12-13 September 2017

14th Meeting of the SAGE Polio Working Group

Conclusions and recommendations

Note for the Record

World Health Organization

Background

The 14th face-to-face meeting of the SAGE Polio Working Group (WG) was held during 12-13 September 2017 at the World Health Organization HQ in Geneva, Switzerland.

The meeting was attended by the following WG members: Dr. Zulfiqar Bhutta, Dr. Peter Figueroa, Dr. Nick Grassly, Dr. T Jacob John, Dr. Elizabeth Miller, Dr. Jeffrey Mphahlele, Dr. Walter Orenstein, Dr. Kimberly Thompson, and Dr. K Zaman. Dr. Ilesh Jani, and Dr. Youngmee Jee joined over the phone. Dr. Walter Dowdle was unable to join.

Dr. Yagob Al-Mazrou chaired the meeting.

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

Context and objectives of the meeting

In preparation for the October 2017 SAGE meeting, the Polio WG meeting was for the following objectives:

1. To review the GPEI programme progress and update, including VDPV epidemiology and IPV supply situation
2. To develop a recommendation on the IPV catch-up campaign
3. To start discussion on "readiness criteria" for eventual bOPV withdrawal

Topic 1: GPEI programme update

The WG reviewed the 1) GPEI programme update, presented by Roland Sutter (WHO), and review of outbreak responses to VDPV type 2 events since the switch by Arshad Quddus (WHO), and 2) Risk assessment for bOPV cessation by Hil Lyons (IDM) and current planning for bOPV campaigns by Steve Wassilak (CDC).

Progress toward interruption of WPV1

The GPEI reported progress in the elimination of WPV in Afghanistan and Pakistan in the first half of 2017, with 4 WPV1 cases in Pakistan and 6 in Afghanistan (as of 6 September, 2017), which represent lower numbers than at the same time in 2016 (i.e. 13 cases in Pakistan and 7 cases in Afghanistan), but still not interruption of transmission. Despite the reductions in cases reported to date, in Pakistan there are still a number of environmental isolates (65 isolates as of 5 September 2017) and there is substantial (about 2%) genetic divergence between some of these isolates implying multiple ongoing chains of transmission.

In Nigeria, no WPV1 cases or isolates were detected in environmental surveillance since September 2016. The access in Borno State is improving, but still large parts of the state remain inaccessible, significantly affecting the quality of surveillance and Supplementary Immunization Activities (SIAs).

Emergence of VDPV2 after the OPV2 withdrawal and outbreak response

Since the tOPV-bOPV switch in April 2016, the Sabin viruses in most OPV-using countries disappeared as expected following the efforts to intensify population immunity to

transmission. After the switch, 40 VDPV2 were reported from all sources; 6 iVDPV2, 28 aVDPV2, and 6 pending classification. Excluding the iVDPVs and based on sequencing analysis, almost 50% (16/34) VDPV2 possibly emerged after switch. In addition, 6 post-switch cVDPV2 outbreaks occurred in four countries (i.e. Pakistan, Syria, Nigeria, and DRC), which falls within the range of the pre-switch estimates, but also demonstrates failure to sufficiently increase serotype 2 imunity through high quality SIAs prior to the switch. Most cVDPV2 cases were below 2 years of age in conflict affected areas or hard-to-reach population and either did not receive any OPV or were inadequately immunized. So far no international spread of cVDPV2 viruses has been documented.

The Advisory Group on the use of mOPV2 has reviewed and recommended to the Director General of WHO that mOPV2 be released from the Global Stockpile for all 6 outbreaks. 5 out of 6 outbreaks were reviewed within 3 days (except for Syria). mOPV2 has become available in the outbreak country within 7 days of DG authorization in 5/6 outbreaks (exception: Syria). First SIA took place within 14 days of confirmation of outbreak in 3/6 outbreaks (Delay in the two DRC outbreaks and in Syria).

In Pakistan, there was an outbreak in Quetta block in October 2016, responded to by two mOPV2 rounds in Quetta district, one mOPV2 round in surrounding districts, and one IPV round in the three districts of Quetta block. Following the SIAs, no cVDPV2 has been reported so far in 2017 (last isolate in Dec 2016).

In Nigeria, there were two separate cVDPV2 outbreaks; one in Borno (detected in environmental surveillance and in a WPV1 case contact) and second in Sokoto (environment and AFP case). There were three SIAs with mOPV2. The lot quality assurance sampling (LQAS) indicated that most Local Government Areas (LGAs) have achieved the target (90%) coverage in the areas evaluated. However, this may not represent all polio-infected areas due to inaccessibility, in Borno.

In DRC, there were two separate cVDPV2 outbreaks in Haut Lomami and Maniema detected in 2017. The outbreaks were responded to with two rounds of mOPV2 and one target mop-up completed. The quality of the second round (about 90% of lots accepted in LQAS) was better than the first round (about 70% of lots accepted) in LQAS.

In Syria, the first case onset was on 3 March 2017 (22 nt difference) with a total of 39 cases and 31 contacts positive for cVDPV2 as of 11 September 2017. Two rounds of mOPV2 were completed in Deir Ez-Zor and one round in Raqqa governorates respectively, under very complex security and conflict situations. The independent monitoring by Red Crescent indicated overall good quality of SIAs in Deir Ez-Zor (coverage >88%). IPV is being used in the SIA in the outbreak zone and also for vulnerable populations in Northen Syria, Turkey and Lebanon.

Pakistan and Nigeria did not report any VDPV2 outbreak related virus yet, following the mOPV2+IPV outbreak response.

Risk assessment for bOPV cessation and planned bOPV campaigns

The WG reviewed an analysis by IDM on VDPV 1 and 3 risks after bOPV is withdrawn and the need for additional bOPV campaigns prior to the withdrawal. Previously, IDM predicted that the risk of cVDPV 1 and 3 emergence at the time of bOPV cessation should be relatively lower (0.5/year) than cVDPV2 (2.6/year), with high immunity against VDPV type 1 and 3, and the use of bOPV and IPV in routine immunization schedules. However, the literature on past experience suggests the paralytic burden may be higher for type 1 than type 2 once reverted. An analysis by Kid Risk (presented at the October 2016 meeting), suggests similar cVDPV risks for types 1 and 2 and highlights that the dynamic risks depend on population immunity to transmission at the time of bOPV cessation, which depends on routine immunization (RI) coverage and SIAs conducted between now and bOPV cessation.

The GPEI Supplemental Immunization Activities Options Task Team (SIAOTT), in part based on the work of the GPEI Risk Assessment Task Team (RATT) and IDM, developed four SIA options for bOPV SIAs, focusing on countries with weak routine immunization systems and substantial subnational susceptible populations. These options have different levels of maintenance SIAs and additional pre-cessation SIAs, with costs of 1.0-1.3 billion USD for the period 2018-2021. Most of the cost is due to currently endemic countries with placeholder SIA generated separately from RATT/IDM estimates. These SIA options are subject to continued modification.

The task team concluded that risk of cVDPV1 or cVDPV3 is relatively low at present due to biological properties and high population immunity, but will increase if population immunity declines, with countries with weak routine immunization systems/subnational susceptible populations representing particularly critical areas. In the context of GPEI ramp down and priority to trim expenditures, the question remains as to the appropriate maintenance level of SIAs up to bOPV cessation to prevent cVDPV outbreaks up to and after bOPV cessation.

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 14 September 2017, 29 countries reported the designation of 94 Poliovirus Essential Facilities (PEF), which plan to retain infectious and potentially infectious poliovirus materials after OPV cessation.

Transition planning

The program update included mention of the polio transition and the likely serious programmatic impact of GPEI ramp-down. Many streams of work are ongoing, including country-level transition, independent monitoring and high level awareness raising, post-certification strategy development and transition planning (at WHO, UNICEF, CDC). WHO established a team to facilitate the transition work.

WG decisions/recommendations

- The WG expressed concern over the continued WPV transmission in Pakistan and Afghanistan, manifested by the continued widespread detection of genetically

divergent WPV in AFP, healthy children and environmental samples. The WG concluded that the GPEI must urgently intensify its vaccination activities especially focusing on identifying and improving coverage in populations with low immunity to get over the threshold for herd immunity as soon as possible and sustain this high level of population immunity in all areas through to bOPV cessation. The WG noted the deteriorating security situations in some parts of Pakistan (e.g. Baluchistan, FATA) and Afghanistan, and urged the programme to carefully monitor and address it. The WG emphasized the importance of quality of the supervision, monitoring and evaluation in all areas, and particularly those with recent virus circulation. Lastly, the WG encouraged the programme to continue employing innovative operational measures to reach individuals in inaccessible areas.

- In the context of declining population immunity against type 2, the WG highlighted its previous recommendation that countries with co-circulation of WPV and cVDPV2 should administer at least 2 doses of mOPV2 before the next bOPV round.
- The WG acknowledged the progress towards controlling the cVDPV2 outbreak in Syria but noted serious access and security issues which must be overcome to rapidly interrupt circulation of cVDPV2 in this area.
- Considering the risk assessment of types 1 and 3 and the discussion of planned bOPV SIAs, the WG reaffirmed its previous (October 2016) recommendation that GPEI should maintain high population immunity against types 1 and 3, especially in high risk countries and sub-national high risk populations, until bOPV cessation.
- The GPEI should monitor the changes in geopolitical situation and address decline in population immunity among distressed and challenged populations.
- The WG emphasized the importance of achieving and sustaining high quality surveillance and data management through and beyond bOPV cessation.

Topic 2: Introduction of IPV in the routine immunization

The WG reviewed the IPV and OPV supply situation presented by Ian Lewis (UNICEF) and implementation of IPV in routine immunization presented by Tracey Goodman (WHO).

IPV and OPV supply situations

Currently, all tier 1 and 2 countries continue to receive IPV supply. However, in some countries, the IPV supply to the private sector is also affected since the tOPV-bOPV switch. Moreover, there are 36 tier 3 & 4 countries that are not currently receiving IPV.

- 19 countries have not introduced IPV due to the supply situation.
- 17 countries that had introduced IPV with their supply through UNICEF but have experienced IPV stock-outs since April 2016 because the available IPV doses were prioritized for the tier 1 & 2 countries.

The IPV stand-alone supply available to UNICEF is expected to stabilize in 2018 but still be constrained. Both of the manufacturers are offering realistic projections on supply availability for 2018 consistent with actual quantities they have supplied in the recent past. All 36 countries without access to IPV, will have access to IPV to introduce IPV into their routine immunization in 2018, which should allow them to either restart immunization or introduce IPV into their Expanded Programme on Immunization (EPI) during the first half of 2018. In addition, 2 million doses will be set aside for outbreak response in 2018.

The GPEI planned to secure 300M, 519M and 300M doses of mOPV1, 2 and 3 respectively for the stockpile. As of today, GPEI maintains full amount for types 1 and 3, and about half (250M doses) for type 2 in bulk. The Vaccine Supply Task Team under the Eradication and Outbreak Management Group (EOMG) met in September and reviewed the GPEI stockpiles.

Lastly, the WG also reviewed the bOPV supply situations. While offered and awarded quantities meet forecasted demand including buffers, there remain risks to supply, including 1) Risks of additional market exits of manufacturers, 2) Usual risks related to production of biologicals, 3) Risks of demand reductions due to the GPEI budget pressures, which could lead to earlier departure of manufacturers and potentially insufficient bOPV supplies up through bOPV cessation, and 4) Risks of cold chain constraints. GPEI (esp. UNICEF) will continue close monitoring and ensure suppliers meet their commitments to the accepted awards. Some WG members pointed out that financial risks now appear to present a threat to the program, and discussed concerns about the concept of any attempts to stretch the GPEI budget (i.e., do less with less) to compensate for the failures to stop transmission to date.

Implementation of IPV in routine immunization

To date, 4 countries have decided to move to fIPV in their routine immunization programs (India, Sri Lanka, Bangladesh & Nepal). Recently, the PAHO TAG recommended 14 countries to implement a 2 fractional dose sequential schedule (these countries represent 6% of global birth cohort), and, of those, Colombia, Nicaragua, Honduras, Ecuador, Cuba, & El Salvador will start preparations in Q4 2017. WHO is actively following up with countries in other regions (AFRO, EMRO) for introduction of fIPV in their routine immunization.

In many countries, IPV coverage has achieved a similar level as DTP3 coverage, but the performance has been variable.

In April 2017, SAGE recommended a review of the tier classification with respect to prioritization of IPV allocation. The review incorporates the size of the population with no IPV protection and the recent VDPV2 events. Imperial College developed a concept note related to the risk of a VDPV2 outbreak in all tier 3 and 4 countries based on known risk factors (e.g. estimated country-specific serotype 2 immunity in children under 3 years old, movement of people from infected areas, iVDPV reports) and suggested allocating IPV supply priorities accordingly.

In Oct 2016, SAGE recommended that when sufficient supplies of IPV become available, countries with delayed IPV introduction or stock-outs should catch-up children who did not receive IPV in RI. Currently, about 25 million children have been missed in countries denied access to IPV (i.e., delayed introductions and stock-outs as of Sept 2017). However, due to the available and projected supply, insufficient IPV doses are available to begin these catch-up activities. IPV supplies will likely increase to support some catch up in mid-2018, and sufficient supplies are likely to be available such that full catch-up of the 1 full IPV dose could become available during 2019. The GPEI requested guidance from the WG related to prioritization of the available IPV doses for catch up.

WG decisions/recommendations

- The WG expressed concern that significant populations still do not have access to IPV, and welcomed the forecast that all countries will have access to IPV to include a single full dose or 2 fractional doses of IPV in their routine immunization programs in 2018.
- The WG endorsed the proposed approach to prioritize IPV allocation for the IPV introduction in tier 3 and 4 countries, based on the presented risk ranking. The WG recommended further revision of concept note and risk assessment as more information becomes available and if the GPEI wants to use the risk assessment to address other topics.
- Due to the supply constraints, the WG agreed that low-risk bOPV-using countries may currently adopt two fIPV, but not two full doses, with the first dose at or after 14 weeks, and the second dose at least 4 months after the first dose. In such cases, countries should continue bOPV in their routine schedule.
- The WG reaffirmed the previous SAGE recommendation that countries should provide catch up doses. The WG recommended that countries should provide one full dose or two fIPV doses for children in countries which delayed the introduction of IPV or had stock out due to supply shortage as soon as supply becomes available, with the following guidelines
    - IPV supply for catch-up should be allocated based on risk and readiness
    - The decision on whether to provide catch up via routine or campaign should be made based on the cost and expected increase in coverage.

Topic 3: Discussion on future immunization policy

IPV supply and demand forecast

The WG reviewed the updated forecast of global IPV demand and supply. After the certification of WPV types 1 and 3 eradication (expected in 2021-22), a two full-dose IPV schedule could be implemented in all OPV-using countries. The current estimate is that the demand for the two dose schedule (about 240M if all countries adopt two full doses and about 200M if some countries adopt a fractional dose IPV schedule) is likely to be met in 2021-2022.

Development of antiviral drugs

The WG reviewed the progress of antiviral development. To date, the Polio Antivirals Initiative (PAI) identified two potential candidates including Pocapavir and V-7404 with the best antiviral properties of all compounds evaluated to date. Pocapavir completed a multi-arm placebo controlled mOPV1 challenge study in 2013, demonstrating a significant reduction in the duration and magnitude of virus excretion. However, there was also evidence of treatment emergent drug resistance observed in the study. Pocapavir is currently being used to treat NPEV and poliovirus infected patients on a compassionate use basis. Two immune deficient poliovirus excretors have been treated. One patient stopped excreting after 2 days of treatment and the other patient stopped excreting susceptible virus after 2 days but continues to excrete resistant virus at last follow up.
For V-7404, Pfizer completed Phase 1 single ascending dose with a conventional tablet formulation, demonstrating good tolerance but low and variable plasma concentrations.

ViroDefense is optimizing an oral spray dried drug formulation and preparing a dossier for IND submission to the FDA in Q1 2018. ViroDefense is optimizing the formulation of the combination product (Pocapavir and V-7404 called ViroD7000) and is expecting to complete the studies necessary to begin patient treatment with ViroD7000 in late 2019.

Readiness criteria for full OPV withdrawal

Previously, SAGE defined the trigger point and readiness criteria for OPV2 withdrawal (October 2014). The trigger point was absence of persistent cVDPV2 and readiness criteria included:

- introduction of at least one dose of IPV vaccine in all countries;
- licensure of bOPV for routine immunization;
- establishment of a global stockpile of mOPV2 vaccine and protocols for its use;
- appropriate containment and handling of poliovirus type 2 infectious and potentially infectious materials;
- verification of eradication of wild poliovirus type 2 globally.

While some of these criteria were met, others were not met (e.g. IPV introduction in all countries, absence of persistent cVDPV2). The GPEI presented a first pass at some assumptions that would underlie bOPV withdrawal, including consideration of:

- Poliovirus type 2 (Sabin 2, VDPV2, cVDPV2) elimination (i.e., demonstrated ability to successfully stop serotype 2 OPV);
- Ability to perform surveillance to look for iVPDVs (e.g., Primary Immunodeficiency Deficiencies (PIDs) surveillance) established in high risk countries);
- iVDPV2 burden is minimized outside industrialized world;
- Certification quality surveillance has been established in areas that are currently not accessible (parts of Nigeria, Somalia, Afghanistan, etc.).

The WHO Secretariat proposed the following trigger and three readiness criteria for full OPV withdrawal (i.e., bOPV cessation)

- Trigger: Wild poliovirus serotypes 1 and 3 eradication certified by GCC
- Readiness criteria
    - Adequate population immunity, especially in high-risk communities
    - No poliovirus type 2 outside of containment
    - No persistent cVDPV1 or 3 circulation (circulation beyond the six months after the first notification)
    - Availability of sufficient IPV supply for all countries to adopt two IPV dose schedule (either IM or ID)

The WG agreed in principle that we may need to revisit readiness for bOPV withdrawal separate to withdrawal of all OPV as there could be a situation following certification of WPV1 and 3 and cVDPV1 and 3 where withdrawal of bOPV1 and 3 would be justified though certification of cVDPV2 was not yet assured and use of mOPV2 was still needed.

WG decisions/recommendations

- The WG emphasized the need for continued funding for both bOPV and IPV in routine immunization and SIAs to ensure sufficient population immunity before and after the certification.
- The WG endorsed the concept of developing trigger and readiness criteria for bOPV withdrawal. It proposes to continue the discussion over the next 12-18 months. For the next WG meeting, it requested the Secretariat to
    - revise the trigger and readiness criteria, based on the WG discussions and inputs from stakeholders
    - summarize the risk assessment and surveillance quality in different countries
- The WG acknowledged the progress in the development of antiviral drugs, and encouraged the PAI to implement the proposed development plan, especially with the combination drug product (ViroD7000).

Topic 4: Resource requirements

Long-term funding policy for IPV

The WG also reviewed the future funding policy for IPV. In June 2017, Gavi's Board approved extending Gavi's support from 2018 through 2020, under the arrangements approved by Nov-13 Board and subject to polio-specific funding being available. Overall IPV cost is estimated to be US$ 195 – 250 million for 2019-20 with approximately US$ 90 million available in estimated unused funds and an additional donor pledge. GPEI is working on fundraising to cover the funding gap, however, uncertainty remains about IPV price since the tender is still out.

After 2020, the Gavi Board will discuss continued support for IPV post-eradication as part of the Vaccine Investment Strategy (VIS) discussion in 2018. GPEI and Gavi will continue to investigate potential funding modalities for IPV.

WG decisions/recommendations

- In the context of the polio endgame and post certification strategy, the WG emphasized the importance of securing adequate financial resources at national and international levels to sustain essential functions, such as polio vaccine stockpiles, surveillance, outbreak response and SIAs.

Summary and next steps for the SAGE Working Group

The conclusions from the WG will be presented at the October SAGE meeting for further discussions. In the future, the WG will continue to review and 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
- Progress towards the final OPV withdrawal