09-10 February | 2017

13th Meeting of the SAGE Polio Working Group

Conclusions and recommendations

Note for the Record

World Health Organization

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Background

The 13th face-to-face meeting of the SAGE Polio Working Group (WG) was held during 9-10 February 2017 at the World Health Organization in Geneva, Switzerland.

The meeting was attended by the following WG members: Dr. Zulfiqar Bhutta, Dr. Walt Dowdle, Dr. Peter Figueroa, Dr. Nick Grassly, Dr. Ilesh Jani, Dr. Youngmee Jee, Dr. Jacob John, Dr. Liz Miller, Dr. Jeffrey Mphahlele, Dr. Walt Orenstein, Dr. Kimberly Thompson, and Dr. K Zaman.

Dr. Yagob Al-Mazrou (Chair) was unable to attend so Dr. Figueroa acted for the Chair.

This note presents a summary of the main findings, conclusions, and recommendations of the meeting.

Context and objectives of the meeting

In October 2016, SAGE reiterated its concern over the global supply shortage of Inactivated Poliovirus Vaccine (IPV), which will persist into 2017-18. Given this situation and the high efficacy of 2-dose fractional intradermal IPV, SAGE strongly recommended that: countries should start preparing for a fractional intradermal 2-dose IPV schedule, e.g. at 6 and 14 weeks, in lieu of a single intramuscular full dose at 14 weeks.

SAGE also reviewed the Polio WG discussion on future polio immunization policy and requested the WG present its recommendations on future immunization policies for consideration by SAGE in April 2017.

The specific objectives of the WG meeting were:

1. To review the GPEI programme update, including the IPV supply situation
2. To review scientific data on the use of IPV in polio eradication, outbreak response and routine immunization
3. To make a proposal on future immunization policy (including duration of vaccination with IPV after OPV withdrawal (i.e., post-OPV immunization schedule) for the April 2017 SAGE meeting.

Topic 1: GPEI programme update

The WG reviewed the GPEI programme update, presented by Michel Zaffran (WHO), IPV and OPV supply situations, presented by Ian Levis and Ann Ottosen (UNICEF) and Diana Chang-Blanc (WHO), and epidemiology of Vaccine-Associated Paralytic Poliomyelitis (VAPP) after the tOPV to bOPV switch in India by Ondrej Mach (WHO).

Progress toward interruption of WPV1

The GPEI reported significant progress in the elimination of WPV in Afghanistan and Pakistan in 2016, with 20 WPV1 cases in Pakistan and 13 in Afghanistan with onset of paralysis in 2016 (as of February 26, 2017), which represent significantly lower numbers than in 2015 (i.e. 54 cases in Pakistan and 20 cases in Afghanistan). The GPEI reported on three transmission corridors: Nangahar/Kunar-Khyber Peshawar (last case reported February 2016), Pakita-FATA/KP (where WPV1 circulation continues in Bermal, Afghanistan, but not reported on the Pakistan side over the last 6 months), and Kandahar/Helmand-Baluchistan (WPV1 and VDPV2 circulation continues). The GPEI reported aggressive response in this area and no cases in Karachi since January 2016. In both countries, AFP surveillance indicators meet minimum required standards of quality.

In Nigeria, the GPEI reported four WPV1 cases in July and August 2016 in Borno, but no WPV1 cases or isolates in environmental surveillance since then. However, most of Borno state continues to be inaccessible, significantly affecting the quality of surveillance and Supplementary Immunization Activities (SIAs). While Borno has overall good AFP indicators, there are few AFP cases reported from inaccessible parts of Borno.

cVDPV2

Since the tOPV-bOPV switch in April 2016, the detection of Sabin viruses in most OPV-using areas appears to have declined as expected. The GPEI reported 20 VDPV2 isolations from environmental or AFP surveillance with 3 cVDPV2 outbreaks confirmed (i.e. Borno and Sokoto in Nigeria, Quetta in Pakistan) and two pending

classification (Chechen Republic/Moscow (Russia) and Mozambique). The cVDPV2 case in Borno is a persistent cVDPV2 from the pre-OPV2 withdrawal period (37 nucleotide changes from Sabin). The Sokoto, Nigeria (12-17 nucleotide changes) and Quetta, Pakistan (9-18 nucleotide changes) outbreaks most likely represent viruses derived from OPV used before the switch, and they demonstrate that some areas failed to conduct sufficient good quality tOPV rounds prior to the switch to prevent the development of cVDPVs post-switch. The GPEI responded to the Nigeria/Pakistan outbreaks with mOPV2. Detection of Sabin virus in AFP cases and environmental surveillance in some countries (e.g. India, Iraq and Nigeria) after the switch revealed some limited continued use of tOPV, which triggered thorough investigations.

Containment

The GPEI established the Containment Working Group (WG) to support the Global Certification Commission (GCC) in its oversight role of GAPIII, and the Containment Advisory Group (CAG), which reports to the Director General of WHO, to provide scientific guidance on containment related matters. As of 16 January 2017, 30 countries reported the designation of 78 Poliovirus Essential Facilities (PEF), which plan to retain infectious and potential infectious poliovirus materials after OPV cessation.

Transition planning

The GPEI continues the process of developing a strategy for after certification of all WPV eradication. The post-certification strategy aims at defining the essential functions that need to be sustained to maintain a polio free world post certification. The high level goals of the strategy include: 1) contain polio sources, 2) detect and respond to any outbreaks, 3) protect populations (including post-certification strategy such as bOPV cessation) and 4) manage effectively and monitor to ensure ongoing polio functions are embedded in existing structures (e.g. beyond GPEI as required) and are properly monitored to sustain a polio free world.

IPV and OPV supply situations

The WG reviewed the current IPV and OPV supply situations. IPV supply continues to fall short of demand, with one manufacturer reducing projections even further since the last WG call in December 2016. Manufacturers are supplying only 50% of the UNICEF-originally awarded quantity for 2014-2018 (e.g. expected supply of ~50M in 2017 vs. contracted amount of ~110M). One supplier was able to improve phasing of their committed supply through a general improvement of the monthly production plan and was able to reallocate 1.5 million doses from another customer. A potential additional quantity of up to 1.6 million doses will be confirmed end of March 2017, and possible additional quantities may become available in Q4, to be confirmed later in the year. The other supplier reported a further decline in supply (~4M doses), with no strategies available to address this shortfall from this supplier. To close the gap between expected supply as of December 2016 and current expectations, the options include i) interrupting supply to Tier 2 countries until October 2017; ii) request Tier 2 countries to adopt a fractional IPV schedule (which would not be a short term solution); or iii) postponing the availability of 2 million doses initially kept in reserve for outbreak response/SIAs from June to November 2017. The prospects for supplying IPV to Tier 3 and 4 countries now appear delayed until sometime in 2018. The current UNICEF tender contract expires at the end of 2018, so UNICEF will issue a new tender in Q2 2017.

A preliminary cost analysis by Kid Risk indicated that a two fractional doses schedule instead of 1 full IM dose may help alleviate the IPV supply situation and reduce costs (with BCG needles and syringes), if logistically feasible, but it may also have a substantial impact on industry's incentives to invest in production.

The WG also reviewed the bOPV and mOPV supply situations. UNICEF will maintain 150 million doses as a bOPV buffer in finished product, reaching 150 million doses in June and maintained throughout 2017. UNICEF noted the mismatch between the WG recommendations from the prior meeting to maintain high levels of bOPV demand to support regular continued SIAs between now and bOPV cessation and the current GPEI SIA placeholder calendar, which has a high intensity of pre-cessation campaigns. The WG raised concerns about the future availability of OPV in the context of delays in achieving eradication and implementing bOPV cessation. Overall, the programme originally procured 1.12 billion doses of mOPV stockpile (519 million doses of type 2, 300 million doses of type 1 and 300 million doses of type 3, down from the originally planned 2.5 billion due to reduced budget). Currently, there are 24 million doses of finished mOPV2 available in the

stockpile through to end of March with pending awards of 119 million doses for October/December 2017 delivery, totalling 269 million doses. This reduces the mOPV2 bulks in the global stockpile to 250 million doses. To revisit the size, composition, timelines and structure of the stockpile and provide guidance for the future based on initial experience, the GPEI established a cross-functional Polio Stockpile Working Group to report back in Q2 2017.

VAPP epidemiology after the switch

Lastly, the WG reviewed the epidemiology of Vaccine-Associated Paralytic Poliomyelitis (VAPP) after the tOPV to bOPV switch in India. The VAPP risk in India appears significantly decreased since the introduction of IPV and the switch, with no VAPP related to type 2 reported and a reduced number of VAPP cases associated with OPV1 and OPV3 and an increased age of VAPP cases among zero-dose and one-OPV-dose children.

WG decisions/recommendations

- The WG noted the progress in the elimination of WPV in Afghanistan and Pakistan and the improvement of surveillance in Pakistan. However, the WG concluded that the GPEI must address significant remaining gaps in all 3 endemic countries to achieve elimination of WPV and cVDPV2. These gaps include the unreliability of SIA monitoring data (e.g. LQAS and independent monitoring indicating high level of immunization coverage despite ongoing transmission), inadequate surveillance, and inaccessibility as a result of insecurity (as demonstrated in isolation of cVDPV2 in Borno with 37 nucleotide changes from Sabin) and not immunizing repeatedly missed children. The WG urged the GPEI to make all possible efforts to continue improvement and focus on performance, including the independent assessment of the field operation, detailed investigation of missed children in endemic countries, targeted campaigns for missed children, and improved surveillance.
- In endemic countries with co-circulating WPV and cVDPV, the need to interrupt both WPV and cVDPV2 is critical. However, the WG noted that higher priority should be given to the elimination of cVDPV2 because of the increasing risk of significant type 2 outbreaks due to the increasing size of the cohort of children with no type 2 immunity, following OPV2 withdrawal in April 2016.
- The WG remains concerned about the ongoing IPV shortage and the increasing number of children without any immunity against type 2. The WG urged more countries to consider the adoption of fractional IPV in their routine schedule to mitigate the global supply shortage.
- The WG also recommended that the GPEI reassess its tier classification of countries with respect to prioritization of IPV to take into account the size of the population with no IPV protection, the recent emergences of type 2 events, and the longer-term risks that IPV use could help to mitigate (e.g., iVDPVs, containment failures in countries with PEFs).
- The WG expressed concern over the significant number of PEFs (78 PEFs in 30 countries), and encouraged countries to limit the number of PEFs to the extent possible. The WG further urged the GPEI to put more attention on managing containment risks and the process for the implementation of containment.

Topic 2: Benefit of IPV in eradication, outbreak response and RI

Given the significant IPV shortage, the GPEI should optimize the use of the limited amount of IPV available. In this regard, the WG reviewed different perspectives on the benefit of IPV in 1) achieving WPV1 eradication, 2) outbreak response against cVDPV2, and 3) routine immunization to provide protection to individuals from the risks of iVDPVs and the potential reintroduction of live polioviruses.

The WG reviewed a presentation of epidemiology/vaccinology by Walt Orenstein (Emory University) and a presentation of virology by Mark Pallansch (US CDC). The WG also reviewed poliovirus modelling performed by 3 different modelling groups (Kimberly Thompson (Kid Risk), Nick Grassly (Imperial College), and Guillaume Chabot-Couture (Institute for Disease Modelling).

WPV1 eradication/Outbreak response to cVDPV2

The clinical and epidemiological studies indicate that IPV is very effective in preventing paralysis in vaccine recipients. However, IPV shows limited ability to induce intestinal immunity. Two studies in India showed IPV does reduce the prevalence and duration of faecal shedding following challenges in previously OPV vaccinated children in the study. However, a single dose of IPV administered to children un-primed by a prior dose of OPV containing type 2 has minimal effect on faecal shedding and these children are likely playing the major role in transmission. Nonetheless, one modelling group presented an epidemiological analysis on the incidence of poliomyelitis and poliovirus isolation in environmental samples after campaigns with IPV and OPV in Pakistan and Nigeria indicate a substantial impact, which is significantly greater than that with OPV alone. Mathematical modelling by one modelling group of hypothetical cVDPV2 outbreaks in Pakistan suggests IPV in addition to mOPV2 may give a modest additional increase (up to 5-20%) in intestinal immunity among young children against type 2 that depends on past exposure to type 2 OPV (i.e. geographically heterogeneous). Another modelling group presented a contrasting perspective, showing modelling results of using IPV in addition to OPV compared to using OPV alone for outbreak response for hypothetical cVPDV2 outbreaks in Nigeria and Pakistan that showed minimal benefit of adding IPV for outbreak response because the added IPV does not significantly increase population immunity and is not cost-effective. The WG agreed that mOPV2 campaigns with high coverage should be the priority in response to a cVDPV2. The modelling by one group in Pakistan indicated that the use of IPV may be useful in boosting intestinal immunity in areas outside the mOPV2 use (e.g. areas that the virus is likely to spread, but are not responded by mOPV2), although modeling by another group demonstrated the importance of using enough mOPV in the outbreak response to shut down transmission and showed that in the context of using sufficient amounts of mOPV2 to stop and prevent transmission, the additional use of IPV offers minimal impact and is not cost- effective. A third modelling group showed that when OPV can be used in outbreaks response, either to respond to cVDPV2 outbreaks after OPV2 cessation or in efforts to stop WPV1 circulation, adding a dose of IPV did not significantly improve the mucosal immunity of the target population and adding one more dose of OPV would be equivalent if IPV and OPV campaigns achieved equivalent coverage. However, the coverage of OPV campaigns is likely to be better than that of IPV campaigns given that OPV is distributed house-to-house while IPV is distributed at fixed posts. They also found little difference in the impact of an IPV dose in outbreak response whether the dose was given during the first or last campaign of the outbreak response.

The effect of IPV depends on coverage, OPV status (naive vs. OPV-vaccinated with waning intestinal immunity), OPV take, and adequacy and timing of OPV use. In addition, the WG raised questions about the implications of using IPV in addition to OPV in SIAs on coverage. Giving IPV and OPV at the fixed sites as opposed to the house-to-house, possibly reduces the overall coverage, particularly in the difficult-to-reach populations that vaccinators may already repeatedly miss and that most likely account for most transmission.

Routine immunization

The review of a large body of scientific studies demonstrated that IPV is highly effective in inducing individual protection.

- Multiple studies in a range of settings show nearly 100% seroconversion rates and high antibody titers to all 3 serotypes following 3 doses of IPV
- Some studies show >90% seroconversion rates after 2 doses when initiated after 8 weeks of age (immunogenicity of IPV improves for IPV schedules that avoids interference from maternally-derived antibody)
- Intradermal administration of 2 or 3 fractional doses of IPV provided lower or similar seroconversion rates to the same number of full doses. For example, in a study conducted in Bangladesh, two doses of IPV given intramuscularly at 6 and 14 weeks reported a seroconversion rate of 94.9%, 91%, and 97.5% against types 1, 2, 3 respectively, compared with 87.5%, 80.9% and 88.8% if fractional doses were given intradermally. One study in Cuba reported that three doses of IPV given intramuscularly at 6, 10 and 14 weeks led to seroconversion rates of 89%, 96%, and 99%, compared to 53%, 85%, and 69% for fractional dose IPV given intradermally.
- Two fractional doses of IPV can induce higher seroconversion rates than one full dose of IPV given at a similar age as the first of the fractional doses.

This effect of IPV in individual protection is increasingly important as the world now relies on IPV for type 2 individual immunity in birth cohorts born since the switch. However, there is insufficient evidence that IPV

induces community protection (e.g. mucosal immunity). Some evidence (e.g. India) suggests lower shedding upon reinfection, which may reduce transmission if re-infected individuals account for an important part of the population responsible for transmission. In India, children who received 3 doses of DTP-IPV have a significantly lower rate of poliovirus shedding than in control children (without IPV) 7 days post challenge. Yogyakarta, Indonesia, which introduced IPV relatively early into its routine immunization, did not detect VDPVs after switching from OPV to IPV in 2007. However, the sustained WPV1 transmission among IPV-only vaccinated children in Israel suggests the limited ability of IPV alone in inducing mucosal immunity. Dynamic transmission models show limited benefit of routine immunization with IPV in reducing transmission in most settings (i.e., in places with conditions conducive to relatively high faecal-oral transmission). In this context, the models suggest a relatively higher benefit for IPV in settings with relatively "low force of infection" as opposed to "high force of infection." The models also demonstrate differences in the relative forces of infection of different types of live polioviruses (OPV, OPV-related viruses, WPV, cVDPV) and the different serotypes, which show the relatively lower transmission potential of parent OPV compared to WPV or cVDPV. The epidemiological experience of no or limited transmission of imported OPV viruses in Israel following its switch from OPV to IPV, but transmission of imported WPV1 demonstrates the importance of the nature of the imported virus. The Israel and Yogyakarta experiences of no generation of cVDPVs from probable imported parent Sabin viruses, which have lower force of infection than existing cVDPVs or WPVs, suggest that high IPV coverage in areas with relatively low fecal-oral transmission may have some impact on prevention the generation of new cVDPVs from imported parent Sabin viruses.

Dynamic transmission modelling for Pakistan and Afghanistan showed that IPV in RI led to very limited benefit in preventing emergence and transmission of cVPDV2, because the issue in this epidemiological block relates to insufficient tOPV use prior to OPV2 cessation to prevent the creation and circulation of cVDPVs.

The models demonstrates small reductions in paralytic incidence because some individual children who received IPV after the switch were not paralyzed by poliovirus infection after the switch. This benefit is clearly related to the coverage achieved with poliovirus vaccines in routine immunisation.

Proposed changes in type 2 outbreak response protocol

As of 9 February 2017, 20 VDPV2 emergences (3 cVDPV, 12 aVDPV, 3 iVDPV and 2 unclassified) have been reported since the switch in May 2016. Countries did not implement outbreak response for 9 events, because detections occurred within 6 mos. from switch, included relatively few NT changes (i.e., suggesting inappropriate continued use of tOPV rather than sustained transmission), and/or the country assessed population immunity as high and the transmission as likely to die out without a response. Fractional IPV was used to respond to one type 2 detection in India that occurred in an area with a high proportion of the population primed with tOPV and good surveillance. SIAs with mOPV2 from the global stockpile have been implemented in Nigeria/Lake Chad and Pakistan, and proposed for Afghanistan and Mozambique and Russia by WHO DG's Advisory Group for mOPV2 stockpile. Target populations for individual mOPV2 SIAs ranged from 97K (Sokoto rapid response) to 48.2 million doses (Nigeria/Lake Chad).

Based on the 9-month experience since the switch and consideration of the IPV situation, the WHO secretariat proposed a few changes in the type 2 response protocol. Major proposed changes for the next six months include:

- **In response to an unclassified (e.g. 'new') VDPV2 or aVDPV2**: Instead of defaulting to an immediate SIA the program proposes no vaccination response (only enhanced investigation and surveillance) unless the event is considered as high risk for further transmission. "High risk" is determined by a composite index of multiple factors in three categories (virology, situational context, and potential for international spread).
- **In response to a cVDPV2**: Instead of the originally proposed 4-5 SIAs, the programme proposes at least 2 'high quality' SIAs with mOPV2 in all outbreak areas and additional SIAs as needed to provide at least 2 'high quality' SIAs (i.e., if prior coverage <80% or evidence exists of persistently missed children or continued transmission). The WG emphasized the importance of both rapid and high quality responses at this stage in the GPEI.
- **Use of IPV**: Consider adding 1 fIPV dose for surrounding high risk populations to boost mucosal immunity in areas outside the scope of mOPV2 response in one SIA only if 1) supply is available; 2) operationally feasible, and 3) mOPV2 SIA coverage not compromised.

- **Scope/target for a mOPV2 response**: Instead of starting with 500k for SIA1 and 2+million for subsequent 3-4 SIAs, the target population should include 2 million for each SIA with the focus on two high-quality SIAs that occur within 14 days of initial sequencing results provided by the GPLN. Additional populations and further extension of the scope of the mOPV2 outbreak response should occur if warranted due to high population mobility or other risk factors.
- **In endemic areas (co-circulating WPV1 and VDPV2):** Prioritize cVDPV2 over WPV1 and proceed as indicated in the type 2 protocol.

The program further proposes to continue current protocol recommendations for other responses (e.g. to iVDPV2, Sabin2, etc) and to update the protocol in areas in which new guidelines have already been endorsed by the GPEI (e.g for general guidance on vaccine management and classification of cVDPVs).

The epidemiology and response experience related to type 2 detections will be re-evaluated over the next 6 months and further revisions proposed as necessary.

WG decisions/recommendations

- The WG re-emphasized that the primary vaccine of choice to eliminate WPVs and respond to cVDPVs is OPV (bOPV1&3 and mOPV2). IPV may offer additional benefit in stopping poliovirus transmission in and around outbreak zones, but current supply constraints require prioritisation of IPV use in RI in countries at risk of VDPV2 emergence and spread (tier 1 and 2)
- The WG agreed that IPV has a significant role in RI in protecting children against poliomyelitis caused by cVDPV2 in countries using bOPV for routine immunization. IPV use is increasingly important as population immunity for type 2 began decreasing at the time of the switch. Access to IPV in RI is important from an equity perspective and therefore, the WG concluded that IPV supply should be prioritized for routine immunization.
- In recognition of the severe global supply constraints for IPV, the WG endorsed the following proposed IPV allocation over the next six months:
    - Prioritize available supply for routine immunization, especially to Tier 1 and 2 countries.
    - No IPV for SIAs in endemic countries or type 2 outbreaks over the next six months
- The WG endorsed the specific proposed changes in type 2 response in principle, noting the following:
    - It is critical to ensure the high quality of SIAs and speed (e.g. within 14 days after detection).
    - Given the expected IPV supply constraints over the next six months and the above prioritization for use of IPV, the reference to IPV use should be taken out of the type2 outbreak response protocol.
    - It is important to identify and address high risk populations during the outbreak and ensure that SIAs reach these populations.
    - The WG encouraged the replenishment of finished vials of mOPV2 to avoid possible stock-out.
    - In endemic countries with co-circulating WPV and cVDPV, the need to interrupt both WPV and cVDPV2 is critical. However, the WG noted that higher priority should be given to the elimination of cVDPV2, because of the increasing risk of significant type 2 outbreaks due to waning type 2 population immunity. Recognizing that simultaneous administration of mOPV and bOPV may be operationally difficult in endemic countries, the WG noted that in situations where both vaccines are required, the two OPVs may be given two weeks (or less if operationally feasible) apart.
- The WG recommended that the Advisory Group of GPEI Eradication and Outbreak Management Group on mOPV2 vaccine provision in response to type 2 poliovirus event or outbreak and/or WHO DG Advisory Group for mOPV2 stockpile should make a recommendation on each new type 2 event, considering specific situations such as population immunity and IPV and mOPV supply.

Topic 3: Discussion on future immunization policy

In October 2016, the SAGE recommended that

- Post-OPV cessation, the immunization schedule should aim to achieve at least 90% seroconversion for individual protection, which will be achieved with at least 2 doses of IPV (either full or fractional)

- Countries will need to continue routine immunization with IPV after the certification of polio eradication for an extended period (e.g. 5, 10 or more years).

SAGE requested the Polio Working Group to make more detailed recommendations (e.g. minimum duration of use of IPV, options for IPV schedule) for the post-OPV immunization schedule to SAGE in April 2017.

The WG reviewed a summary of evidence and WHO secretariat's proposal, status of new OPV/IPV development, future funding policy for IPV through 2021, the availability and cost of different ID devices, and a summary of clinical data on fIPV.

Currently, the programme anticipates OPV withdrawal in 2021 or later, one year after Global Certification Commission (GCC) certification of WPV eradication (i.e. GCC certification minimum 3 years after the last WPV1 case and minimum one year between GCC certification to OPV withdrawal).

Given the uncertain IPV supply, the WHO proposed to make availability of adequate IPV supply a prerequisite for OPV withdrawal. The WHO Secretariat defined an adequate supply as: a) two full doses to Tier 1 countries, b) two fractional doses for all other OPV using countries, and c) a stockpile for outbreak response. Regarding future immunization policy, countries fall into 3 broad categories: 1) Countries hosting poliovirus essential facilities whereby GAP III requirements necessitate ongoing and indefinite routine immunization with IPV (Sabin retaining countries should have at least one dose of IPV with coverage ≥90% that of DTP3; WPV-retaining countries should have at least three IPV doses with ≥90% coverage); 2) Countries maintaining IPV for country-specific reasons (e.g. national security and bioterrorism risk); and 3) "all other countries." The WHO Secretariat expects that more than 50% of the birth cohort (e.g. children in relatively high-income countries currently using IPV, and China, India, Indonesia and other countries) will continue using IPV as long as they need to meet the GAP III requirements.

The WHO secretariat proposed that in the post-OPV era, all countries should continue IPV use in the routine immunization for more than 10 years, to ensure durable protection for the long-term and minimize the risks for poliovirus re-emergence from VDPV/WPV emergence (Mathematical modelling and past epidemiology suggested VDPV/WPV types 1 and 3 could potentially emerge 0-4 years after the OPV withdrawal), iVDPVs could excrete for up to 5 years in middle income countries and for 10+ years in high income countries), and containment failure (it could happen even after 10+ years). The recommendation of IPV use for 10+ years should also provide incentives for current producers to stay in the market and for prospective IPV producers to enter the market.

Studies indicated at least two fractional or two full IPV doses (for prime and boost) are required to achieve 90% or more seroconversion (individual protection). However, the first dose should be given after 14 weeks and the interval should be greater than 5 months to optimize seroconversion. Practically, IPV should be given at or after 14 weeks (e.g. with DTP2 or DTP 3) and at or after 9 months (e.g. with measles in most countries). Ideally two full doses IM should be given, but the WHO Secretariat proposes that two fractional doses given in this schedule are fully acceptable.

The WG reviewed the updated estimates of global IPV demand and supply. A two full-dose IPV schedule will require more than 200 million doses in 126 OPV-using countries. The current estimate is that this level of supply (200M) is likely to be available only in 2023-24 primarily from new Sabin IPV suppliers. The WHO Secretariat expects "sufficient supply" of IPV may become available earlier (2021-2022) if some countries adopt a fIPV schedule (assuming demand will be around 150-200 million doses). However, significant uncertainties remain regarding the future IPV supply and national choices between two full and fractional IPV doses, which may result in more than 150 million doses variation in potential annual IPV demand.

The WG also reviewed the future funding policy for IPV. Currently, the GPEI covers the cost of IPV and its introduction in routine immunization into Gavi eligible countries through Gavi and provides subsidies to some non-Gavi countries as well as technical support. The GPEI is likely to continue to support IPV cost in Gavi eligible countries until 2020, either from savings due to the IPV supply shortage and/or new contributions. After 2020, the Gavi Board will need to consider continued support for IPV post-2020 through its own funding. Gavi and the GPEI are discussing post-certification of WPV eradication policy and IPV support for Gavi

supported countries, including future funding and application of Gavi policies on eligibility and co-financing, but did not have resolution of this at the time of the WG meeting.

The Bill & Melinda Gates Foundation (BMGF) is leading the development of new OPV (nOPV) vaccines with improved genetic stability designed to reduce the risks of VAPP and VDPV generation when deployed from a stockpile for outbreak control or re-introduced into routine immunization. Two type 2 nOPV candidates with improved genetic stability and reduced neurovirulence in vitro, and immunogenicity and growth profiles similar to mOPV2, are expected to be in the clinical trials in Belgium in Q2 2017.

The WG reviewed the experience with and availability of different devices to administer vaccine intradermally, including a few alternative intradermal injection devices (e.g. ID adapters, disposable syringe jet injectors) in addition to 0.1 mL auto-disable needle and syringes. Two devices (ID adapter by Helm and Tropis ID jet injector by PharmaJet) have regulatory clearance, with the PharmaJet Tropis device currently under WHO prequalification review and a prequalification specification and verification protocol is being developed for the ID adapter and other needle based ID capable technologies. PATH assessed feasibility and quality of injection with different injection devices. First, it assessed the self-sealing and fragmentation of vial stoppers and confirmed that IPV vial stoppers maintained performance even after multiple (up to 100) piercings with a 27G needle. It also concluded that the dead space varies by brand and model of syringe, but for these devices dead space is very small so that it is possible to administer 5 doses of fIPV with a 1-dose vial (and potentially six doses, due to vial overfill). PATH also reviewed injection quality data and concluded that injection performance measured by bleb size and fluid loss varied between studies, but the clinical relevance of these measures is yet to be established. In the Cuba study, healthcare workers preferred ID jet injectors to needle and syringes, and in the Gambia study found that jet injectors were more acceptable to infants (as determined by crying) as well as parents.

The WG reviewed the updated clinical study data comparing two doses of intradermal fIPV against one full intramuscular IPV dose in terms of seroconversion and type 2 antibody titres. Based on the results of seven studies the WG concluded that two fIPV doses if delivered as well in the field as in the clinical trials are more immunogenic than one full IPV dose. Two fIPV doses are more immunogenic if given four weeks to four months apart and started at or after 14 weeks based on the results of one study.

WG decisions/recommendations

- The WG reiterated that Sabin bOPV should be fully withdrawn from the routine immunization as soon as possible following the GCC certification of global WPV eradication.
- The OPV withdrawal needs to be globally synchronized and planned, and should be possible within 12 to 15 months of certification. The WG noted that the programme will need to ensure sufficient bOPV supplies to support maintaining high population immunity to transmission for serotypes 1 and 3 until coordinated bOPV cessation and develop and maintain mOPV stockpiles, potentially with genetically more stable new OPV if that option becomes available.
- The WG re-confirmed that all countries should continue using at least one dose of IPV after the OPV withdrawal. If IPV supply and funding allows, the WG recommends that countries should adopt a two dose IPV schedule as a preferred option to ensure adequate individual protection against wild or vaccine-derived poliovirus.
- If an OPV-using country is to adopt a two dose IPV schedule after OPV withdrawal, two doses of IPV should be given at or after 14 weeks (e.g. with DTP2 or DTP 3) and at 9-12 months (e.g. with measles). Ideally, two full doses IM should be given, but two fractional doses may provide a similar level of seroconversion based on the results of clinical trials, although no data provide information on the duration of protection (e.g. sufficient antibody) following the receipt of 2 fractional or full IPV doses.
- The WG noted that countries with PEFs should continue the use of IPV as long as required. However, the WG recommended that CAG should review and reconsider the current secondary safeguard requirements in the GAP III as some countries with Sabin facilities have inadequate DTP3 coverage.
- Most WG members agreed that countries, without poliovirus essential facilities, should maintain IPV in their routine immunization schedule for at least 10 years after global OPV withdrawal, to address immediate (VDPVs), intermediate (iVDPV) and longer-term (containment failure and bioterrorism) risks. The recommendation of the use of IPV for 10+ years encourages IPV suppliers to continue IPV supply in the pre and post eradication periods and this ensures the equal protection against the risks

of intentional or unintentional release of poliovirus in the long run. The WG also noted that there is not clear commitment by the donors to support IPV cost. If there is no external funding for IPV available, countries need to prioritize available resources for IPV over other pressing needs. Ideally, all countries would have access to IPV-containing hexavalent vaccine and willingness-to-pay for this vaccine out of their national budgets for use in their routine programmes.

- One WG member disagreed and indicated that existing economic analyses only support a recommendation to continue IPV immunization for minimum 5 years in all countries after the OPV withdrawal. The WG member noted that the long-term risks faced by countries will differ such that the relative benefits of IPV use would differ in the long-term (with relatively high-income countries benefitting more from IPV due to increased risks from iVDPVs and PEFs), and that application of a uniform recommendation does not account for the differences in risks, benefits, or the long-term willingness-to-pay for IPV. The WG member also emphasized the importance of considering the opportunity costs associated with requiring continued spending for long-term use of IPV given the cost-effectiveness and other competing investments in public health.
- The WG recommended that countries ensure optimal use of bOPV prior to bOPV withdrawal in order to ensure the highest possible population immunity against type 1 and 3 at the time of the withdrawal and asked the Secretariat to ensure that its bOPV SIA calendar and ordering for bOPV reflect this recommendation and to provide projections about OPV supply as OPV manufacturers make plans to sunset OPV production.

Summary and next steps for the SAGE Working Group

The results of the WG will be presented at the April SAGE meeting for further discussions. The Secretariat and WG will also prepare and complete “evidence to decision” tables for the review by the SAGE.
In addition, the WG will continue to provide technical oversight on major areas, such as:

- Progress towards elimination of WPV and cVPDV
- Polio vaccine supply issues (both IPV and OPV)
- Risk mitigation strategy before the OPV cessation (e.g. bOPV campaigns before the cessation, detection of iVDPV cases)
- Update on iVDPV epidemiology and development of antiviral drugs
- Remaining issues in future immunization policy