12th Consultation with OPV/IPV Manufacturers and National Regulatory Authorities

Note for the Record
Welcome and Introduction

The Polio Endgame 2013-2018

Bruce Aylward (ADG/Polio Emergencies and Country Collaboration)

Type 2 wild poliovirus was eradicated in 1999. Between 2000-2011, the main efforts of the Polio Eradication Initiative were focused in four countries: India, Pakistan, Nigeria, and Afghanistan. However, in 2011, the wild poliovirus transmission was interrupted. One of the key developments that led to the progress in India was the development of bOPV. The development and deployment of bOPV was the result of a collaboration between Manufacturers, NRAs, and the GPEI. Since 2010, type 3 wild poliovirus has declined globally. Furthermore, type 3 hasn’t been detected since November 2012 (11 months ago). However, since 2000, 14 countries have reported cases type 2 vaccine-derived polioviruses. In 2008, the WHA passed a resolution stating that following eradication of wild poliovirus, the use of live poliovirus vaccine would have to stop. However, due to the increasing risks of type-2 vaccine outbreaks, in 2012 the WHA passed a resolution calling for a new endgame plan built around sequential OPV cessation that would begin with the withdrawal of OPV2. Additionally, in 2013, a key study was published in the NEJM that demonstrated that a single-fractional dose (1/5th of a full dose) of IPV seroconverted 47% and primed 94% of infants against type 2 when IPV was administered intradermal. This evidence for a viable affordable IPV option was a critical component of the polio endgame. In November 2012, SAGE recommended that all countries introduce a single dose of IPV into their routine immunization program.

The purpose of IPV introduction is to reduce the risk of type-2 outbreaks following OPV-2 cessation by: (1) preventing polio if exposed to a VDPV2 or WPV2, (2) improving the response to mOPV2 in an outbreak, (3) reducing transmission of a reintroduced type 2, and (4) boosting
immunity to WPV1&3. The goal of polio eradication of polio is to complete the eradication of all wild, vaccine-derived, and Sabin polioviruses. The biggest difference between previous polio plans of action and the polio endgame strategy is the plans for IPV introduction, OPV2 withdrawal, and routine immunization strengthening. The current timeline of the endgame is to complete eradication by the end of 2014, withdrawal OPV in April 2016, and complete certification in 2018. It was emphasized that OPV2 cessation is not dependent on wild virus interruption. Once the pre-requisites for OPV2 cessation are in place OPV2 will be withdrawn even if wild poliovirus still has not be eradicated. Currently, 124 countries only use OPV in their routine immunization schedules, 73 of which are GAVI eligible and will receive support from GAVI.

There are three major implications of the polio endgame for manufacturers: (1) robust mOPV1, bOPV, and tOPV supply will be needed until 2018, (2) the label on bOPV must be changed to allow for routine use, and (3) low-cost IPV is needed for low-income settings. It is possible that the demand for mOPV1 will increase in the near future to accelerate eradication in the endemic countries. Additionally, in the short term (next 2 years) the program will likely use whole-dose intramuscularly delivered IPV, however after this initial period the GPEI will transition to more affordable IPV options that meet the target price of $0.50-$0.60.

In summary, a continued supply of current OPV products will be needed over the next six years, and the exact mix will depend on the wild virus epidemiology. Collaboration to achieve registration of products needed for OPV2 cessation is necessary (bOPV and IPV).

**Session: OPV requirements for Eradication**

**Polio Eradication: Progress & Risks, SIAs and Vaccine Demand**

Hamid Jafari (Director, Polio Operations and Research, WHO)

During 2013, significant progress in reducing the number of wild poliovirus cases occurred in endemic countries. In particular, there are three major accomplishments: (1) no type 3 wild poliovirus has been detected since November 2012 globally, (2) there has been a 40% decline in endemic virus, and (3) no endemic transmission in Afghanistan has been observed since November 2013 (only importations from Pakistan). However, there has been significant international transmission including the ongoing outbreak in the Horn of Africa (Somalia, Kenya Ethiopia, and South Sudan) and detection of wild polio virus in the sewage in Egypt and Israel (no paralytic cases). Despite the progress, some challenges remain in endemic countries. In some areas of Pakistan with ongoing insecurity and gaps in SIA quality, it is estimated that 300,000 children have been missed. Additionally, in Waziristan a ban on vaccination has resulted in approximately 260,000 unvaccinated children. In Nigeria, insecurity and military operations have halted SIAs in some regions and it is estimated that 500,000-1,000,000 were missed as a result. In May 2013, a polio outbreak was confirmed in Somalia. The immediate response to this outbreak was rapid and aggressive. Due to this aggressive response, there is initial epidemiological evidence that the outbreak has peaked in accessible areas and it is on the decline. In Israel, a wild poliovirus has been circulating in the sewage since February 2013. Israel has high IPV coverage, but does not use OPV in the routine immunization schedule. As a result the population lack mucosal immunity. Finally, there are two regions reporting ongoing transmission of a type-2 VDPV. One is circulating in the border regions of Chad, Cameroon, and Nigeria and a second outbreak is occurring in Pakistan. To prepare for the tOPV-bOPV switch, the program is aiming to stop transmission of all VDPV2s by the end of 2014, and tOPV campaigns will be needed in the areas of ongoing circulation.
The major risks which jeopardize the completion of polio eradication are: (1) the inaccessible children living around the world (~2 million), (2) the ongoing insecurity and attacks on health care workers, (3) gaps in campaign quality, and (4) delayed and slow SIA response to wild poliovirus. The GPEI evaluates the risk of an outbreak in non-endemic areas based on the extent of the immunity gap and the risk of importation. Based on these considerations, the highest risk areas are: the Horn of Africa, Afghanistan, Syria, Lebanon, Jordan, Iraq, and Central Africa.

Every year the program has used more OPV than it originally forecasts. Supplementary immunization Activities (SIAs) continue to be the main strategy of the GPEI to manage risks in the highest risk areas. The program is also increasingly using short interval additional dose rounds to rapidly raise population in previously inaccessible areas where there are large numbers of naïve children. In 2013, there was very high demand for bOPV, high demand for tOPV for SIAs, a reduced demand for mOPV1, and an expansion of target age groups. In the next year, intensive SIA activities are planned to stop the transmission of WPV. In 2015-2016, a consolidation phase will take place with additional SIA activity. The primary vaccines for SIAs will be bOPV and tOPV, but there will also be some targeted use of mOPV1. The tOPV demand will be especially high in 2015 to boost population immunity prior to the tOPV-bOPV switch. In the short term, it is likely there will be demand fluctuations between bOPV and tOPV depending on the epidemiological situation. To reduce the uncertainty and risk surrounding the tOPV-bOPV switch, WHO will communicate with manufacturers about the progress and timeline of the switch.

Overview of OPV Supply: current status and looking forward
Meredith Shirey (Chief, Vaccine Center, UNICEF Supply Division)

Historically, there has been a strong interdependence between program strategies, epidemiology, and the OPV supply chain. At the beginning of 2013, there was a tight supply of OPV. The needs of endemic countries were met, however some high-risk countries had to modify their plans (smaller target groups or change in vaccine) because of the limited supply. For example, detection of wild virus in Israel and Gaza has triggered an international response of campaigns in Syria and Jordan. This increase in demand has led to the need to prioritize SIAs within available supply. This demonstrates the domino effect that results after the detection of wild virus. Also, one draw back of the tight supply is the inability to build sufficient buffer stocks. Securing buffer stocks are important in order to anticipate and rapidly respond to outbreaks.

In 2013, Nigeria and Pakistan received the most vaccine (almost 500 and 300 million doses respectively). One challenge in meeting the demand was that only a limited number of suppliers were licensed in both countries. The demand generated by the Horn of Africa outbreak also led to extremely short lead times for a sustained response. UNICEF recognizes the difficulty this poses for manufacturers, and thanked them for their work. Over the past few years there has been limited demand for mOPV1, and as a result limited quantities are available. But the demand has increased and mOPV1 is expected to be used in outbreak control.

The demand for 2014 is projected to be similar to 2013, although it might be slightly higher. The demand will be very high in the beginning of 2014 because the GPEI is planning a high number of SIAs for the low season. Supply availability during the first half will be tight and cumulative availability decreases by the end of 2014 but we expect to award additional quantities to meet this expected increased demand.

It was requested that manufactures maximize filing in 2014 and accelerate production for Q1 of 2014. In the mid-term, manufactures need to continue bulk production to ensure sufficient
supply to meet continued high global SIA demand. bOPV needs to be registered in all OPV using countries, and multiple suppliers need to be registered in large countries to ensure flexible supply. In the future, a strategy needs to be developed for operationalizing the switch both upstream and downstream.

Session 1: Discussion

It was noted that in addition to the currently available data from the CDC trial in Bangladesh, there are also ongoing clinical trials that will provide immunogenicity data on the immunogenicity of bOPV when used in the routine immunization schedule with IPV. Additionally, extensive data from post-marketing reporting have not revealed any safety issues to date associated with the use of bOPV.

It was clarified that in the context of global IPV introduction, the global IPV demand over the next two years will grown to approximately 100 million doses. However, if IPV is introduced in small inaccessible areas, this demand will be relative small (1-2 million doses) as it will be specifically used in areas with limited access and large pools of unvaccinated children.

Session 3: IPV and the Polio Endgame

IPV Introduction and Status

Michel Zaffran (Coordinator, Expanded Programme on Immunization, IVB, WHO)

Currently there are 124 countries using only OPV, and 1 countries has officially announced they will introduce IPV beginning next year (Albania). The Immunization Systems Management Group (IMG) is an coordinating body that is responsible for overseeing and coordinating partners efforts for the introduction of IPV, the withdrawal of OPV2 and the strengthening of routine immunization in focus countries.

There are five different work streams being managed by the IMG: IPV implementation, regulatory issues, financing, communications, and routine immunization strengthening. The IMG has created a joint-work plan to guide and coordinate the activities of all partner organizations, including WHO, UNICEF, CDC and GAVI. The objective of the implementation group is to ensure all OPV using countries have access to information, technical and financial support to introduce IPV and switch from tOPV to bOPV. In order to prioritize countries for technical support, countries have been segmented according to four risk tiers. Due to the large body of work required to introduce a vaccine into 124 countries, the IMG will prioritize technical support to countries most at risk of a type 2 vaccine derived poliovirus outbreaks in the post OPV2-cession era. Another critical part of IPV introduction is assuring that an IPV standalone product in the desirable presentation is licensed in every country. Given the complexity of the polio endgame, accurately communicating around IPV introduction is also a significant challenge. In order to facilitate communication, the WHO and UNICEF have developed technical documents (Frequently Asked Questions) and a website (insert) to help share information with key stakeholders on IPV introduction. A budget has been developed for the introduction costs of IPV and includes the cost of the vaccine, introduction grants, GPEI subsidies, technical support and partner costs. The total cost is initially estimated to be $328-$449 million USD. One challenges in IPV introduction is that in order to introduce in the next two years, countries must make rapid decisions about when and how to introduce IPV into their national routine immunization programme. Price clarity will be crucial in assisting countries make decisions as soon as possible. Another challenge is the delay that might occur between when a country
decides to introduce the vaccine and when they will actually be able to introduce. This will depend on multiple factors, including availability of affordable IPV, licensing of IPV, and system readiness and staff training.

Preliminary demand forecasts were generated at the global level to estimate IPV demand in the next five years. The demand estimates will be updated monthly and are expected to become more refined as more information becomes available on countries decision to introduce IPV. In November 2013, the Strategic Advisory Group of Experts (SAGE) on immunization will recommend at what age the single dose of IPV dose should be administered.

The Role of the GAVI in IPV Introduction
Melissa Malhame (GAVI Alliance)
GAVI has historically focused on improving access to new and underused vaccines in the world’s poorest countries. GAVI’s current portfolio includes mostly routine vaccines (pentavalent, pneumococcal, etc.), campaign vaccines (yellow fever, meningococcal A, measles, act.), and stockpiled vaccines used for outbreak response. IPV would be added to the existing routine vaccines portfolio. Normally, after GAVI makes a decision to support a vaccine, the organization opens an application window and accepts proposals for support. The proposal is then reviewed by the GAVI secretariat, an independent committee, and the GAVI Board.

During its June 2013 meeting, the GAVI board decided to support the GAVI playing a leading role in the introduction of IPV in the 73 GAVI eligible countries. This new partnership of GAVI and GPEI is includes the alignment of the GAVI CEO and WHO ADG and implementation through subgroups supported by both organizations.

In November 2013, the GAVI board will make a decision on opening a funding window for IPV and on possible exceptions to the GAVI policies to support that introduction. The three main possible exceptions are related to eligibility and graduation, co-financing, and prioritization. The possible exceptions include: the inclusion of all graduating countries, no immunization cover filter of 70% DTP3, and no co-financing requirement. A supply and procurement roadmap was jointly developed by GAVI, WHO, BMGF, and UNICEF. The roadmap outlines the market landscape, the supply and procurement strategy, target outcomes, and the joint stakeholder action plan. The roadmap demonstrates the supply is likely to meet demand in almost all scenarios, and it also considered the potential possibility of an IPV-containing hexavalent in the future.

IPV Regulatory Implications
Roland Sutter (Coordinator, Research and Product Development, Polio, WHO)
The first priority of IPV introduction is to have at least one IPV product registered where required. After this, the next priority is to have two stand-alone products registered, especially in large countries that make up a significant portion of the international demand. There are currently four classifications for regulatory requirements: (1) countries that accept pre-qualified vaccine which is almost always procured through the UN system, (2) countries which implement an expedited procedure for the registration of pre-qualified vaccine, (3) full national registration led by the national regulatory authority, and (4) countries where the typical regulatory pathway is unknown. Of the top 47 highest priority countries for IPV introduction, the large majority of the either accept pre-qualified vaccine or implement the WHO expedited procedure. In a limited number of countries (approximately six) full national registration will be required. In other countries, the regulatory pathway needs to be clarified as soon as possible.

In summary, WHO and partners are working to assure IPV registration by the required time. However, the currently available registration information is incomplete and sometimes
inaccurate. WHO encourages manufacturers and NRAs to share and update registration data with WHO as soon as possible in order to clarify the procedure. Also, one of WHO’s priorities is strengthening NRAs and when possible, WHO encourages countries to use the expedited procedure for IPV. Manufacturers should also do their best to expedite the registration of IPV where required. Finally, NRAs are requested to prioritize the review of IPV dossiers in their countries. WHO is ready to provide support to all partners when needed.

bOPV Regulatory Implications
Jaqueline Fournier-Caruana (Prequalification, WHO)

Currently there are six pre-qualified bOPV products (including bulks and fillers). The current indication for bOPV use is that bOPV can be used for supplementary immunization activities or outbreak control. However, for routine immunization, tOPV remains the vaccine recommended by the WHO. To define the Regulatory pathway and requirements for use of bOPV in routine immunization, in July 2013 WHO invited key NRAs to define the regulatory pathway and requirements for the label change.

At the consultation, the participants concluded that a variation to the current dossier to the national license would be the appropriate and that a non-inferiority study demonstrating the seroprotection of bOPV in the routine schedule would be sufficient for the label change. A clinical trial was recently completed by the CDC in Bangladesh comparing the immunogenicity of bOPV and tOPV in the recommended infant schedule. The results showed that the protection of bOPV against polio 1 & 3 was not inferior to the protection induced by tOPV. The data were shared with the NRAs and clearly supported the change. The clinical trial report is being shared with the manufacturer and the Belgium authority to support the label change. In the future, the WHO plans on making this data available to all bOPV manufacturers to submit to their NRA to support the label change for other bOPV. In addition to the available data from Bangladesh, additional data are being collected in other studies including a study in India and Pakistan. The challenging timeline of the bOPV switch requires a strong collaboration between WHO, partners, manufacturers, and NRAs.

UNICEF IPV Tender Process
Meredith Shirey (Chief, Vaccine Center, UNICEF Supply Division)

UNICEF issued a multi-year tender for IPV on 4 October 2013. The purpose of the recently released IPV tender is to support the Polio Endgame Strategy with the introduction of IPV into all OPV-using countries procuring through UNICEF by end of 2015 and to provide longer-term visibility to manufacturers to support supply planning and pricing objectives. This will require flexibility to meet unprecedented introduction goals. The request of the tender is based on the timeline of the endgame. The three objectives are to secure supply, to achieve affordable prices, and to develop a healthy IPV market. This is a multi-year tender for 2014-2017/2018 for GAVI and non-GAVI countries. There was a request for proposal to allow for comprehensive offers from manufacturers. The RFP requests stand-alone IPV with a preference for 5 dose vials, but invites offers for alternative presentations and products, including IPV dose-sparing products, IPV-combination productions, and sabin-based IPV. The tender forecast is based on a sub-set of the 124 OPV using countries and excludes PAHO member states. The tender forecast does include demand for middle-income countries with an analysis of likelihood of coming through UNICEF for their supply. The initial estimated procurement forecast is for 428 million doses during the full tender period. Some uncertainties in the current demand forecast include: wastage rate for a 5 dose vial, country requests for more than 1 dose of IPV, DTP3 coverage, and others. Because of the frequently changing information, UNICEF will provide quarterly updates
Final

to Proposers on demand. A more detailed explanation of the tender will be given at the special tender meeting taking place the day following this consultation (October 11th), where the technical details of the tender will be discussed. All interested parties are encouraged to attend.

Session 3 Discussion
The Belgium NRA confirmed that they are currently reviewing the clinical trial data which would support the use of bOPV in a routine immunization program. It was recognized that all decisions will be made by national regulatory authorities in each respective manufacturers country. It was also noted that WHO considers that there is no added value to repeat clinical trials with bOPV for each specific product because bOPV has been shown to be equivalent. Stability data should be sufficient to demonstrate equivalence. Because of the shortened timeline, there is a major benefit to avoiding this repetition.

It was also noted that there would be no need for a label to approve of the simultaneous use of OPV with IPV or to allow for a single dose to be used. Specifications on schedules are based on recommendations from the relevant advisory body. In this situation, the relevant body is the Strategic Advisory Group of Experts or SAGE is the global advisory body.

Session 4: Research and Product Development for the Endgame
Development of Affordable IPV
Roland Sutter (WHO)

The GPEI target of affordable IPV is $0.50-0.60 per immunizing dose. Another goal of the GPEI is to develop alternative intradermal delivery technologies for house-to-house campaigns which would be used for outbreak response in the post-eradication era. Three options are being pursued to achieve affordable IPV including adjuvanted IPV, intradermal administration of a fractional dose of IPV, and process optimization of IPV.

The WHO has clarified the intradermal IPV regulatory pathway and is conducting clinical trials to hopefully support the label change. However, the currently available technique for intradermal injections is difficult and presents significant operational issues. For this reason, new intradermal technologies are being developed in a step-wise approach. The first option is to use currently available needle adapters. These are devices attached to syringes that help health care works with the difficult mantoux technique. Another option is a needle-free jet injector. These devices are likely to be available in the mid-term and includes devices such as Pharmajet and Bioject. The final technology being developed is microneedle patches. The advantages of microneedle patches are no need for health care workers, improved heat stability, no sharp wastage, affordable cost, and GMP material available in the short term.

A secondary goal is to develop a safe production procedure for IPV which especially does not use wild poliovirus. The three safer IPV options being developed are: sabin-IPV, further attenuated alternate IPV strains, and non-infectious Virus-like particles. This also includes developing further attenuated IPV strains to enable safer production. In the far future, a non-infectious vaccine would be the most preferred.

Sabin-IPV clinical Trials
Wilfried Bakker (Intravacc: Institute for Translational Vaccinology)

Intravacc is collaborating with the WHO to develop a novel IPV based on the attenuated Sabin-strains (siPV). They have produced 3 master seed lots, 3 working seed lots, 6 monovalent pools, 2 pre-clinical final lots, and 6 clinical final lots. Three clinical studies have been done
including two trials in Poland (in adults, and in infants) and one in Cuba (in adults). Based on rat studies, a target dosage was selected (10-16-32 D-antigen units per single human dose, for type 1, 2, and 3, respectively) and the clinical study in infants included the target dosage plus a higher and lower dosage. A dose-escalation study was performed in infants. The results showed that Sabin-IPV and adjuvanted Sabin-IPV are well-tolerated and immunogenic. Titers induced by Sabin-IPV are more effective in neutralizing against Sabin strains, but are still sufficiently high enough to also be protective (reciprocal serum dilution titer of 8, or log₂ (titer) = 3) against wild-type strains. Process optimization is taking place in a lab-scale model in order to further prove the economic benefits of Sabin-IPV. The final product will be co-developed by Intravacc and the local manufacturers to select the final antigen content.

Closing Remarks

WHO and UNICEF thanked the national regulatory authorities and manufacturers for their vital collaboration and contribution to the polio eradication initiative. In conclusion, the demand for both bOPV and tOPV are increasing. It was emphasized that immunity against type-2 needs to be built in vulnerable communities before OPV 2 cessation using tOPV. The most complex issue is that the demand for tOPV will continue to increase until right before the switch at which point the demand will decrease to zero globally. It was highlighted that the synchronized withdrawal of OPV2 will be an inter-governmental decision, not a simple programmatic decision by the GPEI. Also, type 2 cessation will move forward regardless of wild virus eradication (these activities are independent and being pursued in parallel). The first IPV pilot is expected to occur in Kenya in December. The partnership between GPEI and GAVI was recognized as key in successfully completing the endgame. The label change and registration of bOPV is critical. The GPEI will provide the clinical trial data which manufacturers can then share with their respective NRA to get the license. Additionally, based on discussions with low-income countries, the GPEI strongly feels that affordable IPV is defined as $0.50-$0.60 price. Therefore, further work will be done to accelerate development of intradermal and adjuvanted IPV. GAP III is still the framework for managing containment going forward. However, due to the slightly modified timelines due to the phased withdrawal of OPV type 2, GAP III will be modified to adapt to the timelines of the Polio Eradication Endgame. WHO understands that the endgame presents uncertainty and risk from a manufacturer’s perspective. WHO and UNICEF will do their best to inform manufacturers 18 months minimum before the switch and give lead times on programmatic vaccine needs.