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IMMUNIZATION PRACTICES ADVISORY COMMITTEE (IPAC)
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Final meeting report and recommendations

IPAC Members present:

Shelley Deeks (Chair)
Robin Biellik
Xavier Bosch-Capblanch
Jonathan S. Colton
Francois Gasse
Najwa Khuri-Bulos
Folake Kio-Olayinka
Sanath Lamabadusuriya
Christopher Morgan
Jean Marc Olivé
Jane Soepardi
Robert Steinglass

Opening and Introduction

Dr Shelley Deeks (chair) opened the meeting and welcomed Dr Jean-Marc Olivé, an independent consultant with over thirty years' experience in EPI, to his first meeting.

Session I. Updates from SAGE and Global Advisory Committee on Vaccine Safety (GAVSC)

A. Updates from SAGE meeting (*Shelley Deeks, IPAC*)

Dr Deeks updated the committee on the November 2011 and April 2012 SAGE meetings, with particular focus on the sessions regarding polio, pneumococcal disease, hepatitis A and influenza. Programmatic considerations of polio, influenza, and hepatitis A vaccine were discussed among IPAC members. WHO will conduct further internal discussions to determine whether an IPAC subgroup needs to be developed to consider programmatic implications of the polio end-game strategy.

B. Updates from Global Advisory Committee on Vaccine Safety (*Patrick Zuber, WHO HQ*)

Dr Zuber reported on the topics reviewed during the December 2011 GACVS meeting. These are reported in WER 2012, 87, 53-60 and include the initiation of the work on vaccine safety during pregnancy and lactation; update on pandemic A(H1N1)2009 influenza vaccines; update on the global network for AEFI monitoring; update on rotavirus vaccine safety; and launch of the Global Vaccine Safety (GVS) Initiative as the implementation mechanism of the Global Vaccine Safety Blueprint.

The GVS Initiative is a collaborative effort administered by WHO. A planning group composed of representatives from interested organizations has been established to steer the initiative. Its main focus, as advised by GACVS and SAGE is on enhancing vaccines safety monitoring in all countries.

Session II. Programmatic Implications of Rotavirus age-limitations

A. Rotavirus Update from Global Advisory Committee on Vaccine Safety (*Patrick Zuber, WHO HQ*)

With respect to current rotavirus vaccines, GACVS concluded that Rotarix and RotaTeq continue to exhibit a good safety profile, but may be associated with an increased (up to 6-fold) risk of intussusception after the first dose of vaccine in some populations. The levels of risk observed are substantially less than those observed with the previous vaccine, Rotashield. The benefits of rotavirus vaccination without age restriction would greatly exceed the risks, particularly in developing countries with moderate and high mortality from rotavirus disease. Finally, active surveillance of intussusception in countries that plan to introduce rotavirus vaccines should be seriously considered.

B. Feedback from WHO Ad-Hoc Expert Consultation on Optimising Rotavirus Vaccines (RV) Schedules (*Najwa Khuri-Bulos, IPAC*)

Dr Najwa Khuri Bulos updated IPAC on the key conclusions of the consultation, which was held in February 2012. The objective was to review rotavirus vaccine schedules as previously recommended by SAGE in light of new studies from developing countries, and to decide if schedule modifications might be necessary based on this new evidence. This consultation was in preparation for the SAGE meeting in April 2012, where this topic was to be discussed.

Two major questions were reviewed extensively. The first addressed the effectiveness of rotavirus vaccines under different vaccination schedules and with different doses, given in various WHO mortality strata, taking into consideration age of the child, breast feeding status, concomitant vaccine administration and interval between vaccine doses. The second question addressed the evidence available on the benefits and risks of the current (and alternative) RV immunization schedules for children living in different WHO mortality strata.

The consultation concluded that there was no evidence to warrant a change in the current SAGE recommendations on dosing. It was noted that while "RV efficacy and effectiveness is lower in settings with high under-five mortality," there is "limited evidence to conclude that giving a third dose of RV1 is superior to the currently recommended two dose schedule".

The consultation concluded that "evidence available (although limited) and review of operational realities suggest that SAGE members should consider once more the merits and trade-offs (benefits and risks) associated with administration of rotavirus vaccines using a vaccination schedule without age-restrictions." Furthermore, the consultation recommended that SAGE consider removing age restrictions on the first and last dose of rotavirus vaccination and to consider recommending administering rotavirus vaccine concomitantly with other EPI vaccines wherever possible.

C. Feedback from SAGE on Rotavirus Vaccine Schedule (*Shelley Deeks, IPAC*)

At the April 2012 SAGE meeting, SAGE recognized that age restrictions around rotavirus (RV) vaccine dosing exclude the most vulnerable children who are often accessed and evaluated through outreach programs; by removing age restrictions, these programs can immunize children most vulnerable to disease, which will avert disease despite a possible small increase risk of intussusception. SAGE continues to recommend the first dose be administered with DTP-containing vaccines as soon as possible after 6 weeks of age, but recognises that late vaccination is better than no vaccination. SAGE further stated that countries should be empowered to make their own choice about ages based on local data and decision-making processes. The WHO RV vaccine position paper will be updated.

Discussion:

IPAC members noted that SAGE and GACVS have provided clear recommendations on the benefit and safety of RV vaccine, which should now be widely and clearly publicized. Several members noted that the age profile of onset of RVGE and compliance with vaccination schedules varies across countries. IPAC stressed the continuing importance of timely vaccination to prevent not only RVGE but also other infections. Based on SAGE's recommendations, the challenge will be to communicate the overwhelming benefit of timely RV vaccination to reduce morbidity and mortality; this will be enhanced by using this vaccine without narrow age limitations -- even as more cases of intussusception may be expected by lifting the age restrictions, by virtue of the epidemiology of intussusception.

In most countries intussusception is not a reportable condition. Without background rates, there is concern that improved surveillance for intussusception will result in increased reporting of co-incidental cases which may cast doubt on the role played by RV vaccine introduction. Some participants raised concern that use of the vaccine according to the new SAGE recommendations will be seen as an "off-label" use. Furthermore, as intussusception is a rare event, it may take several years to accumulate evidence on the dose- and age-specific role of RV vaccination in its etiology. Some members advised that countries and NITAGS will want to have evidence-based documents from WHO before agreeing to use RV vaccine "off-label". The planned update of WHO's position paper on RV was welcomed by members.

In light of the new information and recommendations concerning safety and timeliness, it was suggested that IPAC's role, consistent with its mandate, should be to discuss next steps related to introduction and roll-out of RV vaccine from a programmatic and operational perspective.

Recommendations and Decisions by IPAC

1. IPAC recommended that the previously agreed rotavirus vaccine training case scenarios be kept, but that additional training scenarios be developed to address relaxation of the age limitations for rotavirus vaccine, as was concluded at the SAGE April 2012 meeting.

Session III. Controlled Temperature Chain (CTC)

A. Progress with CTC: strategy & update (*Michel Zaffran*, *WHO HQ*)

The Controlled Temperature Chain (CTC) approach aims to take advantage of the fact that many vaccines are more stable than indicated by their current licenses. The key thrust of the strategy is to enable the use of certain vaccines outside the standard $+2^0$ to $+8^0$C range without requiring any reformulation and endorsed through a regulatory process. The regulatory approval will allow for 'on-license' use and is important for ensuring the vaccines remain potent and safe throughout their lifecycle. Furthermore, regulatory precedent for reflecting stability in vaccine licenses does currently exist in Canada, the United States, and the European Union.

Many countries have already been taking advantage of the existing stability in today's vaccines, using certain antigens outside the cold chain for limited periods of time, relying on the Vaccine Vial Monitor (VVM). However, although field studies have confirmed the potency of vaccines used in this way, this use is considered 'off-license' use, which is not condoned or supported by manufacturers and regulators.

This CTC work initially started using hepatitis B vaccine as a pathfinder. However, in-vitro potency data are not completely predictive of hepatitis B vaccine integrity; thus there is no direct correlation with clinical efficacy. It was determined that further data, in addition to in-vitro data, would be needed to demonstrate integrity of the vaccine after high temperature exposure before a license variation can be considered. The timing for this work therefore is longer than anticipated, and a re-licensed hepatitis B vaccine will not be available before 2014.

In the interim, the meningococcal A vaccine, MenAfriVac, emerged as a strong candidate for CTC use. As a result, the CTC pathway is currently being charted using the meningococcal A vaccine in a campaign setting, while work on hepatitis B vaccine continues.

The benefits from a CTC approach include reducing programmatic costs and constraints, such as diminishing the burden of ice pack freezing and surge capacity needs, increasing options for immunization strategies, decreasing human resources requirements and reducing the risk of freeze damage to vaccines.

B. Regulatory process for label variations (*Tong Wu, Health Canada*)

Since 2009, Canada has been providing on-license guidance for the use of vaccines after exposure to temperatures above +8°C. This was done at the request of the provincial/territorial immunization programs, which identified significant amounts of vaccine having to be discarded after being inadvertently exposed to cold chain breaks.

Given that vaccines are complex biologicals, an in-depth scientific review is required in order to assess if and how a vaccine can be safely used at temperatures above +8°C. These reviews are product specific, and require real time and temperature stability data. The specifications that are assessed should be linked to expected clinical outcomes and follow a 'worst case scenario' hypothesis, that is: if the vaccine is released right at the edge of its release specification, suffers the maximum amount of degradation possible, and is still required to meet the specification at the end of its shelf life. When conducting an assessment, Health Canada uses the following principle: Loss of potency during entire recommended storage period (regression method) + loss of potency during proposed period of CTC (regression method) must ≤ defined "expiry window" supported by clinical trials. This means that duration approved for CTC is shorter than what is supported by stability data.

C. Use of MenAfriVac in a CTC for campaigns (*Simona Zipursky, PATH*)

The need to keep vaccines in a +2° to +8°C cold chain is a constraining factor for many immunization campaigns; those planned across sub-Saharan Africa to introduce the new meningococcal A vaccine, MenAfriVac® are a good example. However, data obtained from the vaccine manufacturer show that MenAfriVac®has been proven stable at temperatures of 40°C for several weeks. Collaboration among the vaccine manufacturer, PATH, WHO, and the Canadian and Indian regulatory bodies is underway in order to obtain a license variation for this vaccine. This variation will allow countries to use MenAfriVac® at ambient temperature, for limited periods of time, in a CTC.

This work involves four inter-related streams: (i) regulatory license variation; (ii) development and endorsement of operational guidance; (iii) country introductions; and (iv) operational research. IPAC's expertise was sought in area (ii) operational guidance and the request was made of IPAC to provide specific inputs to improve the draft field guidelines. The intent is to pilot these guidelines in the campaigns currently planned at the end 2012.

D. Sub-group perspective and next steps (*Francois Gasse, IPAC and working group lead*)

The IPAC working group provided input into the guidance document and CTC work stream. In order to ensure vaccine quality, maintaining the vaccine under the conditions specified on the label and approved by regulators (at +40°C or below) was an issue that needed to be addressed. The sub-group recommended that peak temperature chemical indicators accompany vaccines when stored or transported in cold boxes or vaccine carriers, while electronic loggers be reserved for large volume storage or transport settings. Further, the sub-group recommended that, when possible, vaccine carriers and cold boxes be used to transport vaccines even in a CTC. The version of the guidance circulated to IPAC reflects these comments, and the sub-group's position.

Discussion:

IPAC members were extremely supportive of the work accomplished on CTC and commended WHO/PATH Optimize and the sub-group on the exciting progress made in this area. The CTC strategy, if successful, would be a revolutionary change for immunization. The guidance document was felt to be clear and well written.

A range of general points were raised by IPAC members, encouraging WHO to a) share the best practices used by Health Canada with other National Regulatory Authorities (NRAs); b) consider reflecting the license variations granted by functional NRAs in the product inserts of pre-qualified products to help low-middle income countries in decision-making; c) continue exploring the development of new VVM types that reflect the higher stability of new vaccines; and d) continue working on improving the freeze stability of vaccines and support countries in preventing vaccine exposure to freezing temperatures.

Key technical inputs contributed by IPAC included the following:

- *Clarify the term CTC*. There needs to be a consistent definition and use of CTC terminology. This will protect it as a trustworthy brand, assuring that certain criteria must be complied with—e.g. CTC is the use of vaccines under monitored conditions, following a regulatory approval. The situation is monitored if there is a risk that the temperature could exceed the regulatory approval.
- *Clarify the scope of the guidance*. It is important to note that some countries have stocks of the meningococcal A + C vaccine; therefore it is essential to clarify that this is only for meningococcal A vaccine. It may be worth considering adding in the brand name for clarification.
- *Provide more guidance to support decision making*. The decision-making section would benefit from the use of a decision-making tree or algorithm.
- *Add a planning timeline example*. It would be useful to have a more comprehensive timeline provided as an example, starting at the decision-making process through to the campaign, including training and communications components etc.
- *Strengthen the AEFI section*. Further guidance in this area is needed, along with clear messages and protocols to follow. In addition, the language currently causes more alarm than is needed, based on the data. Special attention should be paid to community-level messaging around AEFIs.
- *Add aide-memoires*. Add aide-memoires for district and health centre levels.
- *Enhance guidance around supervision and monitoring*. Supervision guidance should include gathering information to assess the CTC in the country, which will help build the global evidence base.
- *Consider integrated campaigns*. As more and more campaigns are being done in an integrated manner, consider adding a section on this.

Some IPAC members expressed concern about assuring adequate training and use of temperature threshold indicators. While it is essential to ensure that the vaccine is not exposed above the specified peak temperature, IPAC members observed that threshold indicators could undermine the strong long-term reliance on VVMs in situations where threshold indicators signal that the vaccine must be discarded and VVMs signal that the vaccine is appropriate to use. The committee requested more in-depth discussion on the utility of temperature threshold indicators. Members also raised concern with the precision of the definition of CTC, as previous definitions were not limited to vaccines that had regulatory approval for non-standard storage and distribution.

A revised version of the guidance, incorporating IPAC's comments, will be circulated to the committee in June.

Recommendations and Decisions by IPAC

1. IPAC welcomed and supported the "*The Use of Meningitis A vaccine in a CTC during campaigns*" guidelines and recognized the great effort and amount of work completed to date.

2. IPAC requested a dedicated teleconference to focus further on the guidelines, review changes that have been made, and obtain more background information on temperature threshold indicators.

3. Further, IPAC requested WHO to clarify the definition of CTC in relationship to on- and off-label implementation of this concept.

Session IV. Topic Updates

A. Visual cue icon refinement (*Jon Colton, IPAC)*

Prof Colton presented on the finalization of the design of the visual cue icons. All recommendations from the September 2011 IPAC meeting were accomplished. The approved visual cues were refined to improve legibility (increased widths of numbers and lines; increased white space around numbers in calendar icon). Non-production, prototype labels were test printed by Fiocruz and Sanofi Pasteur and placed on vials. These were sent to the IPAC members prior to the meeting for review and comment, which were generally positive. The icons may be further refined, depending on the results of the pilot study(ies).

B. Visual cue pilot RFP (*Xavier Bosch-Capblanch, IPAC and working group lead*)

Dr Bosch-Capblanch presented the draft Request for Proposals (RFP) text entitled "*Process evaluation of visual cue vaccine vials introduction*", on behalf of the visual cue subgroup (Xavier Bosch-Capblanch, Folake Kio-Olayinka, Chris Morgan and Rudi Eggers). He pointed out that the visual cue design and issues around the health workers' understanding have been resolved or addressed. IPAC previously decided that the visual cue will be introduced in countries in two phases (pilot introduction and then scale-up). The pilot introduction study is a "process evaluation" to inform scaling up and not an 'effectiveness' study of the visual cue on wastage reduction or safety outcomes.

Several clarifications were requested, including how pilot countries would be selected, how the regulatory aspects of introducing the visual cue in vaccine vials label will be handled, and how proposals will be evaluated. These issues will be addressed in the next version of the RFP. It was also noted that it would be essential to clarify beforehand the potential use of the findings to inform decision-making and eventual scale up of the visual cues. This will be addressed in the protocol phase of the study in which a detailed analytical plan and decision framework will be requested from the bidder.

Members agreed to provide further written feedback on the RFP to WHO and the subgroup within seven days after circulation of the next draft.

C. Programmatic suitability for pre-qualification of vaccines (*Rudi Eggers, WHO HQ)*

Following the last IPAC meeting, the newly established PSPQ Standing Committee met to conduct a "dry-run" using existing vaccines to test the Standing Committee's procedures and documentation. The Standing Committee consists of five members: Alan Brooks (chair), Julie Milstien, Abdulreza Esteghamati, Jane Soepardi (IPAC member), Robin Biellik (IPAC member). Alan Brooks resigned his position and has been replaced by Julie Milstein as chair. Subsequent to the dry run, the PSPQ SC process has been streamlined further, and the first vaccine review

(PCV13 in a pre-filled syringe) is under way. It is expected that the first review will be finally decided by mid-March. In addition, the malaria vaccine (RTSS14) was presented to the PSPQ SC for an opinion.

Recommendations and Decisions by IPAC

1. IPAC endorsed in principle the "*Process evaluation of visual cue on vaccine vial introduction*" request for proposals, subject to minor revisions. IPAC encouraged WHO to proceed with the pilot in a timely manner.

Session V. Programmatic Considerations of Alternatives to Thiomersal-Containing Vaccines

A. Update from WHO Informal Consultation to develop further guidance on vaccines for the UNEP Inter-governmental Negotiating Committee Meeting 4 (INC4), and Update from SAGE conclusions (*David Wood, WHO HQ*)

Dr Wood informed IPAC on the outcomes of a WHO scientific meeting conducted in April 2012, the purpose of which was to generate evidence feeding into deliberations of the Intergovernmental Negotiating Committee Meeting (INC4), an international body preparing a global legally binding instrument on mercury reduction. [1] The proposed treaty concerns the immunization community because thiomersal, a mercury-based preservative, is used in most multi-dose vaccine formulations. Key conclusions of the consultation were that a) the global burden of thiomersal among mercury-based products is extremely small; b) replacement of thiomersal with an alternative preservative may affect the quality, safety and efficacy of a vaccine; c) re-submission would require major work in re-testing and re-regulation with no guarantee of success; and d) there are no viable alternative preservatives available in the near- or mid-term.

Experiences by vaccine procurement agencies (UNICEF and PAHO) demonstrate that while single-dose vials are procured for newer vaccines such as DTP-Hep B-Hib, multi-dose vials (most of which are thiomersal-preserved) remain a critical part of immunization programs, and this perspective is also reported from countries. There would be a high risk of disruption to routine immunization programmes and mass immunization campaigns if multi-dose vials are not available. The consequences would be a predictable and sizable increase in mortality, for very limited environmental gain. There is insufficient existing manufacturing capacity to remove thiomersal and switch to single-use vials; and such a switch would require a substantial increase in costs and resources for implementation of immunization. There are some risks to vaccine access during the treaty negotiations: if countries opt for thiomersal-free vaccines, then they are likely to face interruption to vaccine supply, particularly for the most basic routine vaccines. In addition, IPAC was informed that environmental regulatory requirements may increase if the treaty is ratified, thus creating potential difficulties in access to thiomersal as a raw material in vaccine manufacture.

During their meeting deliberations in April 2012, SAGE expressed grave concern that current global discussions may threaten, without scientific justification, access to thiomersal-containing vaccines; reaffirmed that thiomersal-containing vaccines are safe, essential and irreplaceable components of immunization programmes; supported urgent global communications at the highest levels; and supported on-going dialogue between the health sector and the environment sector at global and national levels to facilitate a common understanding of the critical role of thiomersal-containing vaccines. Noting the potential threat to thiomersal-

[1] The documents from the WHO Informal Consultation to develop further guidance on vaccines for the UNEP Inter-governmental Negotiating Committee Meeting 4 (INC4) are located at: http://www.who.int/immunization/sage/meetings/2012/april/presentations_background_docs/en/index.html

containing vaccines, SAGE requested WHO to produce a report on the security of the supply of such vaccines and also encouraged donors to invest in the development of new vaccine technologies that facilitate the delivery of effective, affordable vaccines to populations most at risk.

B. Impact assessment of thiomersal-free vaccines on supply chain *(Anthony Battersby, WHO consultant)*

Mr Anthony Battersby presented an analysis which evaluates the financial, programmatic and environmental impact of removing thiomersal from vaccines. This research was based on a survey of manufacturers and modelling based on procurement patterns by UNICEF and PAHO, as well as available data from selected countries. The report highlighted that global production of pharmaceutical-grade thiomersal is sourced from one single producer at approximately 2,434 kg per annum, 64% of which goes to vaccines. This represents a negligible proportion of the environmental burden of mercury.

Development costs and time to shift to thiomersal-free vaccines are considered substantial, with clinical trials estimated to cost at least $1M per vaccine, with the outcome of trials and future vaccine stability unknown.

The likely increase in cost varies inversely with cost of vaccine, so that the cost increase to DTP is several hundred percent over current costs, and some vaccines such as influenza, are disproportionately affected. The annual cost of PAHO or UNICEF supplied vaccine is estimated to rise from $522 million to $855 Million. At country level, Kenya's vaccine costs would potentially rise from $45 million to over $55 million, with the cost of its air freight bill for international vaccine shipments rising by an estimated $750,000 per year; with a commensurate increase in carbon dioxide emissions.

Volume implications for cold chain storage are significant, varying from 165% to 324%, with major impact on central and peripheral stores. Workload implications go beyond expansion in funding, and affect storekeepers, clinic session staffing, training needs, and service provision. Outreach operations may also be significantly affected, with no current alternatives to multi-dose vials for use in extended outreach, birth dose outreach (e.g., hepatitis B vaccine) or campaigns (such as those for prevention of meningococcal). Waste management implications are of the order of a tripling of impact with a shift to all single-dose vials, increasing vial waste from 2,350 m^3 (based on 2011 PAHO and UNICEF procurement data) to between 3,850 m^3 and 7,600 m^3.

Overall removal of thiomersal would almost certainly lead to severe vaccine shortages. It would also entail: major impact on manufacturing, distribution, vaccine costs and environmental waste; greater workload for logistic and nursing staff; a transition period of the order of 10 years; and a high risk of serious program disruption. Absence of thiomersal would also seriously interfere with the manufacture of particular vaccines such as pertussis and seasonal and pandemic influenza vaccine.

C. Discussion Points *(Chris Morgan, IPAC and lead focal point)*

Dr Morgan synthesized the key evidence presented and proposed language for IPAC to consider as a committee statement, with emphasis on programmatic concerns.

Discussion:

IPAC members discussed the safety assurances relating to thiomersal, noting that a recent update of evidence for safety had been considered by SAGE and GACVS. Members discussed alternative technologies to thiomersal, including mechanical approaches to drawing multiple doses in an aseptic manner as well as alternative preservatives, noting that no satisfactory option is currently feasible. Members noted that other important stakeholders, including GAVI, PATH and a representation of manufacturers, continue to align with the WHO position, and

members discussed the need for communications to involve a broad range of partners, including those beyond the health sector. Discussions identified the need to develop a long-term vision, with a strong basis in programmatic requirements, for future vaccine formulations, presentations and delivery systems.

It was noted, however, that the evidence presented was based on interviews and modelling and therefore, concrete figures on burden of cold chain and costs may be subject to great variability.

IPAC concluded it is essential that thiomersal-containing vaccines be exempted from the legally binding global instrument being drafted to reduce or abolish mercury-containing products. The programmatic issues for countries to consider are significant. The consequences for immunization programs of removing thiomersal from vaccines include the risk of losing access to some vaccines currently in high use at low cost (e.g., TT, DTwP, and hepatitis B vaccines). Immunization services would be severely disrupted if multi-dose vials that require thiomersal were no longer available. Implications include multi-fold increases in the costs of vaccines, and their transportation and storage, in addition to increased workload of logistic and nursing staff and the increased cost and complexity of waste management. Evidence from one study elaborating a theoretical scenario presented in IPAC suggested that the annual vaccine costs may be expected to rise by over 60% and shipping costs to rise in the order of 120%.

Members noted the need to make credible information readily available to countries to respond to community and professional concerns regarding the effect of the non-removal of thiomersal. It was stressed that communications need to include deaths averted through the use of vaccines that contain thiomersal and the potential consequences in terms of deaths and disease as a result of disruptions in vaccination programs.

Recommendations and Decisions by IPAC

1. IPAC concluded that the abrupt removal of thiomersal-containing vaccines would be extremely disruptive with disastrous consequences for vaccination programs and infant, child, and maternal health, likely resulting in increased mortality and morbidity. As a result, IPAC concluded that it is essential that thiomersal-containing vaccines be exempted from the global mercury-free treaty. IPAC noted that there are severe programmatic consequences of a shift away from thiomersal-containing vaccines, including interruption to vaccine supply and dramatic increases in program costs and resource requirements for countries to manage such a change.

2. Although IPAC recognises and supports the global initiative to reduce exposure to mercury in the environment, IPAC supports the position expressed by SAGE that thiomersal-containing vaccines are safe, essential, and irreplaceable components of immunization programs, especially in developing countries, and that removal of these products would disproportionately jeopardize the health and lives of the most disadvantaged children worldwide. Thiomersal-containing vaccines are estimated to avert at least 1,400,000 childhood deaths each year.

3. IPAC called for an intensified and unified effort at global and national levels to improve communication strategies to inform decision-makers and the wider public about the negative effects of a rapid transition away from thiomersal, using a wide set of partnerships beyond the immunization and health sectors.

4. IPAC recommended that WHO build upon the opportunity presented by the global initiative to remove mercury from the environment to heighten attention to improving vaccine formulations, presentations and packaging, logistics, program delivery, vaccine wastage, and waste disposal systems. IPAC calls for an intensive research investment into programmatic improvements (e.g., new technologies for maintaining sterility when

withdrawing doses from a multiple dose vial, new requirements for vaccine handling, logistics and waste disposal, etc.). Furthermore, as countries will come under increasing pressure to reduce environmental exposure to mercury, IPAC supports continued research into effective, feasible and affordable alternatives for new vaccine preservatives.

5. IPAC requested feedback from INC4 consultations at IPAC's October 2012 meeting.

Session VI. Hepatitis B birth dose implementation

A. Summary of progress since April 2011 (*Robin Biellik, IPAC member and working group lead)*

The implementation of the hepatitis B vaccine birth dose was discussed at the April 2011 IPAC meeting. At that meeting, IPAC members provided inputs on the draft WHO background paper developed by Burnet Institute entitled "*Best practices and needs for the delivery and monitoring of hepatitis B vaccine birth dose*." Subsequently, three external peer reviewers also provided extensive comments.

Incorporating the feedback received from IPAC and external peer reviewers, Ms Priya Mannava and Dr Chris Morgan of Burnet Institute substantially revised the paper, which is now entitled: "*Practices to improve coverage of Hepatitis B birth dose vaccine*." Substantive revisions include the extension of the literature search through March 2012, a major reorganization and re-examination of the evidence in the form of a systematic review, with evidence graded in accordance with WHO standards, and significant streamlining of the language with better alignment for the target audience. The support of the AusAID's Compass: Women's and Children's Health Knowledge Hub was acknowledged.

In April 2011, IPAC further recommended that appropriate guidance materials on the implementation of hepatitis B vaccine birth dose be developed. CDC Atlanta agreed to lead in developing a management manual in collaboration with Burnet Institute and WHO. The document, which is still in its conceptual stage, will include a policy brief, job aides and a programme manager's problem-solving guide. A session of the IPAC Hepatitis B Birth Dose Working Group (Robin Biellik, Chris Morgan) has been scheduled for 19 April 2012 to define the programme of work.

Dr Biellik emphasized that Dr Morgan would maintain his role as a WHO consultant during this session, and would recuse himself from IPAC deliberations on the paper.

IPAC members were requested to:

- endorse the updated *Practices to improve coverage of Hepatitis B birth dose vaccine* document for WHO publication;
- confirm that it constitutes a satisfactory evidence base for the development of complementary operational materials on planning and implementing Hepatitis B birth dose; and
- Provide input on the proposed contents / outline for those operational materials.

B. Revisions to document on implementation practices (*Priya Mannava and Chris Morgan, Burnet Institute, Melbourne*)

Dr Morgan, acting in his role as WHO Consultant, presented the revised version of the review of practices to improve coverage with hepatitis B birth dose vaccine. The presentation noted that effective practices to improve hepatitis B birth dose coverage included:

- service delivery arrangements to increase access to skilled childbirth care, integration of vaccination with maternal and newborn care (detailing some specific practices to enable this), linkages with private providers and special measures to reach infants born outside health facilities;
- health workforce considerations addressing attitudes, specific training, and options for task shifting to expand available vaccinators;
- medical technologies that allow storage of vaccine close to the location of birth, consideration of Uniject™ presentations of the vaccine and the need to maintain supply of monovalent formulations;
- health information practices for birth registration, pregnancy tracking and accurate definition of the birth dose (as within 24 hours of birth) in national and regional monitoring;
- financing arrangements that provide adequate funding and minimise costs to families;
- addressing community concerns including planning communications to address the potential of coincidental newborn deaths; and
- leadership and governance practices such as clear national policy, guidance that accurately defines the birth-dose, strong central communications, and consideration, where appropriate, of use of the vaccine in controlled temperature chain or the accreditation of additional vaccinators.

The presentation also noted the importance of harmonising references to hepatitis B birth dose vaccination, with accurate definition of timeliness in global, regional and national guidelines when addressing the newborn period. Dr Morgan also noted potential linkages to other technical consultations within WHO, such as those for community-based postnatal care.

C. Update on Hepatitis B vaccine birth dose guidance materials (*Nancy Glass, CDC Fellow)*

In 2006, the WHO Western Pacific Regional Office (WPRO) produced an operational field guide entitled "*Preventing mother-to-child transmission of Hepatitis B*". The CDC has agreed, in collaboration with the Burnet Institute, WHO HQ and WPRO, to develop a management manual that builds on the WPRO manual and is applicable in the global context. The proposed title for the manual is "Implementation and Strengthening of the National Perinatal Hepatitis B Vaccination (Birth Dose) Program: Guide for EPI Program Managers" and will contain:

- a policy brief for national programme managers responsible for advocating for hepatitis B birth dose;
- job-aides on how to introduce birth dose; and
- a problem-solving guide for programme managers addressing low hepatitis B vaccination coverage in facility-based and home-births.

An outline of the manual listing the proposed chapters and annexes was distributed at the meeting for comments and suggestions.

Discussion:

IPAC members universally commended the Burnet Institute for the rigorous revisions to the document "*Practices to improve coverage of Hepatitis B birth dose vaccine*", referring to the document as an excellent review which is more complete and well-structured than the earlier version. IPAC members provided a series of comments and suggestions to further improve the document prior to finalization. Members expressed that the analysis of best practices constitutes a "scoping review" rather than a "systematic review". The authors agreed to take all comments and suggestions into account at the Working Group meeting on 19 April.

Recommendations and decisions by IPAC

1. IPAC endorsed in principle the "*Practices to improve coverage of the hepatitis B birth dose*" document with modifications, including the substitution of the term "systematic review" by "scoping review", a brief description of the quality of evidence attached to

the description of findings, and a 'toning down' of some of the recommendations statements (*Vote: unanimous consensus*).

2. IPAC confirmed that this document should be used as part of the evidence-base for the development of complementary operational materials on planning and implementing a hepatitis B vaccine birth dose guideline (*Vote: unanimous consensus*). IPAC noted that the document, while an essential piece of the evidence base on hepatitis B birth dose practices, is not suitable in isolation as a basis to set policy direction.

Session VII. Multi-dose Vial Policy

A. Country Implementation of multi-dose vial policy (*Diana Chang Blanc, WHO HQ*)

The objectives of this analysis were to consolidate information from regions and countries on the implementation of the multi-dose vial policy (MDVP) in WHO member states and to identify key deviations in national policy application from the global WHO policy. Country implementation status and deviations from the current global MDVP help provide context prior to revisions of the current policy.

National MDVP data were collected from 75% of 194 WHO member states; nearly 60% of member states have an established national MDVP. Of countries with an established MDVP, 58% of these policies have at least one deviation from the global MDVP. The most common deviations of national policies from the global MDVP are modified discard time limits for open vial use in a subsequent immunization and application of MDVP to outreach sessions. Of countries with an established MDVP, 39% articulate a modified time limit. The 6 hour limit for reconstituted vaccines was relatively unchanged; however, the 28 day limit for liquid vaccines was reduced to 14 days or less, primarily clustering around 7 days. It should be noted that these modified discard time limits were most commonly reported by countries in the European and West African regions. In terms of limiting the application of the MDVP to fixed immunization sites only, this was not common, but was most frequently reported in South-East Asia (5 countries) and Europe (8 countries). In conclusion, a revision to the WHO global MDVP would impact many Member States, but the policy if well-articulated should pose no problem for countries to adapt.

B. Trends in multi-doe vaccine vial use in UNICEF procuring countries, 2000-2011 (*Jodi Liu, WHO consultant*)

Trends in multi-dose vaccine vial use were evaluated as part of developing the evidence-base for a revision to the MDVP. The objectives of this study were to identify national trends in multi-dose vaccine vial use and to assess factors influencing the change in the use of various vial sizes in UNICEF procuring countries during 2000 to 2011.

The evolution of multi-dose vial use contains micro-patterns but no clear overall pattern was observed over 2000-2011 with DTP-based, hepatitis B, and measles-containing vaccines in UNICEF procuring countries. Over the study period, shifts from larger to smaller multi-dose vials, and vice versa, have occurred. DTP procurement shows preference for 10 dose over 20 dose vials, although the number of procuring countries has decreased over time. Two countries switched from 1 to 10 dose presentations of DTP-Hib. DTP-HepB/Hib procurement has largely been dictated by global supply availability and has shifted from 2 to 1 to 10 dose vials. With the increasing use of pentavalent vaccine, hepatitis B procurement has shifted from 10 to 1 dose vials to accommodate hepatitis B vaccine birth dose. No trends were observed with DTP-HepB and measles-containing vaccines, which are most commonly used in 10 dose vial presentations. However, recognition of country interest for 5 dose vials of measles vaccine has been increasing.

The use of multi-dose vials is affected by global supply and country-driven preference, which may be influenced by a combination of factors such as price, funding sources, cold chain requirements, wastage and safety concerns, programmatic feasibility, and historical usage. Although the use of different vaccine presentations has changed over the past decade, multi-dose vials remain commonly used in UNICEF procuring countries and remain a vital part of immunization programmes.

C. Update on multi-dose vial policy revisions (*Diana Chang Blanc, WHO HQ*)

Ms Chang Blanc updated IPAC on key steps undertaken towards the revision of MDVP since the September 2011 meeting. An issues paper and an activity plan have been drafted to which working group members have contributed (Robert Steinglass, Francois Gasse, Jon Colton, Najwa Khuri-Bulos, Thierry Gastineau). About fifty percent of activities in the work plan have advanced, with the two preceding presentations representing key outputs.

Remaining activities will take additional time to undertake, so an interim action will be to update individual prequalified web pages to include applicability of MDVP, product by product, to facilitate interpretation by country. This will require screening of all prequalified products for proper categorization.

To date, there are no compelling scientific reasons or programmatic benefits to alter the 6 hour or 28 day discard points. Furthermore, the study on MDVP implementation in Member States demonstrates that most countries apply these limits; about twenty surveyed countries from two regions concentrated around ≤ 7 day discard.

The three substantive issues remain the outcomes of the visual cue pilot, the placement change of the vaccine vial monitor for certain vaccines and the need to further define 'appropriate cold chain conditions'. Work in these areas will continue to proceed.

Discussion:

IPAC members noted the lack of data on the implementation of the policy at operational level and their impact on vaccine wastage, particularly as reliable vaccine wastage calculations are difficult to retrieve at country level. Brazil has recently published an article on vaccine wastage, but the country does not apply the MDVP. There are still limited data on whether the application of MDVP leads to wastage reduction and cost savings, as is often presumed. The Fiji wastage study currently under development may provide more information. There is growing recognition that 5-dose vials, as opposed to 10 dose or 20 dose vials, can bring programmatic value in certain settings.

Members remarked on the inter-relationship between the issue of thiomersal and MDVP, and the need to maintain a long-term perspective on the revision because of the changing landscape. As countries shift to one-dose presentations, MDVP may lose its relevance over time. When drafting the policy, WHO was encouraged to proceed with the assumption that visual triggers (VVM, visual cue) will be in force.

Discussion on the scientific basis behind the 28 day time limit was raised, with some promoting the idea to abolish the time-limit altogether as it is based on estimated vaccine supply delivery cycles at peripheral level rather than scientific necessity. However, most countries apply the 28 day time limit, so changing a policy that is well-understood in the field would need to be weighed against any marginal benefit that could be gained from the change in message and practice.

Members were requested to provide any additional feedback on the MDVP issues paper within the next seven days.

Recommendations and Decisions by IPAC

1. IPAC recognized the importance of the work conducted on MDVP since its September 2011 meeting. IPAC is looking forward to feedback on future outputs.

2. IPAC recommended that WHO take a long-term perspective for MDVP revision and give careful consideration to the programmatic issues impacted by or inter-related with MDVP.

Session VIII. Immunization in Practice (IIP)

A. Revisions to Immunization in Practice (*Jhilmil Bahl, WHO HQ*)

The last version of the Immunization in Practice document was published in 2005. It now is only accessible at http://www.who.int/immunization_delivery/systems_policy/training/en/index1.html.

A detailed table of contents was shared with IPAC members in February 2012 and members gave very extensive feedback which will be incorporated in the revision. The IPAC meeting session focused on issues for which WHO will seek further guidance from IPAC members, including disease and vaccine listing, how to handle different presentations of the same antigen, trade-offs between print media and internet, and proper cold chain conditions.

A session of the IIP Working Group (Folake Kio-Olayinka, Jean-Marc Olivé, Francois Gasse) has been scheduled for 19 April 2012 to focus on the Microplanning module. The timeline for development of IIP is early 2013, with draft versions available in late 2012.

Members were requested to provide any additional feedback on the IIP table of contents within the next seven days.

Discussion:

Meeting participants widely recognized IIP as a useful field guide and resource for health workers as well as partner staff. Some members stressed the importance of keeping the guide simple and not too bulky. Others leaned towards a more comprehensive guide as sometimes the handbook is the only resource available in the field and used by staff at all levels.

Discussion turned to the idea of producing a comprehensive 'modular' set on the web, with support to countries who choose to 'print on demand' those modules most relevant to them. Having a web-based version would also make the update process easier as polices will continue to change in the coming years. While this idea was considered valuable, there remained insistence that a print-based core version was still required as sub-national levels do not have adequate internet connectivity to download large versions of material.

Members observed that 'Immunization in Practice' will incorporate several practice issues that are being discussed in IPAC (e.g., visual cue, controlled temperature chain, multi-dose vial policy); it is therefore critical for WHO to approach the development of this document collaboratively, engaging widely IVB staff, IPAC and key partner agencies.

Members suggested conducting a 'market survey' of field users and asking what they would like included in the updated guide and in which format. In terms of next steps, WHO agreed to execute this; additionally, WHO will conduct further discussion in the department on the best format for the guide, taking into account feedback provided by IPAC members.

Recommendations and Decisions by IPAC

1. IPAC reiterated strong support for "Immunization in Practice" and recognition of the need for this reference manual.

Annex A: IPAC working group composition

	IPAC	WHO region	WHO focal point
Controlled Temperature Chain	Francois Gasse* Thierry Gastineau Jane Soepardi Debbie Kristensen		Michel Zaffran
Hep B birth dose	Robin Biellik* Chris Morgan		Diana Chang Blanc
Immunization in Practice	Francois Gasse Folake Kio-Olayinka Jean-Marc Olivé		Jhilmil Bahl
Programmatic Suitability of Vaccine Candidates for WHO Prequalification PSPQ	Robin Biellik Jane Soepardi		Rudi Eggers Nora Dellepiane
Rotavirus Vaccine: consequences of age limitations on vaccination programme	Robin Biellik Robert Steinglass*	Nadia Teleb (EMRO)	Jhilmil Bahl
Rotavirus Vaccine: Vaccine safety-related	Shelley Deeks Najwa Khuri Bulos		Ana-Maria Henao Restrepo
Routine and Supplemental Doses	Vance Dietz Folake Kio-Olayinka*		Tracey Goodman Tony Burton
Visual Cue (to transition to MDVP)	Robert Steinglass* Francois Gasse Najwa Khuri-Bulos Jonathan Colton	Richard Mihigo (AFRO) Oommen John (SEARO)	Rudi Eggers
Multi-dose Vial Policy	Robert Steinglass Francois Gasse Najwa Khuri-Bulos Jonathan Colton Thierry Gastineau	Martha Velandia (PAHO)	Diana Chang Blanc
Visual Cue Pilot	Xavier Bosch-Capblanch* Folake Kio-Olayinka Chris Morgan		Rudi Eggers
Vaccine Presentation and Packaging Advisory Group VPPAG	Robert Steinglass Debbie Kristensen Osman Mansoor		Solo Kone
Vaccine Safety	Najwa Khuri- Bulos		Patrick Zuber

* Lead focal point