9th WHO/UNICEF CONSULTATION WITH OPV/IPV MANUFACTURERS AND NRA's
2 December 2010, GENEVA, WHO/HQ

Summary

The meeting was jointly hosted by WHO and UNICEF and chaired by Dr Bruce Aylward, Director of the Global Polio Eradication Initiative (GPEI). Its purpose was multiple:

- To update manufacturers and National Regulatory Authorities (NRA's) on the latest progress and new strategic plan of the Global Polio Eradication Initiative;

- To inform manufacturers on UNICEF polio vaccine tender plans, including for new products such as bivalent OPV (bOPV);

- To bring manufacturers and NRA's up-to-date on post-eradication risk assessment and the ongoing research and programme of work to develop appropriate policies and products for managing these risks (including new developments in the elaboration of pre and post-eradication IPV policy); and

- To strengthen existing collaboration between manufacturers and NRA's involved in the Global Polio Eradication Initiative.

After a short introduction of all participants (list of participants enclosed), the agenda was presented and approved.

1. B. Aylward presented the strategic plan 2010-2012 launched in June and described the new lessons, tactics and tools. In December 2009, bOPV 1&3 has been introduced in Afghanistan and since this time more than 600 million doses have been used in endemic countries. Four countries currently have endemic polio due to co-circulation of polio types 1 and 3 – Northern Nigeria, Afghanistan, Pakistan and India (Bihar and Western Uttar Pradesh). Tremendous progress has been reported in India and Nigeria where the number of cases has never been so low. Seroprevalence studies in India have demonstrated a very high immunization coverage while the number of genetic clusters of viruses circulating in Africa has been reduced to four. In Afghanistan and Pakistan, despite a multi-pronged approach in place and strong political support, progress was compromised by high insecurity in Afghanistan and floods in Pakistan. The vaccine demand is extremely high since countries are aware of the risks if they decrease the immunization rounds. Among other risks, a gap in AFP surveillance remains the biggest challenge and explosive outbreaks in Tajikistan and Congo have shown the difficulty to sustain eradication in polio free areas. The real challenge is to finish the job and priorities are given to the immunization of migrant population, aggressive mop ups and environmental surveillance. Thanks to the huge effort of all partners, strong advocacy made by the DG and the regional Directors, there is a big opportunity to finish the job in India and Nigeria. The funding gap of about 810 million USD out of 2.6 billion is an additional challenge to close.

2. The audience was updated by J. Fournier-Caruana on the current status of licensing and prequalification of mOPVs and bOPV. To date 6 mOPV1, 3 mOPV3 and 4 bOPV1&3 have been prequalified and licensed in countries where the products are manufactured and then in areas where they are used in mass campaign. Additional mOPV1, mOPV2 (for stockpile), mOPV3 and bOPV are in the pipeline and should be prequalified in 2011. Process for the revision of the current PQ procedure was presented with a final endorsement by the Executive Board expected in May 2011. The new procedure will go into force shortly after.
3. Detailed projections have been made of the demand on all OPV types over the period 2011-2015 (C. Maher), based on planned activities and epidemiology. These projections will be reviewed every six months. They do not include stockpiling. Trends of 2010 demand were clearly a very high demand of bOPV, high demand of tOPV, continued demand of mOPV1 and decline in the need of mOPV3. Same trends are expected for the period 2011-2015. Comparison between estimation made in October 2009 and December 2010 demonstrates an higher demand. It is understood that there will be fluctuations on a yearly basis depending upon programmatic and epidemiological changes.

4. UNICEF undertakes all OPV/IPV procurement with the overall objective of Vaccine Security (I. Lewis). The best way to achieve uninterrupted and sustainable supply of affordable and quality vaccines is by engaging and keeping manufacturers informed of programmatic strategies and changes and vaccine requirements for polio eradication activities. As an important component to Vaccine Security, vaccine costs are closely monitored with awards reflecting any unjustifiable prices increases. Lower weighted average prices contribute to a significant savings to countries and the GPEI.

In 2010 (YTD), UNICEF has procured over 1.9 billion doses OPV, with value of $279 m, for delivery to 70 countries for routine immunization and SIAs (~90% of procurement has been to for SIAs).

Availability of tOPV and bOPV should be tight but manageable throughout the first half of 2011. Any changes in availability from manufacturers or unplanned/changes in demand for SIAs will have a significant effect on overall availability of tOPV and bOPV. No major risk with the demand of mOPVs.

For the Polio stockpile tender, an evaluation is ongoing. By mid 2011 UNICEF SD will revert to manufacturer with OPV type requirements for 2012. For IPV requirements, a tender is expected to be issued during first quarter for approx. 500,000 doses and additional IPV will be depending on programmatic requirements.

5. In June 2010, a WHO Position Paper on Polio Immunization was published (WER, vol. 85, 23 - pp 213-228) by the Strategic Advisory Group of Experts on immunization (SAGE). Main determinants for country decisions have been outlined and possible vaccination policies described. Beside the already recommended full OPV schedule, including birth dose, sequential IPV/OPV or IPV alone are also suggested, based on the potential for poliovirus importation and transmission of each country.

A comprehensive policy guidance on the use of IPV in the post-eradication era is also expected in April 2012 (R. Tangermann). Primary objectives of the post-eradication immunization strategies in low income countries will be: reduction of emergence and/or mitigation of the consequences of cVDPV, following WPV eradication and OPV cessation; maintenance of the reaction capability to wild polio re-introduction in case of biocontainment failure; achievement of the lowest acceptable costs of IPV. Four different approaches will be available to the Governments in the post-eradication era, from complete cessation of polio immunization to 1, 2 or 3-4 doses of IPV, in order to prime or to fully establish the population immunity.

For wild poliovirus containment, the use of Sabin-IPV production technology is recommended. Finally, it is underlined that wild PV2 is absent in the worldwide circulation since 1999, but serotype 2 is predominant in causing cVDPV outbreaks: for this reason SAGE requested IPV WG to review and provide opinion by April 2012 on feasibility of discontinuing routine use of type 2 OPV, replacing tOPV vaccinations with bOPV.

6. After interruption of wild poliovirus circulation, continued use of OPV would compromise the goal of a polio-free world; based on this consideration, the mandate from the 61st WHA (2008) was to develop appropriate strategies and products for managing risks in the post eradication era, including a) safer processes for IPV production and b) affordable strategies for its use (R. Sutter).

a) For a safer production process, Sabin-IPV development is envisaged, whose process optimization is now ongoing at NVI, as well as the exploration for use of alternate seed strains for future IPV or the evaluation of non-infectious approaches to IPV production (i.e. packaging cells
and capsid protein synthesis). To facilitate IPV production in developing countries a Sabin IPV technology transfer is programmed and the availability of Master Seeds lots needs to be guaranteed.

b) For an affordable IPV, four supplemental post-eradication strategies are proposed: reduction in the number of doses (1-2 versus 3-4 doses); reduction in the size of each dose (through the use of adjuvants or fractional doses); reduction in the antigen content per dose; and reduction in the cost of production (optimization of growth media, increase cell density, alternative inactivation methods). Needle-free devices for the administration of IPV have also been evaluated and collected data suggests the feasibility of this approach.

7. The global action plan for polio virus containment in the post-eradication era (GAP III) needs to focus not only on the containment of wild polioviruses and Sabin attenuated vaccine derived strains, but also on the possible development of novel polioviruses for vaccine production, i.e. any alternate seed strain with equivalent or greater attenuation than Sabin. Wide experts consultation will be arranged to achieve containment of these viruses, based on review of properties of the virus in comparison to wild and Sabin strains. After WPV eradication and OPV cessation, all polio viruses will need to be limited to essential facilities in a minimum number of countries (not more than 20); approved laboratories will need to be designed and managed properly (primary safeguards). To minimize the consequences of reintroduction of attenuated strains, dedicated facilities will be located in areas with high general population immunity (secondary safeguards); in case of wild poliovirus facilities, these will be located in areas with high standards of hygiene and sanitation including closed sewage systems (tertiary safeguards). In preparing GAP III, phase I surveys for WPV materials and annual update of global inventory of facilities with WPV materials is continuing as well as the preparation of phase II to establish national regulatory frameworks (C. Wolff).

8. OPV and IPV WHO Technical Report Series (TRS) will be soon revised (M. Baca-Estrada). Concerning OPV (TRS 904 Annex 1 and 910 Annex 1), a Working Group meeting with experts including Manufacturers and NRA’s has been held in July 2010. Major outcomes from this meeting will be published as a meeting report and will form the basis for the revision of the current WHO Recommendations (i.e. TRS 904 and 910). The following are some of the key outcomes of the meeting: Neurovirulence test performed on transgenic mice (TgmNVT) can be used to prepare working seed lot of virus (WSL) from an existing Master seed viral lot (MSL) if this test is already validated for lot release of a specific product in order to prove consistency of production; MAPREC for the 3 serotypes will be included with information on recommendations for maximal level of mutant content; it will be clarified that thermostability of OPV is a vaccine-specific characteristic and not a direct correlation with long-term stability; mOPV and bOPV will be also described; potency specification of OPV 3 will be updated. The structure of the new TRS will be more complex, including sections to address non clinical and clinical evaluation. The meeting report will be published early 2011 and the submission of the revised TRS to ECBS is expected for August 2011. Further discussions are needed to assess the comparability of TgmNVT and monkey NVT (MNVT) as well as to establish testing of Sabin WSL for sIPV (e.g. TgmNVT V’s MNVT). Workshops and proficiency studies are required to harmonize testing and one or few laboratories need to be identified to maintain MNVT expertise. Development of nonradioactive method for MAPREC test is also strongly encouraged. Future activities will also be undertaken to revise the WHO TRS 910 Annex 2 for IPV production processes and controls. The introduction of IPV based on Sabin strains (SIPV) or any new attenuated strains requires written standards on development (e.g. inactivation methods, formulation, reference material and assays) and clinical evaluation, Consultation with IPV experts will be organized in 2011/2012. Drs Tiequin Zhou and Jackie Fournier-Caruana will coordinate the revision of the WHO recommendations for both OPV and IPV/SIPV.

9. P.Belt (on the behalf of W. Bakker) from NVI reported the current status of Sabin IPV development. Facing the need of stopping OPV vaccination in the post-eradication era and with the awareness that traditional IPV production, using wild-type poliovirus strains, is not feasible in
developing countries because of containment risks, Sabin-IPV appears to be a feasible future strategy. Sabin strains are in fact currently used in developing countries to produce OPV and the risks related to unwanted release of polioviruses appear to be lower. Sabin IPV production process has been developed through down-scaling the process used for Salk-IPV. Sabin poliovirus Seed lots (Master and Working) of the 3 serotypes have been generated and culture conditions identified. Subsequently, 6 monovalent pools have been manufactured and tested. A formulation composition has been selected including aluminum hydroxide as adjuvant. Pre-clinical lots (both adjuvanted and non-adjuvanted) have been filled in April 2010 and phase I clinical trial is planned for Q1 2011. The next step will be the technology transfer to selected partners in the developing countries and the scaling up for local full size GMP production. In parallel possible process developments and/or optimizations (i.e. alternatives for inactivation, animal component free media, cultivation methods) will be explored.

10. The Institute of Medical Biology of the Chinese Academy of Medical Sciences (IMB CAMS-China) started the development of Sabin IPV in 1983. Production process and tests panel were derived from traditional Salk IPV production. A specific formulation for sIPV has been selected, based on immunogenicity and neutralization studies. 3 trivalent lots have been prepared from 9 monovalent pools and used in clinical trials. Phase I and II clinical studies have been completed in 2008 and 2010 indicating that no serious adverse reactions occurred with any of the dosages tested. Although it is recorded a light difference between the antigenicities of Sabin-IPV and wild viruses, results obtained are encouraging. Phase III clinical trials are predicted to start in Feb 2011.

B. Aylward underlined the concluding remarks of this meeting. A tremendous progress towards eradication has been obtained through SIAs, but vaccine demand will increase in the next future, being bOPV the most widely used. UNICEF will face again with a funding gap. Frequent update of information to manufacturers is needed to drive the global production; a balance in the use of bi-trivalent vaccines and monovalent vaccines already produced is important, not to lose a number of doses readily available. Before stopping OPV vaccination, in the post eradication era, WHO needs to have set up a good IPV alternative, and Sabin IPV is highly encouraged, mostly because of the good clinical results already obtained. It is recognized that the presence of Manufacturers committed in the production of this vaccine is of paramount importance and it will be necessary to find the way to share all the information with manufacturers and NRA's, as soon as they become available.