Tele-conference of the SAGE IPV Working Group, September 29, 2010
Draft minutes

1 - Participants:

SAGE working group members: Liz Miller (Chair, UK), Hyam Bashour (Syria), Walter Dowdle (US), Peter Figueroa (Jamaica), Walter Orenstein (US), Nick Grassly (UK), Antoine Kabore (Burkina Faso), Kimberly Thompson (US), Jacob John (India); Francis Nkrumah (Ghana) could not be reached due to technical problems.

WHO/HQ: Bruce Aylward, Roland Sutter, Hiro Okayasu, Chris Wolff, Rudi Tangermann (all polio eradication team); Philippe Duclos, Tracey Goodman, Raymond Hutubessy (IVB).

2 - Conference call objectives:

This conference call was held in order:

(a) to review the current status of preparations towards achieving the second WG 'deliverable', i.e. to provide SAGE with recommendations on post-eradication polio vaccination policy, by providing WG members with updates on relevant ongoing activities, including studies and meetings, which are expected to provide evidence which is relevant to the WG's recommendations;

(b) to consider, in view of the time needed to generate additional evidence for the final WG recommendations to SAGE on post-eradication polio vaccination policy, whether the target date schedule of April 2011 needs to be extended, and

(c) to agree on the content of an update of the group's activities to be provided to SAGE at their November 2010 meeting.

3 - Updates on major activities affecting the WG's Programme of Work

(a) Meeting of the Polio Research Committee in December in New Delhi

The GPEI's 'Polio Research Committee' (PRC) is expected to review progress in two ongoing areas of work with potentially important implications for the cost and feasibility of WG recommendations on IPV use post-certification. Hiro Okayasu, WHO explained that, first, there are four research groups (UCSF, CDC, and SUNY in the US and NIBSC in the UK) receiving PRC funding to develop alternate seed strains for IPV production. These groups use different approaches (high fidelity - UCSF, codon deoptimization - CDC & SUNY, and 'mutilated strains' - NIBSC). Glaxo Smith Kline (GSK) is already collaborating with NIBSC on evaluating the 'mutilated strains' approach and the Committee will review first
results of these evaluations (e.g. immunogenicity, genetic stability, production yield) at the Delhi meeting. Also, using a ‘non-infectious’ approach to IPV production, a group at SUNY is evaluating further a "packaging approach" where a cell system containing only part of the PV genome is used to support the replication of strains that lack the corresponding genetic information.

Secondly, pre-clinical studies in animals have now been completed at the Netherlands Vaccine Institute (NVI) for IPV production using Sabin-strain PV, and preparations for a phase I trial in 2011 have begun to evaluate safety in adults, children and infants and immunogenicity in infants. Results of phase I trials are expected to be available in 2011. In parallel, two developing country vaccine producers are being selected for the initial SABIN-IPV production technology transfer projects to low-cost production sites. Following the review of full proposals and site visits, WHO will finalize the selection in November 2010.

(b) Expert ‘State of the Art’ consultation on vaccine-derived polioviruses (VDPVs)

Bruce Aylward / WHO explained that the main objective for this meeting, tentatively planned for May or June 2011, is to conduct a comprehensive and detailed review of the current state of knowledge on VDPVs and their significance for the GPEI and post-eradication policy. The meeting will focus on both virological and epidemiological aspects, and explore policy and programmatic implications, in light of increasing knowledge on the risk circulating VDPV (cVDPV) emergence before and after the eradication of wild polioviruses.

In view of the importance of the post-eradication risks of cVDPV emergence, the discussions at this consultation are expected to generate particularly valuable evidence for the WG’s work to finalize post-eradication vaccination recommendations. Bruce Aylward proposed that the WG be invited to attend the VDPV meeting, and continue with its own WG meeting immediately afterwards (see suggested modification to the WGs activity timeline below).

(c) The ‘Global Action Plan III’ for laboratory containment of polioviruses

Chris Wolff (WHO/HQ) gave an update on the development of the third edition of the Global Action Plan for Laboratory Containment of Polioviruses (GAP III). GAP III will have major implications for the future of IPV production and thus for the feasibility and cost of WG recommendations. Under GAP III it is envisaged that, starting one year after wild poliovirus has last been isolated anywhere in the world, IPV production using wild type PV will be subject to full containment measures, including the primary, secondary and tertiary
safeguards described in the Plan, effectively precluding wild-type IPV production in developing countries. Under the GAP III requirements for SABIN virus containment, which would start at the time of cessation of OPV for routine immunization, IPV production using SABIN strains would be subjected to the primary and secondary containment safeguards. Chris Wolff further explained that a draft of GAP III would in October 2010 be published for a 6-month period of public comment; this will inform the finalization of this important document, with significant implications for IPV production and cost, in mid-2011.

(d) Timelines for relevant IPV research studies

Key ongoing IPV studies include a randomized controlled clinical trial in Cuba of fractional-dose vs. whole-dose IPV, given at 4 and 8 months of age, to evaluate the effect of a two-dose fractional-dose IPV schedule, and the priming effect of one dose. Sample collection for this trial is complete, and the results are expected to be available by Q4 2010. The second study which is expected to generate additional evidence for the WG is a polio mucosal immunity trial under planning in India. The objectives of this trial are:

(a) to assess the extent to which mucosal immunity following multiple doses of tOPV reduces poliovirus excretion among 3 age groups (10-11 mos, 5-6 yrs, and 10-11 yrs) of <1 to 11 year old children (baseline assessment); and

(b) to assess the mucosal immunity against poliovirus excretion among 1 to 11 yr old children following a dose of bOPV or IPV (boosting response). The study protocol is currently undergoing scientific and ethical review; study results are expected by Q2-Q3, 2011.

4 - Request by the Regional Director/WHO/EMRO to consider the implications of continued use of type-2-containing tOPV

The Regional Director, WHO Eastern Mediterranean Region, recently sent a communication on this issue to WHO/IVB, with possible implications for the WG's programme of work. In summary, in view of the absence of wild PV type 2, and of the predominance of type 2 cVDPVs among such outbreaks, the RD requested that SAGE consider whether trivalent OPV could be replaced with bOPV for routine polio vaccination, prior to the eradication of the remaining 2 wild poliovirus serotypes.

Philippe Duclos, WHO, explained that in his response, the Director/IVB had noted that the concept of stopping the use of type 2 vaccine, in advance of the two other serotypes, had

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1These safeguards are: primary - production only in appropriate biosafety level production site; secondary - routine polio vaccination, with >90% coverage nationally; tertiary - secondary sewage treatment.
been discussed in the past. However, it had been rejected at that time on grounds that the risks of discontinuing type-2 vaccination altogether would be too great as it was not deemed possible to selectively identify and subject all type 2 wild PVs and cVDPVs to full biocontainment in advance of switching to a bOPV. This situation was further complicated by the lack of a solution to the problem of chronic iVDPV excretors.

In discussing the issue, WG members noted that important questions were still open, particularly regarding how much type 2 wild and vaccine virus remained in research, diagnostic and vaccine production laboratories worldwide. K. Thompson noted that the selective discontinuation of type 2 OPV was an option that was already being considered in ongoing modeling work on policy options for the eventual cessation of all OPV use. Philippe Duclos and Bruce Aylward noted that the planned expert consultation on VDPVs will further explore the issues surrounding type 2 polioviruses, and suggested that the WG could consider further discussion of this issue at its next meeting (see below).

5) Other issues - report by OLIVER WYMAN INC. and discussion on QUIVER report

(a) OLIVER WYMAN report on IPV-containing combination vaccines

The WG had received the final report of the most recent BMGF-supported project on 'The supply landscape and economics of IPV-containing combination vaccines' conducted by the OLIVER WYMAN management consulting firm. The major finding of this report was that the potential exists for a significant improvement in the supply landscape and manufacturing economics of IPV-containing hexavalent vaccine combinations for low-income countries if manufacturers incorporated substantial changes to their production and/or formulation processes. In such a scenario, one or more manufacturers could potentially produce hexavalent IPV-containing combination vaccine in the range of the expected 'break-even' price for a pentavalent combination vaccine plus 'standalone' IPV. However, a number of substantial challenges would need to be overcome before such a product could actually become available, particularly at the desired price level and in large enough quantities.

(b) QUIVER discussion of post-eradication risk assessment modeling

R. Hutubessy summarized the main findings and recommendations of an end-2009 assessment, by the SAGE sub-committee QUIVER2, of the post-polio eradication risk assessment modeling work of K. Thompson and R. Tebbens (report provided to the WG before the conference call). QUIVER considered the modeling approach to be appropriate,
and noted that the work presented on modeling the risks of post-eradication polio outbreaks, the impact of vaccine interventions, and the associated costs, represented an impressive and comprehensive analysis.

The main recommendation from QUIVER was that, without prejudice to the work presented and given the important policy implications arising from it, an independent modeling approach by a separate group, using a comparative assessment, was desirable.

Model-specific recommendations included:

(a) for assessing the risks of emergence of cVDPVs, to incorporate a dynamic model of the emergence of cVDPV - QUIVER noted that this work was already in progress - and

(b) that a meta-population structure should be incorporated into the model, or an individual-based model developed; again, it was noted that efforts to modify and develop existing models accordingly were already underway.

Walt Orenstein noted that post-polio-eradication risk modeling work was already ongoing by a US group called ‘Intellectual Ventures’, which is supported by Mr Bill Gates (rather than the Bill & Melinda Gates Foundation). Kim Thompson had recently met with the group, at which time it was still in the process of formulating its main research questions. Liz Miller, Nick Grassly and Kim Thompson all supported the suggestion that the WG consider asking this group to address specific open questions with implications for post-eradication policy.

At a meeting with the group the following day, Walt Orenstein learned that the group anticipated having at least initial results on their modeling of VDPV emergence and post-eradication policy options in advance of mid-2011.

6) Main decisions and action points from this conference call

Liz Miller, chair of the WG, ended the telephone conference by obtaining the group's agreement on the following decisions and action points:

(a) Extending the time-line for development of post-eradication polio vaccination recommendations for SAGE. In view of the substantial number of relevant issues discussed on the conference call, the WG agreed that the original target of finalizing and presenting post-eradication polio vaccination recommendations to SAGE by April 2011 should now be extended to April 2012.

(b) Next ‘face-to-face’ meeting of the WG. There are two options for when the WG could (physically) meet next; a first option would be to have the WG meeting ‘back to back’ with the expert consultation on VDPVs, planned for May or June 2011 (i.e. the WG would first attend the consultation on VDPVs, and then conduct its own meeting), with at least one telephone conference in the interim. A second option would be to convene an earlier
meeting, in the 1st quarter of 2011, if the WG deemed it necessary. The Chair suggested that this could be reviewed and decided following the November 2010 SAGE meeting.

(c) **WG Presentation at the upcoming SAGE meeting (Nov. 2010).** The group agreed that the WG Chairperson should inform SAGE about the need to extend the time frame for finalizing the second WG 'deliverable' (and thus the period for which the WG serves), and give a short presentation with a synopsis of the relevant ongoing activities, research, and planned consultations which are expected to generate substantial additional evidence that could have important implications for the WG's remaining programme of work.

(d) **Endorsement of QUIVER recommendation for a second post-eradication risk modeling effort.** The WG endorsed the QUIVER recommendation for a second independent approach to model the post-eradication risks by a separate group conducting a comparative assessment to the important model developed by Thompson and Tebbens. The group noted that such an effort is already underway and requested to be kept up to date on the plans and activities of 'Intellectual Ventures'; in view of the importance of risk modeling for finalizing post-eradication polio vaccination policy recommendations, the WG requested WHO / other polio partners ascertain whether expert members of the WG can inter-act directly with 'Intellectual Ventures' on important questions to investigate with their model, as well as the underlying model and assumptions (e.g. N Grassly, K Thompson).

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**Suggested tentative timeline for SAGE IPV WG activities**

**SAGE meeting, November 9-12, 2010**
- Short presentation updating SAGE on the need to extend the timeline for finalizing recommendations on post-eradication polio vaccination policy, including a summary of ongoing research and planned consultations relevant for the WG's programme of work.

**1st quarter, 2011**
- February / March 2011: WG meets either directly or by telephone conference call before the April 2011 SAGE meeting

**May or June, 2011**
- WG attends global consultation on VDPVs, with WG meeting to follow immediately

**SAGE meeting, November 2011**
- Presentation of draft recommendations on post-eradication IPV vaccination policy

**SAGE meeting, April 2012**
- Presentation of final recommendations on post-eradication IPV vaccination options