Starling Hotel, Geneva, Switzerland

Rapporteurs:

Dr Ray Sanders

Tuesday 9 October 2018		Chair: Michel Zaffran
08:30	Registration	
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SESSION 2: Interrupting poliovirus transmission		
09:00	Update on Polio Eradication & Endgame Strategy Vaccine requirements: OPV & IPV demand for 2018-2020	Arshad Quddus
09:30	IPV & OPV supply: current status and looking forward	Ann Ottosen
10:00	IPV and hexavalent vaccine landscape	Dominic Hein
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SESSION 3: Biocontainment		
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11:15	CAG recommendations and GAPIII amendments	David Heymann (on-call)
11:45	Revised WHO TRS for safe production and quality control of Polio Vaccines	Hye-na Kang
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SESSION 4: Research, Policy & Product Development for the Future		Chair: Michel Zaffran
14:00	WHO collaborative study to establish the 1st International Standard for Sabin IPV	Gill Cooper Laura Crawt
14:30	Update on uptake of fIPV in PAHO IPV & OPV supply outlook	Ana Chavez John Fitzsimmons (on-call)
15:00	Update on fractional IPV use: ▪ scientific and programmatic rationale ▪ program implementation and assessment	Roland Sutter Courtney Jarrahian
15:30	*Coffee Break*	
16:00	sIPV supply update & future plans Kunming Institute	Roland Sutter (on behalf of Kunming Institute)
16:30	sIPV technology transfer project (Sinovac)	Weining Meng
17:00	Discussion	All
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List of Abbreviations

AFP	Acute flaccid paralysis
CAG	Containment Advisory Group
CCS	Containment Certification Scheme to support the WHO Global Action Plan for Poliovirus Containment
CP	Certificate of participation
cGMP	Current Good Manufacturing Practices
DTwP	Diphtheria and tetanus toxoid with whole cell pertussis vaccine
ECBS	Expert Committee on Biological Standardization
ELISA	Enzyme-linked Immunosorbent Assay
EPI	Expanded Programme on Immunization
FDA	Food and Drug Authority (United States)
fIPV	Fractional inactivated polio vaccine
GAPIII	WHO Global Action Plan to minimize poliovirus facility-associated risk after type-specific eradication of wild polioviruses and sequential cessation of oral polio vaccine use otherwise known as the WHO Global Action Plan for Poliovirus Containment
GCC	Global Commission for the Certification of the Eradication of Poliomyelitis
GPEI	Global Polio Eradication Initiative
IMB	Independent Monitoring Board
IS	International Standard
NAC	National authority for containment
NIBSC	National Institute for Biological Standards and Control (United Kingdom)
NRA	National regulatory authority
OPV	Oral polio vaccine
bOPV	Bivalent oral polio vaccine containing type 1 and type 3
mOPV2	Monovalent oral polio vaccine type 2
nOPV	Novel oral polio vaccine type 2
OPV2	Oral polio vaccine type 2
tOPV	Trivalent oral polio vaccine containing type 1, type 2 and type 3
PAHO	Pan American Health Organization
PEF	Poliovirus-essential facility
PV	Poliovirus
SAGE	Strategic Advisory Group of Experts on Immunization
SIA	Supplementary Immunization Activities
sIPV	Sabin inactivated poliomyelitis vaccine
TAG	Technical Advisory Group (on Vaccine-preventable Diseases, PAHO)
TRS	Technical Report Series
VDPV	Vaccine-derived poliovirus
cVDPV1	Circulating vaccine-derived poliovirus serotype 1
cVDPV2	Circulating vaccine-derived poliovirus serotype 2
cVDPV3	Circulating vaccine-derived poliovirus serotype 3
WHA	World Health Assembly
WHO	World Health Organization
wP	Whole cell pertussis (-based hexavalent vaccine)
WPV	Wild poliovirus
WPV1	Wild poliovirus serotype 1
WPV2	Wild poliovirus serotype 2
WPV3	Wild poliovirus serotype 3

Overview

The 17th WHO/UNICEF consultation with OPV/IPV manufacturers and National Authorities for Containment (NACs) of the polio vaccine producing countries took place on 9 October 2018 in Geneva. This was the second time the consultation was attended by the NACs who will be responsible for national level oversight and implementation of the Global Action Plan III (GAPIII) for containment certification.

The key objective of the consultation was to strengthen collaboration between stakeholders. The consultation outlined the status and needs of the polio eradication programme with implications for OPV and IPV demand and supply; provided an update on research, product development (including Sabin IPV); and emphasized the importance and necessity of accelerating the containment certification process.

Session 1: Introduction

Welcome, opening remarks

Michel Zaffran (Director, Polio Eradication, WHO)

Participants were welcomed to the meeting on behalf of WHO and the Global Polio Eradication Initiative (GPEI). This meeting is a demonstration of the strong collaboration that has been developed between the GPEI, industry and national regulatory authorities over many years and more recently the National Authorities for Containment (NACs) of polio vaccine producing countries. Although progress continues to bae made towards the goal of global piliomyelitis eradication, there remain a number of challenges, including continued transmission of wild poliovirus (WPV) in a small number of endemic foci and circulating vaccine-derived polioviruses (cVDPV). The GPEI is currently developing a new 5-year strategic plan for poliomyelitis eradication for the period 2019-2023, based on the existing strategy but including a number of new approaches and innovations. The Independent Monitoring Board (IMB) has recently conducted an external review of the programme in the remaining endemic countries and made a range of recommendations. Poliomyelitis vaccines remain the key essential tools for eradication which includes bivalent OPV (bOPV), IPV and monovalent OPVs (mOPV). Continued supply of these vaccines for routine and supplementary immunization activities is a crucial requirement for poliomyelitis eradication and maintaining a polio-free status. Containment of polioviruses, essential to maintain polio-free status post eradication, is a complex and challenging undertaking that requires a strong collaborative approach from the programme, international partners, industry and all WHO Member States. This WHO/UNICEF consultation provides a platform to discuss the key issues and challenges and strengthen the collaboration to achieve global poliovirus containment.

Session 2: Interrupting Poliovirus Transmission

Update on Polio Eradication & Endgame Strategy

Arshad Quddus (Coordinator, Detection and Interruption Unit, Polio Eradication, WHO)

An overview of the Global Polio Eradication programme was provided focusing on progress and challenges in the two remaining endemic countries; Pakistan and Afghanistan. While transmission of wild poliovirus serotype 1 (WPV1) continues in the two neighboring countries, it has been largely restricted to just two common corridor of transmission that span the border area (Northern and Southern corridors) and Karachi. Extensive network of supplemented environmental surveillance exist in both countries demonstrate ongoing poliovirus transmission. In Afghanistan, more than 1 million children are not accessed for vaccination due primarily to security reasons, and remains the major challenge. Reaching high risk mobile population and pockets of chronically non-compliant (refusals) also pose significant challenges in both the countries

Currently active outbreaks of type 2 vaccine derived polioviruses (cVDPVs) are reported from Nigeria, Niger, DRC and Horn of Africa (Somalia and Kenya). In the Horn of Africa region, there is co-circulation of cVDPV2 and cVDPV3. An outbreak of cVDPV1 reported from Papua New Guinea shows circulation in wide geographic areas and also affecting children of age above 5 years. Most of the cVDPV outbreaks have occurred in areas with persistently low immunization coverage, insecurity, and populations that are difficult to access. Program has mounted agressive response to these outbreaks and progress is being monitored closely to address challenges and ensure quality of response

In response to these challenges the GPEI has focused efforts on implementing action plans addressing ongoing transmission in the northern and southern corridors of Pakistan and Afghanistan and expanded community-based vaccination in key areas in Pakistan. Negotiations have also started into improving access to under-immunized populations in Afghanistan. High-level advocacy for political commitment to address the continuing cVDPV outbreaks has also been intensified, including deployment of high level WHO and partner agency staff to support field operations.

The programme's priorities for the coming 6 months include: (1) development of a new Endgame Strategic Plan 2019-2023 that will assume interruption of transmission in 2020, global certification of eradication in 2023 and cessation of OPV use one year after certification; (2) acceleration of interruption of virus transmission in remaining endemic countries (Nigeria, Pakistan, Afghanistan); (3) enhanced focus on stopping cVDPV2 outbreaks; (4) enhanced AFP surveillance to meet

certification standards and expanded environmental surveillance; and (5) development of the mOPV stockpiles to respond to outbreaks post-OPV cessation.

Discussion

The cVDPV1 outbreak in Papua New Guinea is a result of persistently low routine immunization vaccine coverage and a weak health infrastructure in parts of the country

Monovalent oral polio vaccine (mOPV2) mOPV2 is the primary tool and remains the vaccine of choice in responding to cVDPV2 outbreaks. Risk posed by the outbreak far outweighs any risk of seeding associated with mOPV2 use. Ensuring quality and achieving high mOPV2 coverage in the supplemental immunization campaigns will minimize risk of any new emergence and it's spread.

Vaccine requirements: OPV and IPV demand for 2018-2020

Arshad Quddus (Coordinator, Detection and Interruption Unit, Polio Eradication, WHO)

Intense supplementary immunization activities (SIAs) have been conducted in 2017-2018 with almost all activities planned for 2017 and 2018 (quarters 1 to 3) being implemented and almost 1.6 billion doses of bOPV used in 2017. Activities planned for the fourth quarter of 2018 are on track for implementation and it is estimated that 1.4 billion doses of bOPV will have been used for SIAs in 2018. In response to cVDPV2 outbreaks, 162 million doses of mOPV2 have been released from the stockpile and administered in Nigeria, Democratic Republic of Congo, Niger and other countries with 77% being administered in Nigeria and Democratic Republic of Congo alone.

The calendar of SIAs planned for 2019 until OPV cessation is being developed to provide estimates for vaccine supply and financial planning. The calendar is reviewed and adjusted semi-annually following assessment of evolving risks. A total of 24 countries are currently regarded as medium-high or high-risk for WPV transmission, requiring an estimated 1.12 billion doses of bOPV for SIAs in 2019, with an approximate budget of US$326 million. It is further estimated that between 1 billion and 850 million doses of bOPV will be required for SIAs for each of the years 2020 to 2024. This will be in addition to the approximately 600 million doses of bOPV required each year for routine immunization activities.

The current global requirement for IPV for routine immunization, excluding the PAHO countries, is 65million doses, and in 2018, 87 countries requiring IPV for routine immunization were supplied through UNICEF. However, the supply of IPV remains tight and priority for 2019 IPV allocation include; ensure supply for routine immunization and avoid vaccine stock-outs, provide approximately 5.9 million doses for SIAs in remaining WPV endemic countries, approximately 3

million doses for refugees and displaced persons, catch-up immunizations to approximately 43 million children worldwide that missed immunization due to IPV shortage and outbreak response. Countries are being urged to consider using fractional dose (fIPV) schedules for catch-up campaigns.

The long-term OPV requirement forecast for the quantities of finished product to be ordered for the stockpiles from 2018 to include 305 million doses of mOPV2, 600 million doses of mOPV1 and 200 million doses of mOPV3. Substantial financial investments will be required to establish these stockpiles.

Discussion

Prioritization of countries for catch-up campaigns and the promotion of fIPV schedules.

IPV requirements of countries that do not use UNICEF supply and their impact on the global supply.

IPV and OPV Supply: Current Status and Looking Forward

Ann Ottosen (Senior Manager, Vaccine Centre, UNICEF Supply Division)

The supply capacity to UNICEF of Inactivated Polio Vaccine (IPV) remained considerably below the awarded quantities for the 2014-2018 tender period due to delays in scaling up production, but supply is now increasing for the first time since 2014. Throughout the tender period, approximately 47% of quantities on contracts were actually delivered. Initial awards left quantities unawarded for 2018, based on indications from pipeline manufacturers that they would be able to offer a prequalified vaccine by 2018, however, also pipeline manufacturers experienced delays. In 2018 one supplier is now fully meeting the commitment and IPV availability has increased by 50% compared to 2017. Out of a total of 87 countries sourcing IPV supply through UNICEF, 33 countries did not have access to- or had IPV supplies interrupted after the switch from tOPV to bOPV. Despite the supply challenges, this has been the fastest roll out of a 'new' vaccine in recent history, with 122 countries introducing IPV since 2014.

It is currently anticipated that availability of prequalified IPV in 2019 will reach 71 million doses, of which 64 million will be required for routine immunization needs. This will leave approximately 7.5 million doses available for all other needs, which results in an overall shortfall of 45 million doses across immunization strategies for 2019. The current projection includes a 46 million dose requirement for catch-up campaigns and refugee/displaced persons campaigns. Due to the delay in eradication of wild poliovirus, the global withdrawal of OPV has been postponed to 2023/2024, which will also delay the timelines for the introduction of the second IPV dose to 2022/2023.

Additional awards to maximize supply and meet unmet demand is in progress with prequalification of IPV by other producers. An updated forecast will be provided in the fourth quarter of 2018.

Key lessons learned in the recent supply of IPV are that scaling up of vaccine production is challenging even for experienced vaccine manufacturers and for vaccines which have been produced for decades, a finding that will need to be factored in for future highly accelerated programmes. The development of strong collaborative partnerships between vaccine manufacturers, UNICEF, programme partners and countries is essential to manage a supply constrained situation and to optimize programme outcomes. Transparent, detailed and early communications from manufacturers on any actual or anticipated supply issues are required to support country planning in a timely manner and ensure a good understanding and consistent messages.

Oral Polio Vaccine (OPV) continues to be UNICEF's largest vaccine, with an average annual demand in 2016 to 2018 of approximately 1.2 billion doses. Despite extensive work on forecasting demand and supply, demand in 2018 has been 150 million doses higher than projected, and supply has been 50 million doses below projections. This has resulted in the using up of buffer stocks. Additional awards have been required to secure the buffer stocks and meet the needs, with award processes ongoing. There has also been a request from the Global Polio Eradication Initiative (GPEI) to convert bulk already paid for in to global stockpile to bOPV for 2020 to avoid wastage. A new demand which was unplanned at the time of the UNICEF tender in 2017, is the demand for mOPV1 for endemic countries due to evidence of immunogenicity gains and per dose efficacy compared to bOPV, raising requirements to 100 million doses in 2018-2020.

Delays in the interruption of transmission of WPV1 has resulted in an increase in demand since the tender was established, whereas a change in the strategy from planning for pre-cessation campaigns to maintain high levels of immunity through to 2024 has required a change in the forecast. Overall impact is an increase in the overall OPV projected demand by 1 billion doses from 4.2 billion doses in the current tender to 5.2 billion doses. Short term OPV demand for 2018 and 2019 are materializing on the high side of the tender projections, with additional awards ongoing with the next tranche of awards through to 2022, to take place before the end of the year. Projected demands will be available upon finalization of the Supplementary Immunization Activity placeholder calendar, currently under review for sign off by GPEI in October 2018. UNICEF will go back to all bidders requesting reconfirmation of terms and conditions with additional awards anticipated for 2019-2022 at this stage. mOPV1 is being reactivated as a tool for use in endemic countries, requiring

a new tender, which will be issued for 60 to 80 million doses of mOPV1 for delivery in 2019-2020, with the first delivery in January 2019.

Discussion

Introduction of the 2nd dose of IPV has been discussed by SAGE, decisions on the use of IPV have largely been dependent on restricted availability of IPV since 2016.

Use of IPV for targeted catch-up campaigns will prioritize fIPV adopting countries may have to be extended into 2020.

IPV and hexavalent vaccine landscapes

Dominic Hein (Head, Market Shaping, GAVI, the Vaccine Alliance)

The IPV supply situation is set to improve from 2018 with sufficient supply to meet routine demands of all countries procuring through UNICEF and using a single-dose schedule. However, there are currently only 2 IPV manufacturers and the UNICEF tender for 2019-2022 has seen a price increase of 60% - 140% over the 2018 tender price. While the immediate price increase is not satisfactory, competition from new stand-alone IPV entrants starting 2020-2021 is likely to result in more affordable prices in line with current levels. Some of these manufacturers are targeting prequalification but the success rate is difficult to predict at present. In addition, manufacturers in China have Sabin IPV development programs that could cover their own national demand and manufacturers in India have Sabin IPV development plans, and are working on ensuring their facilities are GAPIII compliant to start production and clinical trials.

One vaccine manufacturer currently has a licensed IPV-containing whole cell pertussis (wP) hexavalent vaccine ("Hexavalent") and an additional four have products in development. It is expected that substantial supply of standalone IPV to UNICEF would be available from 2023 and could reach between 210 and 340 million doses in the long term. A dedicated working group has been created including partners from WHO, UNICEF, Bill and Melinda Gates Foundation and the GAVI Secretariat to analyze the potential value of Hexavalent in the context of GAVI's support to polio eradication. The working group defined the decision pathways applicable for GAVI to potentially support the procurement of Hexavalent, and provided programmatic, financial and supply analysis to include in an overall polio support strategy to be presented to the GAVI Board in November 2018. Adoption of a Hexavalent schedule would provide some programmatic advantages over a Pentavalent-based IPV schedule, including minimizing the total injection burden. GAVI is also

considering potential support of the WHO-recommended booster dose, and Hexavalent would be considered alongside the other options of diphtheria toxoid, tetanus and whole-cell pertussis (DTwP) vaccines and Pentavalent for the first booster in the 2nd year of life in case a 4th dose of hexavalent is needed based on polio immunogenicity. Nevertheless, expansion of stand-alone IPV remains the priority for the GAVI Alliance and the advent of Hexavalent vaccines should not adversely impact the availability of IPV stand-alone vaccines.

Discussion

SAGE has recommended use of wP vaccines, so use of acellular pertussis (aP)-containing vaccines is not an option for WHO.

Persistence of the polio immune response following the SAGE-recommended 2-dose IPV schedule is currently considered superior to that of a 3-dose hexavalent vaccine at the 6-10-14 week schedule.

Session 3: Biocontainment

Poliovirus containment: Update on Implementation

Arlene King [Chair, Global Commission for the Certification of the Eradication of Poliomyelitis - Containment Working Group (GCC-CWG) and Member, GCC]

The World Health Assembly (WHA) resolution 71.16 (2018)[1] urges all WHO Member States to intensify efforts to accelerate the progress of poliovirus containment certification, complete inventories for type 2 polioviruses, destroy unneeded poliovirus type 2 materials and to begin inventories and destruction of unneeded poliovirus type 1 and 3 materials in accordance with the latest available published WHO guidance. The resolution also requires immediate reporting of any breach of poliovirus containment to the National IHR Focal Point. Member States retaining polioviruses are urged to reduce to a minimum the number of facilities designated for the retention of polioviruses, prioritizing facilities performing critical national or international functions and appoint a competent National Authority for Containment (NAC) by end-2018. All facilities designated to retain poliovirus type 2 are required to formally engage in the Containment Certification Scheme (CCS) by submitting to their NAC their applications for participation (CP), which is the first step of the global certification process, as soon as possible and no later than 31 December 2019.

[1] WHA71.16 Poliomyelitis – containment of polioviruses. Available at: http://apps.who.int/gb/ebwha/pdf_files/WHA71/A71_R16-en.pdf

As of 7 October 2018, twenty-eight Member States have notified WHO of their intention to retain poliovirus type 2 (PV2) materials in a total of 89 designated poliovirus-essential facilities (PEF). Of these 28 Member States, only 22 have established NACs. To date, applications for CPs have been submitted by NACs to the Global Certification Commission (GCC) for six facilities. Of these applications, one has been endorsed by the GCC, two applications are on hold and three are under review.

The Containment Working Group of the GCC (GCC-CWG) was established in January 2017 with seven members charged with supporting GCC's role in global containment oversight by providing review of containment certification applications. There are plans to expand the GCC-CWG membership in 2018. Major challenges faced include ensuring the establishment of NACs in all countries hosting PEFs before the end of 2018 and accelerating the certification process for PEFs so that CPs can be issued by the end of 2019. To accomplish this, the GAPIII auditing capacity of newly established NACs will need to be increased. Additional challenges include meeting the GCC deadline of April 2019 for implementing the Guidance to minimize risks for facilities collecting, handling or storing materials potentially infectious for polioviruses (PIM guidance), updating all national poliovirus inventories to include poliovirus types 1 and 3, and establishing a verification mechanism to ensure data quality of national inventories. There is an ongoing requirement to increase the awareness of all Member States of WHA resolution 71.16 (2018).

To meet these challenges, a communications/advocacy strategy has been developed and deployment of consultants to support implementation of the PIM guidance is in progress. A series of workshops on the implementation of the PIM guidance at the WHO regional level and training of auditors to strengthen the capacity of NACs is also being established.

CAG recommendations and GAPIII amendments

David Heymann [Chair, Containment Advisory Group (CAG)]

The Containment Advisory Group (CAG) provides recommendations to the Director-General of WHO on technical issues arising from implementation of GAPIII. Recent issues have included providing guidance on the handling of poliovirus-related materials for diagnosis, research and vaccine production, including production of virus-like particles, pseudoviruses, and novel poliovirus strains generated as candidate vaccine strains. Guidance has also been provided on the identification and categorization of poliovirus potentially infectious materials, their destruction, or handling and storage, and on the identification of acceptable alternative containment measures in the period before global eradication. All CAG meeting reports are published and made available at:

http://polioeradication.org/tools-and-library/policy-reports/advisory-reports/containment-advisory-group/. Submissions on issues for the consideration of the CAG can be made using the CAG submission form, and should be emailed to containment@who.int.

Recommendations of the CAG are advisory to WHO and when necessary CAG may commission the Secretariat to generate the evidence upon which recommendations and guidance can be provided. Recommendations has been provided on the requirement for mandatory showering on exiting from the containment perimeter for facilities retaining polioviruses, on the criteria for the safety assessment of novel strains of polioviruses specifically on the S19-poliovirus type 2 strains and nOPV2 candidate vaccines and on the definition of tertiary safeguard requirements around PEFs.

Discussion

Risk assessment criteria for determination of containment requirements for novel strains of poliovirus and the need for NACs to work with manufacturers to review procedures and facilities to ensure safety.

Use of the S19 strains as candidate vaccines and the clinical trial process.

Access by NACs to the revised documents and amendments, use of the WHO mailing list to notify of new information, and the need for NACs to provide current contact information to be included in the WHO mailing list.

Options for the revision of GAPIII to increase the consistency with other documents and collation of all amendments.

Revised WHO TRS for the safe production and quality control of poliomyelitis vaccines

Hye-na Kang (Scientist, Technologies, Standards and Norms, WHO)

The Expert Committee on Biological Standardization (ECBS) has agreed that Annex 2 of the WHO Technical Report Series (TRS) No. 926 (Guidelines for the safe production and quality control of inactivated poliomyelitis vaccine manufactured from wild polioviruses) needs to be revised in line with the poliovirus containment requirements defined in GAPIII. The revised guidelines should specify the measures to be taken to minimize the risk of accidental reintroduction of wild-type poliovirus from a vaccine manufacturing facility into the community after global certification of poliomyelitis eradication. After extensive consultations in 2016-2018, the third draft of the proposed revision has been posted for public consultation and the final document is expected to be adopted by the ECBS at the end of October 2018.

The revised document is expected to provide information and guidance to vaccine manufacturers and relevant national authorities on the biosafety measures required for poliomyelitis vaccine production and quality control during the final poliovirus containment phases (Phase III) as defined in GAPIII. Requirements described in GAPIII should be reconciled with the provisions of current Good Manufacturing Practices as they apply to the manufacturers of poliomyelitis vaccines. Thus, the revised guidelines in TRS should be read in conjuction with other relevant WHO guidance. The revised guidelines would address the containment measures needed during the production and quality control of IPV from wild-type strains, IPV from live attenuated Sabin strains, and OPV and IPV from novel safer strains developed by genetic manipulation.

Discussion

Application of the new TRS requirements restricting future IPV supply and the need for close collaboration with manufacturers to ensure this is avoided.

Session 4: Research, Policy and Product Development for the Future

WHO Collaborative study to establish the 1st International Standard for Sabin IPV

Gillian Cooper [Scientist, National Institute of Biological Standards and Control (NIBSC)]
Laura Crawt (Scientist, NIBSC)

NIBSC produces 95% of global WHO standards and provides a portfolio of International Standards (IS) and reagents for all the quality control testing required for OPV, IPV and for the polio surveillance network. The move towards production of sIPV and entry into the field by new manufacturers, many of whom are new to poliomyelitis vaccine production, has resulted in the need to provide new standards for vaccine development and quality testing. Conventional IPV (cIPV) potency is measured by a validated ELISA, against a suitable reference, and expressed as D-Ag units. The cIPV IS 12/104 used to calibrate such references. For sIPV there is no such reference and no defined requirements in terms of specific D-Ag units/human dose. Current manufacturer-specific references are not calibrated against an IS and it is difficult to assess D-Ag units between manufacturers and across sIPV products. With sIPV products now coming on-line it is essential to address the issue of standardization sIPV.

The first sIPV collaborative study was conducted in 2015 and 2016 and found that there was a high level of consistency between laboratory D-Ag results when using a common method and the cIPV IS, that there was a high proportion of invalid assays and large differences in D-Ag estimates when

using in-house assays, and that assay validity and between lab variability improved for in-house methods when using a sIPV sample as a reference to assess the sIPV study samples. It was agreed to establish the first IS for sIPV and harmonize the sIPV d-Ag ELISA. Candidate 17/160 was chosen as the potential sIPV IS as it showed better overall results in terms of assay validity, within and between laboratory variability and thermal stability profiles. It was also decided to assign new units for the sIPV IS (17/160), to be known as Sabin D-antigen units. Potency in Sabin D-Ag units have been assigned against each poliovirus serotype.

It is important to assess the correlation between *in vitro* and *in vivo* potency (and ideally a link to immunogenicity potency in human clinical studies) for different sIPV products, as has been established for cIPV, and to demonstrate the equivalence of D-Ag units present in different sIPV products. *In vivo* collaborative studies, will be initiated to address this. The objectives will include comparisons of different samples with the same D-Ag content as well as using the recommended human dose from clinic trials. Methodology will also be evaluated.

NIBSC are also undertaking a collaboration with the FDA and PATH to look at new human antibodies as a reagent for the D-Ag ELISA. A collaborative study will be organized to evaluate both human and NIBSC mouse monoclonal antibodies.

Discussion

sIPV IS calibration and availability for calibrating all sIPV products.

Calibration of the potency of new sD-Ag against existing D-Ag standards and progress made in calibrating new products against the new units.

Update on uptake of fIPV in PAHO

IPV and OPV supply outlook

Ana Elena Chevez [Regional Advisor, Comprehensive Family Immunization Unit,
Pan American Health Organization (PAHO)]
John Fitzsimmons (Chief, Revolving Fund Special Program for Vaccine Procurement, PAHO)

As in other WHO Regions, supply of IPV in recent years has been lagged behind by global production capacity. Regional demand for IPV in 2018 exceeds 11.3 million doses and to date 7.8 million doses have been purchased . Regional demand for bOPV was revised to be between 23 and 25 million doses, of which purchase orders for 18.3 million doses have been placed and further purchase of

approximately 3.2 to 7 M ds million doses is in process prior to year end. Regional demand for bOPV in 2019 has been estimated at 26 million doses and supply agreements are in place with 3 manufacturers for a total of 28 M ds. PAHO has continued close monitoring of country vaccine inventories, with active supply management and reallocations to ensure no countries are without IPV or bOPV vaccines. Nine countries have started preparing for the use of fIPV, with support from PAHO and two countries, Ecuador and Cuba, have begun use of fIPV. There has been follow up operational meetings with suppliers to ensure completion of supply plans for delivery in 2019. Together with GPEI and UNICEF, PAHO continues to monitor progress of new IPV suppliers into the global market.

Discussion

Situation with under supply of IPV requirements in PAHO for 2018/19 and actions taken by the Regional Office to minimise shortages.

Update on fIPV use: scientific and programmatic rationale; programme implementation and assessment

Roland Sutter (Special Adviser on Research, Policy and Containment to the Director, Polio Eradication, WHO)

Courtney Jarrahian (Portfolio Leader, Packaging & Delivery Technologies, PATH)

The Endgame Strategy has been to introduce IPV into the routine schedules of all Member States, but given recent constraints on global IPV availability, demand has consistently exceeded supply.[2] In response there has been a tiering scheme to provide IPV to Member States most in need. The need to provide catch-up vaccination for missed cohorts places further strain on IPV supply. SAGE has therefore recommended use of fractional doses of IPV (fIPV),[3] and the PAHO Regional Technical Advisory Group has recommended that all countries in the WHO region of the Americas using greater than 100,000 doses of IPV per year should be prepared to introduce fIPV into the immunization schedule.[4]

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[2] UNICEF. Inactivated Polio Vaccine: Supply Update. Copenhagen: UNICEF; May 2018. Available from: https://www.unicef.org/supply/files/Inactivated_Polio_Vaccine_Supply_Update.pdf.

[3] World Health Organization. Meeting of the Strategic Advisory Group of Experts on immunization, April 2018 – conclusions and recommendations. Wkly Epidemiol Rec. No 23, 2018, 93, 329–344. Geneva: WHO; 2018. Available at: http://www.who.int/wer/2018/wer9323/en/.

[4] XXIV Meeting of the Technical Advisory Group (TAG) on Vaccine-preventable Diseases. 2017 Jul 12-14; Panama City, Panama. Available from: https://www.paho.org/hq/index.php?option=com_docman&view=download&category_slug=tag-final-reports-1626&alias=42498-24-tag-final-report-2017-498&Itemid=270&lang=en.

fIPV, delivered intradermally, is antigen-sparing and can be used to extend limited IPV supplies. When administered in a two-dose schedule it has been demonstrated to be more immunogenic than a single dose of intramuscular IPV, both in terms of seroconversion and antibody titres[5]. Available evidence suggests that fIPV is as effective at boosting mucosal immunity as intramuscular IPV in those who had previously received OPV[6]; in addition results from a recent study have demonstrated that an intradermal schedule of 6 and 14 weeks is better than a 10 and 14 week schedule. In addition to countries that have already introduced fIPV in their immunization schedules, there are several countries, predominantly in Central and South America, that are in the process of implementing introduction of fIPV into routine immunization schedules. It is likely that at least one vaccine manufacturer will pursue an IPV label-change to include intradermal delivery of fractional doses in the near future.

WHO, PAHO, and PATH have generated resource materials for countries in support of the introduction and program evaluation of fIPV, and intradermal devices are available for fIPV delivery.[7] [8] Several countries using fIPV have conducted programmatic assessments of introducing fIPV into routine schedules as well as delivery in campaign settings. Key finding from these assessments are that thorough vaccinator training is needed on ID injection technique and schedule changes, and that in some settings fIPV introduction has resulted in very low vaccine wastage rates and high coverage.[9] PATH has conducted cost modeling that found that fIPV delivery in routine schedules is estimated to have a lower cost per child vaccinated than intramuscular delivery even if wastage rates increase and costlier devices are used; this difference is expected to be increased if 2 intramuscular doses are recommended in the future. In catch-up campaigns, delivery of 2 fIPV doses also costs less per child vaccinated than using 1 intramuscular dose, even when accounting

[5] Anand A, Molodecky NA, Pallansch MA, Sutter RW. Immunogenicity to poliovirus type 2 following two doses of fractional intradermal inactivated poliovirus vaccine: A novel dose sparing immunization schedule. Vaccine. 2017 May 19;35(22):2993–2998.

[6] Gamage D, Mach O, Palihawadana P, Zhang Y, Weldon WC, Oberste MS, et al. Boosting of Mucosal Immunity After Fractional-Dose Inactivated Poliovirus Vaccine. J Infect Dis. 2018 Nov 5;218(12):1876-1882.

[7] World Health Organization [Internet]. Fractional dose IPV page. Available from: http://www.who.int/immunization/diseases/poliomyelitis/endgame_objective2/inactivated_polio_vaccine/fractional_dose/en/.

[8] Pan American Health Organization, World Health Organization [Internet]. Fractional doses of the inactivated poliovirus vaccine (fIPV) page. Available from: https://www.paho.org/hq/index.php?option=com_content&view=article&id=14058:fractional-doses-of-the-ipv&Itemid=1707&lang=en.

[9] Gamage D, Ginige S, Palihawadana P, et al. National introduction of fractional-dose inactivated polio vaccine in Sri Lanka following the global “switch”. WHO South-East Asia J Public Health. September 2018;7(2):79-83.

for the operational costs of campaigns. In addition, fIPV delivery provides particular savings in vaccine costs in light of the new higher prices for IPV in 2019 and 2020.

Discussion

Proposed switch to 2-dose IPV schedule in Iran and vaccine supply requirements.

The high cost of the PharmaJet® Tropis jet injector for intradermal delivery and the practicalities of budgeting for use of this device.

sIPV supply update and future plans - Kunming Institute

Roland Sutter (Special Adviser on Research, Policy and Containment to the Director, Polio Eradication, WHO) on behalf of the Kunming Institute

The Institute of Medical Biology, Chinese Academy of Medical Sciences (IMBCAMS) at Kunming has been a pioneer in the development of IPV made from Sabin strains (sIPV) and has supplied the Chinese market with sIPV since 2015. In China, single-dose vials are provided for use at 2, 3 and 4 months, with a booster dose at 18 months. The Institute has provided almost 1 million doses for private market use in 22 provinces, and more than 13 million doses to the Chinese National EPI programme for use in 31 provinces. A new sIPV facility is now being built that will incorporate sIPV bulk production and filling and packing areas and have a production capacity of 40 million doses per year. The facility is now undergoing certification and validation processes.

sIPV technology transfer project - Sinovac

Weining Meng (Sinovac, Beijing)

The sIPV developed by Sinovac under a Technology Transfer project has been subjected to clinical trials and shown to be non-inferior to cIPV and the sIPV produced by IMBCAMS. Clinical trial phases I, II and IIIa have been completed, and phase IIIb is in process. Phase I demonstrated the absence of any serious adverse reactions, and Phase II demonstrated that post-vaccination seropositivity approached 100% in all trail groups. In the phase III trial the seropositive rate (≥ 1:8) of each trail group was almost 100%, and seropositive rates (≥ 1:64) of the trial groups were all more than 97%.

The sIPV bulk production facility has been built on an existing building at the Changping site in Beijing with the formulation, filling, packaging and storage facility shared with other marketed products. It is hoped that a production license will be granted in 2020 and WHO PQ approved in 2021. The facility is currently awaiting on-site inspection of GMP conducted by China FDA. One approved by the Chinese FDA application will be made for WHO prequalification.

Closing remarks

Michel Zaffran (Director, Polio Eradication, WHO)

The attendees of the consultation were thanked for their participation and continuing contribution towards polio eradication and the implementation of the Endgame Strategy, GAPIII and GAPIII-CCS. Close and active collaboration between vaccine manufacturers, NRAs, NACs, UNICEF and WHO remains essential, particularly given ongoing constraints in global IPV supply, the urgent need to implement containment requirements and the anticipated changes in immunization policy that will be necessary in the post eradication era.