



**World Health
Organization**



Conference Summary

10th WHO/UNICEF Consultation with OPV/IPV Manufacturers and NRA's
27 October 2011
Geneva, WHO/HQ, Kofi A. Annan Room, UNAIDS Building

Jointly Hosted by the World Health Organization and UNICEF
Chaired by Dr R. Bruce Aylward,
Assistant Director-General of Polio, Emergencies, and Country Collaboration (PEC)

Conference Purposes and Goals

- To update manufacturers and National Regulatory Authorities (NRA's) on the latest progress and new strategic plan of the Global Polio Eradication Initiative (GPEI), and the implications for OPV demand globally
- To inform manufacturers on UNICEF polio vaccine tender plans, including for new products such as bivalent OPV (bOPV1&3)
- To bring manufacturers and NRA's up-to-date on post-eradication risks and the status and outcomes of the ongoing research to inform the development of appropriate policies and products for managing these risks
- To share and discuss the new developments in the elaboration of pre and post-eradication IPV policy, particularly the status of the deliberations of the SAGE Polio Working group
- To strengthen existing collaboration between manufactures and NRA's involved in the Global Polio Eradication Initiative

Welcome Opening

Dr Bruce Aylward greeted the participants and shared the following 3 main objectives of the conference:

1. To share the progress made towards eradication and the GPEI's priorities over the next 2-3 years
2. To share the OPV requirements and demands in the short and medium-term over the next 5 years
3. To look ahead to what will happen as we finish eradication and move into the post-eradication era; what this will mean for vaccine policy; and how it will translate to products needed in the post-eradication era

After a tour de table of all participants, Dr Aylward addressed the following changes to the agenda:

- Dr Aylward would give two presentations: the first would update the group on the current priorities and the progress made towards polio eradication, and the second would cover rethinking the polio endgame and what that entails.

Vaccine Supply for Eradication Activities

Polio Eradication: Progress, Priorities and OPV Requirements

Dr R. Bruce Aylward, ADG PEC

Over the past year, by scaling up the use of bOPV, instituting independent monitoring (IM), and aggressively limiting the international spread of polio, the GPEI has progressed towards its goal. Although India, Pakistan, Afghanistan, and Nigeria remain endemic for wild polio virus, India has gone for more than 9 months without a wild-type case and Northern Nigeria has seen a drop of 95% in cases over 24 months. In addition, South Sudan has gone more than 24 months with no polio, Angola's Luanda virus has been silent for more than 9 months, and the introduction of bOPV has led to a sustained drop in type 3 transmission through 2011.

One on-going problem is that viruses from endemic countries circulate to other countries, causing reinfection. Wild type virus from Pakistan, for instance, has led to outbreaks in China and Afghanistan, and outbreaks along country borders remain problematic. cVDPV2 in Nigeria is another concern, as are persistent outbreaks in countries like Chad, which have required additional staffing. These outbreaks and epidemics have implications for vaccine use. bOPV is in very high demand, and there is a sustained high demand for tOPV for routine vaccinations and in campaigns. Demand for mOPV has decreased, but it can still be used for outbreaks in polio-free areas to rapidly rebuild population immunity. In addition, expanded use of short-interval additional dose strategies (SIADs) shortens the time between mOPV and bOPV campaigns, changing the pattern of how vaccine quantity is required.

The next steps are to apply the key lessons learned from places like India, to improve campaign quality and increase surveillance. By increasing staffing, completing LQAS monitoring, and ensuring revaccination of all areas with less than 90% coverage, we can improve OPV campaign quality; and this in turn will affect OPV requirements. We assume that wild type transmission in Pakistan and Afghanistan will continue into 2014, maintaining the need for vaccine and campaigns. bOPV and tOPV remain the primary vaccines for mass immunization campaigns, but limited mOPV1 for outbreak response will still be important, indicating a need for an mOPV stockpile. Globally, OPV requirements will see an overall decrease from through 2016, but we will see an increase in the short-term, between 2012 and 2013.

UNICEF Supply Update for OPV

Mr Ian Lewis, Contracts Officer, UNICEF

A key objective for UNICEF procurement of OPV is that a sustained and uninterrupted supply of OPV of assured quality is available at a price that is affordable to both donors & Governments and will cover manufacturers' costs.. UNICEF and WHO believe this is achieved through a continued dialog with vaccine manufacturers and information sharing on strategic and programmatic decisions. This year, UNICEF will procure over 1.4 billion doses of OPV to deliver to 75 countries. In the long-term, UNICEF expects to procure over 92% of what is in contract for 2012.

The OPV supply and demand through December 2012 was reflected on slides 10 & 11. The aim is for the OPV availability not to go below 20 million doses. This would allow the Programme enough vaccine to respond to any unplanned demand or new outbreak. The OPV availability is very tight through the first quarter of 2012 and will require close co-ordination with WHO to ensure vaccine is available to meeting all critical activities. UNICEF is concerned that only one product is licensed in the endemic countries, and is working with manufacturers to get vaccine licensed in these countries. There is no planned demand for mOPV3, and the demand for mOPV1 is in response to outbreaks.

A pre-tender meeting with the industry and partners is planned for January/February, and UNICEF intends to issue tender awards at the end of June. For IPV tender plans, UNICEF expects to issue tender for 500,000 doses in the first quarter and to prepare a tender strategy for endgame IPV use based on programmatic recommendations. This strategy might include a switch from tOPV to bOPV for routine immunization, and should include the use of IPV in the endgame strategy and how IPV might affect the demand for OPV.

A New Strategy for the "Polio Endgame"?

Dr Bruce Aylward, ADG PEC

The "Polio Endgame" is defined as the management of the post-eradication risks due to OPV. In 2008, the GPEI decided on a parallel approach to the risk management of OPV cessation; a decision driven by three recent developments: new diagnostics, new bOPV, and new, inexpensive IPV options. New diagnostics suggest that type 2 cVDPV is going to be the biggest post-eradication problem; new bOPV provides a viable option to replace tOPV; and new IPV options have the potential to prime or immunize against type 2 if we stop using OPV containing type 2. Three principles guide the new polio endgame strategy: perform a phased removal of Sabin viruses, beginning with high risk type 2; follow by eliminating VDPV type 2 by switching from tOPV to bOPV for both routine and campaign immunizations; and finish by introducing IPV early in areas of high-risk for VDPVs to provide type 2 protection. Rather than waiting for 0 cases and then ceasing OPV all at once, it is better to complete wild type eradication and certification/containment, while simultaneously bringing forward VDPV2 elimination and validation, and following with post-OPV surveillance. It is essential, however, not to distract from wild type virus eradication efforts. This new strategy will mean that vaccine manufacturers should scale up IPV production, build up ID administration, and develop hexavalent options for the post-eradication era.

Dr Aylward then posed some questions to the group for consideration. Can Nigeria stop cVDPV2? They have adjusted their campaigns to use more tOPV in the upcoming months in order to address this issue. What program milestones must be passed in order to manage a tOPV to bOPV switch? In sub-Saharan Africa, we have to accomplish the switch in multiple countries. How complex will it be to restart tOPV after a switch has been made (in the case of an urgent need)? What do manufacturers need in order to scale up their IPV

capacity? It might be good for manufacturers to do an early introduction in Northern Nigeria and Pakistan first, and then scale up globally. Overall, depending on the OPV price and strategy, the new endgame could be cost-neutral, particularly through intradermal use, and it is essential to develop work streams to address any unresolved questions. As always, regulators also play an important role in pursuing this new strategy.

Post-Eradication Policy and Product Development

Preparation for New Polio “Endgame”: Research and Product Development Needs ***Dr Roland Sutter, Program Coordinator, WHO***

Dr Sutter presented the benefits of approaching the endgame strategy with parallel rather than sequential risk management. There are 3 main implications for this new strategy: first, introduce IPV in priority areas with the highest cVDPV risk; second, switch from tOPV to bOPV in a globally synchronized manner as early as April 2013; third, for outbreak control, use IPV, mOPV2, or restart a tOPV option. Licensure of bOPV in all self-producing countries, labelling changes to permit fractional dosage of IPV, and use of needle-free devices for ID administration are all required elements for achieving success with this strategy.

Given the success of expanded OPV use and its global impact on type 3 virus, WHO wants to help self-producing countries achieve licensure of bOPV and encourages further clinical trials to determine why bOPV is so effective and what the effects of a four-dose administration schedule would be. Concerning IPV, finding an affordable IPV strategy relies on reducing the number and amount of dose, enacting label changes to include ID delivery, and effecting policy changes allowing IPV as a supplement to OPV in SIAs. Data showing non-inferiority of fractional vs. full dose is also needed. In addition, the development and implementation of ID needle-free devices for use in developing countries is very important, as is gaining regulatory approval required by NRA's and the prequalification by the WHO for these devices. A study is planned for Cuba in 2012 to investigate immunogenicity of 1 dose IPV followed by 2 dose OPV (mimicking how it would be used in the future).

Regulatory Approaches to bOPV ***Dr Jacqueline Fournier-Caruana, Scientist, WHO***

Dr Fournier-Caruana reminded the participants on the ACPE recommendations in 2007, which included a recommendation by the advisory committee to assess bOPV in a clinical trial and look at seroconversion after bOPV use. The approach was different from that used for mOPVs because there was less information available on bOPV, and the goal was to provide a programmatic advantage by adding bOPV. The WHO recommended that seroconversion from bOPV should be at least equivalent to mOPVs and better than tOPV. A clinical trial in India was then completed, following compilation of a clinical expert report by Pr Peter Folb, completion of a vaccine safety risk assessment, and determination of prequalification requirements.

The conclusions of the trial were very clear: good seroconversion was seen after bOPV use. There was a clear superiority of bOPV to tOPV after 2 doses of vaccine given at birth and 30 days after. ACPE concluded that bOPV constituted an important tool for routine immunization and SIAs as a complement to the use of tOPV and mOPV. An expedited regulatory approach was then used for the licensing of bOPV that includes 3-6 month real-time stability data. Licensure was granted by NRA's and the WHO implemented prequalification (PQ) standards. Currently 7 manufacturers have prequalified bOPV, and Novartis is expected to join in mid-November. Through a common effort by all partners, it is possible to accelerate the NRA licensure and PQ in a short period of time; for now, there is no foreseeable need to revise the formulation, and the WHO encourages the implementation of a strong national post-marketing surveillance system.

Update on Activities of the SAGE Polio Working Group ***Dr Rudi Tangermann, Medical Officer, WHO***

The SAGE Polio Vaccine Working Group (WG) was established in 2008, and was charged with developing a unified position paper on routine OPV and IPV polio vaccination in the pre-eradication era, developing policy guidance on routine IPV use in the post-eradication era, and assessing the utility and feasibility of replacing tOPV with bOPV for routine vaccination pre-eradication. Planning for the polio eradication 'endgame' has been, until recently, based on the sequential management of the main elements of the polio

eradication timeline and 'endgame', i.e. wild poliovirus eradication, followed by certification of eradication and containment, then OPV cessation, elimination of VDPVs and eventual validation of cVDPV elimination. The timeline for such an 'endgame strategy' could be as much as 10 years after certification of WPV eradication. However, recent developments in VDPV diagnostics, the availability of bivalent OPV and the confirmation of more affordable IPV strategies, allow the consideration of a new strategic approach to the endgame that could be more efficient and effective by managing key VDPV risks earlier and in parallel with the eradication of residual WPVs. At their last meeting, the WG concluded that the main rationale for stopping OPV2 pre-eradication was that wild poliovirus type 2 (WPV2) had been eliminated for more than 10 years, and circulating vaccine-derived poliovirus type 2 (cVDPV2) accounted for >80% of all cVDPV cases; also, an estimated 40% of all cases of vaccine-associated paralytic poliomyelitis (VAPP) were due to type 2 vaccine virus.

The WG also identified several important requirements to ensure the success of the GPEI's new strategy. First, we need a formal validation process confirming the absence of WPV2; second, the tOPV to bOPV switch should only occur after all ongoing cVDPV2 outbreaks are controlled, with documented capacity to detect and control such outbreaks everywhere within 6 months; and third, sufficient vaccine bOPV should be available for routine immunization, as well as stockpiles of appropriate type-2-containing vaccines for responding to possible VDPV2 outbreaks. The WG noted that WHO considers that the tOPV to bOPV switch will be programmatically easier than stopping all OPV at once, as previously planned; however, a global consensus is required, and countries will need to coordinate on either a globally synchronized switch or a step-wise phasing out of tOPV. Concerning IPV policy considerations for the post-eradication era, the WG noted that new data will soon be available on what impact IPV could have on VDPV emergence.

IPV Affordability and Availability

Mr Graegar Smith and Mr Ron Bellamy, Oliver Wyman

Given recent development milestones - such as the progression of Sabin IPV programs, successful field trials of ID stand-alone IPV, and advancement of some novel Salk IPV adjuvanted formulations - Oliver Wyman was asked by the Bill and Melinda Gates Foundation to update their prior work characterizing global IPV supply and affordability. This analysis resulted in the following macro-observations.

Significant momentum is building around Sabin-based IPV with many programs focused on full-dose standalone products. At least 5 manufacturer programs are already underway and at least 5 more are interested in pursuing Sabin. While further behind in development, several of these are also pursuing reduced dosage programs and combination products.

A fair amount of activity is also underway surrounding Salk-based product. 4 manufacturers already have established pre-qualified products and 2 are continuing to explore options to develop an affordable hexavalent combination. In addition, ID strategies are beginning to gain traction with several field studies showing promising results with 1/5 dosage levels.

While full dose Salk and Sabin products are relatively expensive to manufacture at \$0.50 - \$1.00 / dose, reduced dosage products can potentially achieve costs below \$0.25 / dose. Amongst these, Salk ID is expected to support the fastest development timeline and product could be ready prior to the expected transition from trivalent to bivalent OPV.

Despite these promising options, further action and investment may be required to ensure that the cost and development targets outlined above are met.

For Sabin-based products there are 5 areas that may require action:

1. Not all programs are fully optimizing their products and manufacturing processes to ensure the lowest possible costs
2. Given uncertainty surrounding final product profiles and manufacturing process efficiencies, there is a risk of oversupply, underutilization, and ultimately higher costs
3. While several manufacturers are focused on adjuvants, none are currently pursuing ID
4. Several manufacturers developing Sabin products lack access to the lowest cost Penta antigens,

- limiting ability to develop the lowest cost Hexa products
5. To help reduce development risks, manufacturers are prioritizing standalone over combinations which is in turn delaying the time-to-market for Hexa products

Similarly, there are 5 areas that may require action for Salk-based products:

1. Long-term, affordable production of, or access to, Salk is highly uncertain for some manufacturer segments
2. Manufacturer interest in adjuvanted and ID strategies has been historically limited
3. There is no established regulatory pathway to follow for IPV ID product
4. IPV demand alone may be insufficient to reach the required scale to drive low device costs and justify device developer economics
5. Most manufacturers are not pursuing both lowest cost Penta antigens and reduced dosage IPV critical to an affordable Hexa

Since this effort was conducted the broader public health community has taken strides to address a number of these open questions. For example, the RIVM / WHO Sabin program has a plan and funding in place to make optimized processes available to tech. transfer recipients and new interest in ID product strategies is being generated amongst key manufacturers. By continuing with these types of efforts the community can ensure that IPV costs and availability will be sufficient to play a key role in global polio eradication.

Post-Eradication Policy and Product Development

Sabin-IPV Development and Optimization

Dr Wilfried Bakker, Project Leader, RIVM

RIVM presented the progress they have made in their Sabin-IPV project. By completing multivariate data analysis of Salk-IPV production and additional lab-scale research, RIVM created a scale-down model for future process improvements and set the initial process specifications for large scale Sabin-IPV production. The Sabin-IPV immune response in rats, expressed in wild-type virus neutralization titres, was shown and compared to that using Salk-IPV. Sabin-IPV was shown to reach comparable virus neutralization titres. The same levels could be reached faster with the addition of an alum adjuvant. Although type 2 Sabin-IPV product shows a slightly different dose response curve when compared with Salk IPV product, analysis shows that you can reach high neutralizing antibody titres with an increased dosage of Sabin type 2. RIVM is finalizing a WHO-sponsored Phase I clinical study in adults in Poland, and is planning for studies in infants based on the Dutch MEB advice from July 2008 that Sabin-IPV immunogenicity and safety should be equivalent or better than that for Salk-IPV.

In addition, work on optimization of the process and the product is being conducted at lab-scale. From process optimization studies, RIVM identified easy-to-implement improvements that bring the yields to comparable levels as that known for Salk-IPV. These improvements included use of increased cell densities for virus replication, reduction of hold-up volumes in clarification filters, and alternative concentration procedures. In addition, after implementation of several modernizations that may go beyond currently used ranges for clinical lot production, such as improved column chromatography, significant further improvements in yields were shown. Also, the use of alternative adjuvants (e.g. VLPs, O/W emulsions, Aluminium salts, and LPS derivatives) was studied to show opportunities for dose sparing. For example, it was shown that using immunostimulating particles increased the immune response to Sabin-IPV type 2 by 11x. The creation of a technology transfer program with hands-on and theoretical courses allows for RIVM to share these developments with their potential partners, who now include LG Life Sciences and Panacea Biotec.

Safety and Immunogenicity of Sabin-IPV on Monkey

Dr Thi Luan Le, Deputy Director, POLYVAC

Due to the continued existence of vaccine-associated paralytic poliomyelitis and cVDPV at the end stage of polio eradication, there is a need to produce inactivated poliovirus vaccine (IPV). The Center for Research and Production of Vaccines and Biologicals in Vietnam developed IPV on attenuated Sabin strains and

conducted preclinical trials in young *Macaca mulatta* monkeys in May 2011. Monkeys were immunized with S-IPV, and observed for weight, temperature, diarrhea. Neutralizing antibody titration was determined, and symptoms and immunogenicity of the monkeys was assessed. The results of the preclinical trials demonstrate that S-IPV is safe for use in monkeys: for a total of 20 monkeys, the mean weight increased and there was no incidence of fever or death. Also, a trend of dose range effect was observed, with high D-antigen units resulting in higher immune response.

Although virulent strains are traditionally used for production of conventional IPV, POLYVAC chose to develop S-IPV because it reduces concern over biosafety for the environment and manufacturers using large amounts of live virus, and because production of Sabin bulks can be used for both OPV and IPV. Reports have shown that S-IPV type 1 has higher efficacy than V-IPV type 1 for protection, but that S-IPV type 2&3 are less effective. By adding AIOH3 for high-capacity production, types 2&3 can, however, be reduced to only 10 units in order to confer immunity.

Strategic Assessment of Delivery Technologies for IPV
Dr Darin Zehrung, Portfolio Leader, PATH

PATH recognizes that the transition from OPV to IPV is an essential step in the polio eradication effort. To accelerate this transition, key stakeholders must buy-in on an agreed up strategy, but there must also be minimal disruption to current OPV campaign practices and costs. Certain unknowns concerning timing of OPV to IPV transition, IPV demand, and IPV use in different scenarios, mean that there is no single delivery technology that meets all of the complex needs and vaccine development variables. PATH completed a strategic assessment of a total of 39 different IPV delivery technologies, to include intradermal (ID) delivery for use in both campaigns and routine vaccinations (Please refer to Mr Zehrung's presentation for detailed descriptions of possible devices).

PATH estimates that many of the devices available short-term, pre-OPV cessation will be ready for research beginning in 2012 and for manufacturers after 2014. These devices include both needle-free (disposable syringe jet injectors) and needle based technologies. For long-term devices, vaccine reformulation will be needed beginning in 2012, with other technologies becoming available after 2017. Additionally, clinical and regulatory processes for ID delivery of IPV are required prior to introduction of ID IPV using any delivery device. Overall, for short-term IPV use (pre-OPV cessation), PATH recommends an advancement in the ID delivery of IPV, which involves IPV demand modelling, evaluating human factors and supply logistics, manufacturing scale-up devices for use, conducting clinical and programmatic studies with new devices, working with vaccine manufacturers and WHO on vaccine relabeling and/or off-label use, and implementing a pilot introduction to fully demonstrate the application of one or more ID capable technologies. In the long-term, PATH recommends investing in easy-to-deliver stand alone IPV formulations, such as oral gel and micro-needle patches, and promoting the development of IPV combination vaccines.

An Intra-dermal Jet Injector for Public Health Immunization
Dr Michael Royals, Head of Global Applications Development, PharmaJet

Dr Royals focused on the Tropis, a new ID device currently in development, which has a reduced risk of cross contamination. Many of the Tropis' specifications were driven by the PQS standards, and the device will be submitted to WHO for PQ when complete. Dr Royals also discussed the importance of FDA clearance, which helps to "demystify" the process of ID use, for promoting these devices for immunization campaigns, particularly for the GPEI project. One issue jet injectors currently face arose from the FDA's permitted use of ID devices for Influenza vaccines. Without consulting the industry, the FDA made an announcement that vaccine could not be given with ID devices, and this demonstrates a continued need for dialogue between agencies on the use of needle-free devices.

Development of New Needle-free Devices
Dr Richard Stout, Executive Vice President, Chief Medical Officer, Bioject

The standard ID delivery device forces vaccine through different layers of tissue based on the strength of injection and can be powered with gas or springs. The spring powered Zetajet device has proven intradermal delivery in pig and human models, and the Biojector needle-free ID injection resulted in painless IV

catheterization. Bioject ID devices have a history of no adverse events, no ulceration of skin, no bruising, and enhanced immunogenicity against Malaria, Measles, HIV, Influenza, etc., even in the elderly and young children. Bioject's products are made of metallic alloy and polycarbonate, tested at 50% over failure rate, and the noise levels are low. The disposables have passed all toxicity tests, showing there should be no reactions or interactions with the syringe, and the specially treated glass will hold up to high pressure. Overall, Dr Stout says that vaccines can be given safely in a simple and easy to use device, and when given intradermally, they can be more immunogenic.

Wrap Up

Dr Aylward thanked the participants on behalf of WHO and UNICEF for the productive discussion around endgame issues and for the manufacturers' valuable perspectives. The GPEI wishes to design a program that will work for everyone and hopes to work collaboratively to provide manufacturers with all the information necessary to make commercial decisions and to navigate regulatory issues.

Dr Aylward restated the potential for IPV tender in the hopefully near future, and that the next landmark in the eradication timeline will be the upcoming SAGE Working Group discussions and the potential agreement on a phase removal of vaccines rather than complete cessation. Because this strategy has clear implications for manufacturers, the WHO hopes to have information to provide the manufacturers with as soon as possible. Following the SAGE deliberations, the Executive Board of WHO will meet in January. SAGE will then meet again in April, at which time they will provide their suggestions on the required number of doses and on a universal vs. a high-risk only approach. Dr Aylward suggests that a universal plan with at least one dose is the direction in which the strategy will go and the GPEI will keep all conference participants abreast of future discussions.