World Health Organization

# WORLD HEALTH ORGANIZATION
# DEPT: IMMUNIZATIONS, VACCINES AND BIOLOGICALS

## IMMUNIZATION PRACTICES ADVISORY COMMITTEE (IPAC)
## 29 - 30 June 2010

# Meeting report and recommendations[1]



IPAC Members present:
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## 1 Opening and Introduction

The first bi-annual Immunization Practices Advisory Committee (IPAC) meeting was opened by Dr Jean-Marie Okwo-Bele, Director of Immunization, Vaccinations and Biologicals (IVB), by welcoming the committee constituting 11 IPAC members (the 12th member could not attend this meeting), 5 IPAC formal observers from representative partners (CDC, UNICEF, PATH, IFPMA, DCVMN), as well as other participants and presenters from WHO headquarters, WHO regional offices, and industry. Dr Shelley Deeks was introduced as the chairperson of IPAC.

Dr Okwo-Bele explained that IPAC, which replaced the Technical and Logistics Advisory Committee (TLAC), was formed to expand the scope of the advisory body. IPAC was especially pertinent to practical and operational aspects that would ultimately help achieve the Global Immunization Vision and Strategy (GIVS) goals.

## 2 Background and Role of IPAC

Dr Rudi Eggers, WHO/IVB Group Leader of Immunization Services Strengthening, summarized the overall role of IPAC, which was to support and advise WHO/IVB in formulation of immunization practices, norms and standards necessary to reach and sustain high level coverage, while providing high quality immunization services to the recipients of vaccines. To be endorsed as WHO position, IPAC recommendations would be reviewed and approved by the IVB Director.

IPAC consisted of 12 independent experts, appointed for a once renewable term of three years, with a chair selected by the Director for a two year term. Members randomly selected the initial term of service as two, three or four years, to avoid all committee members rotating out

[1] As approved by the IPAC on 4 Nov 2010

at the same time (see Annex B). IPAC formal observers were to take part in all aspects of IPAC functioning, except final decision-making and recommendations of IPAC. Dr Eggers emphasized that confidential items which may be in the interest of specific organizations would be handled with the exclusion of the conflicted observer or member.

## *2.1 IPAC Relationships with other committees*

Dr Eggers expounded on the relationship of the IPAC with the WHO secretariat. It was expected that about 80% of IPAC recommendations would deal with operational matters, and the resulting recommendations would be made to the Director IVB directly; whereas the other 20% of IPAC recommendations would deal with strategic matters, which would require further discussion and endorsement by Strategic Advisory Group of Experts (SAGE) before consideration and adoption by the Director. In addition, IPAC may also request consultations with or be consulted by SAGE working groups, Executive Committee for Biological Standards (ECBS) and Global Advisory Committee for Vaccine Safety (GACVS) for recommendations.

Task groups[2], when established according to need, would ideally consist of a WHO technical lead, other experts, and one to two IPAC members who would represent IPAC in the task groups. While IPAC members were not expected to be experts in the topic of the task group, they would act as topic leads when the topic was brought to the full IPAC meeting for discussion. Further, time limited sub-groups[3] may be formed for a particular task at hand. An IPAC member volunteer, on behalf of IPAC, would also be needed to participate in the ongoing standing committees that meet ad-hoc.

# 3 Multi-Dose Vial Policy (MDVP) Revision and Visual Cue

Dr Eggers updated IPAC on the challenges and progress made in MDVP revision. This topic had been initiated under the auspices of TLAC.

## *3.1 Background*

The 2002 "Multi-Dose Vial Policy" (MDVP) was created to allow health workers to keep opened vials of indicated vaccines - where it was safe to do so - for subsequent immunization sessions, provided that certain cold chain and handling requirements were met. Dr Eggers listed new challenges faced with use of MDVP. New, multi-dose, liquid vaccines containing varying amounts of new preservative may be mistakenly kept for longer time periods than optimal, as health workers generally associated liquid vaccines with those that could be kept. Also, fractional doses may be used from a single-dose unpreserved vial, thus rendering vaccine unsafe, if kept. In other cases, adequately preserved new combination vaccines may be mistakenly discarded, thus rendering MDVP too wasteful. These challenges mandated a need for MDVP revision, including development of a new visual cue that should enable a vaccinator, just by looking at the vial, to clearly distinguish between a vial that can be kept and one that has to be discarded regardless of formulation.

## *3.2 Development of a new visual cue*

Dr Eggers described recommendations made by TLAC in 2009. It was decided that a logo on all vials would be the new primary visual cue, while placement of Vaccine Vial Monitor (VVM) on cap or vial would be the secondary cue. TLAC considered several criteria including universality, intuitiveness, legibility, memorability, minimization of text, impact on manufacturer, regulatory impact, compatibility with VVM usage, and the cost of labelling and printing.

A focus group selected the following five pairs of visual cues, to be printed in black and white (to avoid use of colours), for review:

[2] Task Group: Time-limited group to assess and review specific topic.
[3] Sub-group: Small time-limited group to oversee distinct part of a task groups review.


**Icon pairs A B C D E**

TLAC also recommended that the proposed MDVP visual cues be tested on three continents with cultural diversity; on vaccinators, district-level health supervisors, and national-level immunization programme staff. Market research professionals, experienced in product image recognition and consumer assessment, would conduct the testing. A full report on the methodology, data, findings and conclusions should be produced at the end of the study, to allow for an informed decision by IPAC, hopefully in November 2010.

Dr Eggers introduced Synovate Healthcare as the contractor company selected to carry out the above study. Uganda, Cambodia and Peru were selected as candidate countries for this study. Preliminary results from the Uganda study were presented in the following session. Studies in Cambodia and Peru would be completed by November 2010, wherein he hoped that a pilot visual cue pair would be decided by IPAC. As per envisaged timeline, the pilot visual cue pair would be tested in field conditions in 2011, and a final visual cue decided by end of 2011.

## *3.3 Evaluating the ideal visual cue - Update on Synovate study in Uganda*

Ms Melissa Moodley from Synovate Healthcare presented the preliminary results from the visual cue study in Uganda thus far. Her presentation covered three main sections: research overview, project update, and reporting of preliminary findings.

According to Ms Moodley, in order to evaluate the most preferred visual cues that best communicated the discard messages, a two-step research design was employed. Stage one involved assessing the spontaneous understanding of the cues, as well as the ease of communication. Stage two gauged the long term recall of the visual cues.

The first stage of fieldwork in Uganda had achieved a total of 124 interviews, of which 73 respondents were located in rural locations, and the remaining 51 were based either in urban or peri-urban areas. The demographics and background of the health workers interviewed in Uganda were also mentioned. The interviewed health workers had an average of nine years' experience administering vaccinations, and administered a median of 105 vaccinations in a month.

Health workers were presented with the five pairs of visual cues selected for testing, termed pairs A, B, C, D and E respectively (see section 3.2). The data suggested a preference for the visual cue Pair A (clock and calendar). Pair A was more likely to elicit the correct message spontaneously, and was widely perceived as very easy to communicate. Pair A rated consistently higher than other pairs on all metric tests and also caused the least amount of confusion. In addition, data regarding impact of VVM on perception of the visual cues was also presented. About 65% of the health workers reported that the meaning of the pictures (visual cue pair) changed when shown vials with VVM. In terms of recall, when health workers were re-shown the visual cue pairs after a period of at least 2 weeks, approximately 91% of respondents spontaneously recalled pair E (cross and tick); while in 73% of the cases, pair A was the second most recalled set of visual cues.

Overall, these preliminary results suggested that health workers in Uganda favoured pictures that closely resembled items they were familiar with (such as those shown in Pair A). They were drawn to cues that told the story clearly (i.e. communicated the discard message) and preferred cues that gave an indication of the time the vaccine could be used for. It is important to note, however, that these results pertain to only one of the three candidate countries, and as such should be viewed with caution.

## *3.4 Discussion on MDVP*

Several discussion items questioned decisions that had previously been made by TLAC. It was acknowledged that IPAC had to "own" these decisions, and it was therefore valid to review previous decisions, if necessary.

IPAC members raised concerns about the lack of flexibility between pairs of visual cues shown to health workers, stating that it might have affected the outcome of the study. Ms Moodley said that health workers were asked which combinations or pairs they would pick from the group if there were no pairs. In this study, 75% of the respondents preferred to stay with the original pairs, while only 25% made new pairs. In addition, Dr Rudi Eggers explained that the pairs were chosen after much deliberation by TLAC and then endorsed by WHO.

The use of the letters "d" and "h" was questioned over concerns that health workers in non-English speaking countries would probably not understand them. Dr Eggers acknowledged this concern while stating that "d" and "h" would be comprehensible in most, though not all, countries. Nevertheless, non-English speaking countries would have to train their health workers to understand these letters.

The size of the visual cue presented to health workers during field tests was raised as an issue. IVB secretariat circulated a printout of the actual label size used for the study, which closely resembled the size of the labels on actual vaccine vials.

Concerns were raised about whether a good distribution of health workers from different health facilities had been achieved, while selecting candidates for the Synovate study. Ms Moodley replied that Synovate tried to cover most of the regions (rural, peri-urban, urban) of Uganda to include wide distributions of people in the study. However, the study did not include analysis of results in terms of differences between perceptions of visual cues by health workers from different regions. This analysis would be made available in the final report in November.

Concern was also raised about the methodology used by the Synovate team; whether the health workers were prepared in advance, or whether the visual cues were presented to them spontaneously. It was considered an important factor that could influence the outcome of the study. Mr Jeff Lucas from Synovate responded by saying that the study was completely free from "prepping" or any such previous intervention. Administering the questionnaire to vaccine storekeepers was also suggested. Analyzing the results to determine homogeneity of preferences by an individual health facility would be useful; as concern was raised that the views of the first responders could influence the views of subsequent responders, given that news about the purpose of the visit spreads within the facility. However, the researching team took great care to avoid this possibility.

## *3.5 Implications of new visual cue - Input from IFPMA*

Dr Thierry Gastineau, on behalf of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), presented the implications of adding a new visual cue to vaccine vials from manufacturers' perspective. He mentioned that the industry's objectives related to packaging components and texts, to allow end-users to use the vaccines according to the product profile and characteristics. In addition, the industry was concerned with supplying vaccines with minimized production and packaging costs in order to minimize the impact on prices, yet having appropriate flexibility to respond to customer needs, while complying with regulatory requirements.

Dr Gastineau mentioned some visual cues proposed in the WHO document were not feasible in IFPMA's view because they were not legible (e.g: icon pair A), or meaningful (e.g. icon pair B), or may introduce confusions such as the interpretation of the VVM.

IFPMA proposed an altered "Icon pair C" as potential alternative and suggested field studies to test the end-user acceptability of this visual cue:


**Altered icon pair C**

The altered icon pair C replaced the calendar symbol with a trashcan symbol, to improve legibility.

IFPMA suggested that the MDVP revision should include an assessment of alternatives to the 6 hours / 28 days (6h/28d) binary system since a number of vaccines currently claimed other storage durations after first use, such as 7 days, 6 months, or even no restriction. Having only two options leads to potential negative consequences of the current binary system such as vaccine wastage, safety issues, lack of industrial flexibility etc. A more flexible approach was thus needed for storage durations of multidose vials after first use, based on the vaccine characteristics.

## *3.6 Implications of new visual cue - Input from DCVMN*

Dr Reinaldo de Menezes Martins, representing the Developing Countries Vaccine Manufacturers Network (DCVMN), presented inputs regarding implications of a new visual cue. DCVMN considered icon pair E (the tick and cross marks) as the best graphic solution, since it was easy to read, print, and could be reducible.

However, DCVMN had a number of concerns. It seconded IFPMA's opinion about limited space on vials and suggested that extra information could be added to the package insert or as a marking on the secondary packaging. In addition, the issue of appropriate icons for vaccines that did not follow the 6h/28d binary system was raised. It was suggested that the information about discarding the product should be displayed in the country's local language, under the tick and cross icon pairs.

DCMVN also raised concerns about the acceptability of the new visual cue by all national regulatory agencies. In addition, association of visual cue with VVM might be confusing as not all vaccines have VVM. DCVMN was also concerned about the use of the letters "d" and "h" on visual cue pairs, as they were not universal, and suggested that icon pairs B, C and D be discarded for this reason.

## *3.7 Implications of new visual cue - Input from a regional office (WHO African Region)*

Mr Serge Ganivet presented this session on behalf of WHO African Region. He reiterated previous concerns about the use of 6h/28d binary system as well as legibility and language compatibility of symbols and letters used as new visual cues.

Mr Ganivet stated that there should be a visual cue for each antigen and it should be placed on all the vials instead of the cap. He suggested that the visual cue should consist of only one simple message to either discard or not discard after opening. For example,

 -to discard after opening  -not to discard after opening

Mr Ganivet also suggested that the message of 28 days should not be displayed in the visual cue as it would depend on the national policy to keep the opened vial for up to 28 days or not (according to the cold chain situation, staff knowledge, etc.).

In conclusion, Mr Ganivet listed some additional aspects to be considered. These included wider scale field tests in countries with different cultures, including staff from all levels of health work. Systematic training of all the staff with practice exercises was advised. It was suggested that messages be printed on the vials in order of priority (visual cue, VVM and expiry date). Finally, he suggested that the new visual cue policy should be introduced at the same time in all countries and not gradually.

## *3.8 IPAC deliberations and conclusions on visual cue*

IPAC members discussed several issues regarding the development of a visual cue and suggested the following way forward:

### 3.8.1 The 6h/28d binary system

Several IPAC members supported the idea of a more expandable visual cue, which would have more choices than 6h/28d (i.e. binary outcome), and be able to accommodate those vaccines that have to be discarded after 4 hours only, or those vaccines that can be kept for longer than 28 days. The problem was even more pertinent in the light of new multi-dose vaccines.

The challenges faced with the recent influenza pandemic were discussed. The flu vaccine in this case had to be discarded after 24 hours and it caused great shortage of vaccine supply. Hence, minimizing wastage was recognized as critical, especially in such cases. Increasing space available on the vials to accommodate the expiry date was suggested. However, associated practical problems as outlined by manufacturers were also acknowledged.

### 3.8.2 Background to the 6h/28d thresholds

IPAC members requested access to the document and report that contained details about how the 6h/28d binary decision was taken, for better understanding of its importance and logic.

### 3.8.3 Synovate's study design and methodology

IPAC members requested more detailed information about the study design, methodology used, and results obtained by Synovate in conducting its visual cue field tests. Dr Eggers suggested that Synovate share preliminary results as the study progresses. Members were provided with the necessary documents and papers submitted to WHO by Synovate, in their proposal to clarify the methodology used by them.

### 3.8.4 Background information about TLAC recommendations on visual cue

IPAC members discussed that in order to reach a consensus about the new visual cue, full background information and history about TLAC's assumptions and recommendations were needed. For instance, it was pivotal to examine the logic behind TLAC's decision to use five particular icon pairs over other combinations of visual cues, in the Synovate study.

### 3.8.5 Re-examination of a single visual cue

According to current field test study design, two icons as a visual cue pair worked best. However, some IPAC members proposed having a single icon – for example, to keep the vial if a cue was present. This violates TLAC's original assumptions, which were to have cues for all vials.

Dr Eggers responded that if this occurred, the default outcome would be that vials not carrying a cue would be discarded. This could result in increased wastage. For instance, many multidose vials with unpreserved liquid will bear no marking, and will rely on the knowledge of the health workers to throw it away, compromising safety. Therefore, it was decided to have visual cues on all vials, not solely for vials that were to be kept. Dr Eggers mentioned that even though complicated, it was nevertheless an important concern for WHO.

### 3.8.6 Other points of discussion regarding implications of a new visual cue

Concerns about the training of health workers were raised. Dr Eggers said that due to new policy, previously trained health workers could indulge in unsafe practices because their training was now obsolete. Training of the health workers to react differently to a new visual cue was thus, crucial. In addition, MDVP was not well established in several countries. This underscored the need for training of health workers as well as on-the-job follow-up, to ensure implementation of new visual cue policy.

IPAC members also suggested that multiple stakeholders in a larger number of countries be involved in discussions for development of a new visual cue. Awareness amongst local people could be the key for higher success rates.

#### 3.8.7 Designation of IPAC members for visual cue subgroup

IPAC members agreed to strive for the proposed end-September 2010 deadline, to attempt to reach a decision about selecting a visual cue. However, it was noted that the timeline was tight and that further time may be requested. It was also noted that more information was needed. Annotated TLAC meeting decisions (which include decision to reduce number of cues, and outlining of issues for MDVP policy) would be provided to IPAC members.

Najwa Khuri-Bulos, Robert Steinglass and Francois Gasse volunteered to be part of the visual cue revision subgroup and take charge of the issue, with Mr Steinglass assuming the role of "topic lead".

# 4 Programmatic Suitability of vaccines for Pre-Qualification (PSPQ)/Preferred Product Profile

The primary objective of the session was to update IPAC on the progress with the establishment of a procedure within vaccine pre-qualification, to review the programmatic suitability of vaccines being presented for pre-qualification. Again, this agenda item has been carried forward from previous work done by TLAC.

## *4.1 Overview of PSPQ development*

Dr Rudi Eggers underscored the need for revising and defining critical and preferred characteristics of vaccine products, and communicating them to developers and manufacturers in a transparent and reproducible process. As part of the PQ process, product summary files (PSFs) usually determine 'the suitability of the vaccine for the immunization services where it is intended to be used'. However, the emergence of unique vaccine presentations and packaging as well as emergence of new manufacturers and new manufacturing sites has driven the need to explicitly define the characteristics that determine programmatic suitability and the process for assessing compliance with these characteristics.

Dr Eggers proposed the following considerations for IPAC to take note of while reviewing PSPQ requirements-

1. Vaccines currently pre-qualified are to be excluded from revision of PSPQ.

2. Pre-qualification rules provide guidance. However, the decision to pre-qualify or not lies entirely with the PQ team and their advisors. Programmatically challenged products, in order to be considered, would require further justification.

3. The importance of communicating and consulting with UNICEF and PAHO Revolving Fund tendering process.

4. These considerations need to be aligned with the revision of the PQ system currently under way, in the form of eight white papers that refer to different aspects of pre-qualification.

5. The criteria and the process that will be used to ascertain PSPQ needs to be developed and communicated.

## *4.2 Outcome of the informal consultation with the ad hoc committee on vaccines pre-qualification*

Ms Emma Uramis, WHO Geneva, updated IPAC on the outcome of the informal consultation to review and update the pre-qualification procedure. The pre-qualification (PQ) procedure is a service provided by WHO to UN agencies like UNICEF and PAHO to assess the quality, safety and programmatic suitability of vaccines.

Ms Uramis presented the purpose and the principles of the PQ procedure and discussed the rationale for its revision. She stated that the ad hoc committee on vaccines pre-qualification reviewed policy, technical and communication updates, and for this purpose eight working groups were established in advance, each of which produced a white paper including specific proposals.

Ms Uramis elaborated on policy matters that were addressed in the revision, along with need for better guidance on programmatically acceptable product characteristics for pre-qualification and their assessment process.

Ms Uramis highlighted that the ad-hoc committee endorsed the proposed process for reviewing the suitability of vaccines for pre-qualification, as well as endorsed the establishment of a standing committee to review deviations from the defined critical characteristics.

In terms of a scheduled timeline, a final draft consisting of revised PQ procedure would be presented to the WHO Expert Committee on Biological Standardization (ECBS) in October 2010, for endorsement; and subsequently, to the Executive Board in May 2011, for approval. The draft document on PSPQ would be posted for public consultation and when finalized, would be published on the website.

## *4.3 Summary of the White Paper on PSPQ and next steps*

Dr Eggers presented the White Paper on PSPQ[4]. He pointed out that the White paper draft intended to provide guidance to industry, and transparency and objectivity to the PQ Secretariat and the Director IVB on characteristics of programmatically suitable vaccines and their assessment process.

Dr Eggers summarized PSPQ characteristics identified by the White Paper by reviewing existing WHO IVB policy, technical guidance, and discussions by WHO IVB advisory groups as well as EPI staff. Vaccine characteristics were organized into four groups, which are as follows:

1. *Mandatory*. For this characteristic, compliance was compulsory. Failure to meet this characteristic would prevent the vaccine from being further considered for pre-qualification.

2. *Critical*. For this characteristic, compliance was expected. Critical vaccine characteristics would be reviewed by the PSPQ Standing Committee. Only under special circumstances could exception be granted to vaccines that deviate from the critical characteristics. Decision would be taken by the PQ Secretariat and would include consideration of recommendations from the PSPQ Standing Committee, and consideration of topics such as public health need and access to vaccines.

3. *Unique* (characteristics not otherwise specified). The PSPQ Standing Committee would review these characteristics. Vaccines complying with these criteria may be pre-qualified if considered by the PQ Secretariat on advice of the PSPQ Standing Committee.

4. *Preferred*. These characteristics were intended to indicate what WHO and national immunization programmes would want in a best case scenario and expect in the future. They were meant to guide vaccine manufacturers during development of new vaccine formulations. A vaccine not complying with preferred characteristics would not be prevented from further review for pre-qualification. However, it is noteworthy that a preferred characteristic may be deemed critical, in future revisions.

Each of these characteristics were defined by criteria such as thermostability storage, antimicrobial preservatives, VVM, dose volume, co-administration with other vaccines, visual

[4] White Paper: Assessing the Programmatic Suitability of Vaccines for WHO Prequalification, 8 April 2010, presented to the "Informal consultation with the ad hoc committee on vaccines pre-qualification for the revision of the procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations Agencies, WHO Geneva, Switzerland, 19-21 April 2010.

cue regarding handling and discard, packaging, injection material and so on. For detailed criteria, please refer to White Paper on recommendations for PSPQ of vaccines.

Dr Eggers further explained that the PSPQ Standing Committee (when formed) would be aligned to IPAC and would be under strict confidentiality obligations, having no conflict of interest. However, it may engage in confidential discussion with manufacturers and additional technical experts, and may also recommend validation by research of the acceptability of non-compliant characteristics.

## *4.4 IPAC discussions and conclusions on the White paper and PSPQ policy revision*

### 4.4.1 Clinically significant interactions between vaccines

Concern was raised by some participants regarding criteria relating to data on the co-administration of vaccines as one of the mandatory characteristics. They pointed out that although certain interactions may be dangerous, there might be other interactions between vaccines that may be harmless. In addition, certain vaccines with dangerous interactions may not be administered in all countries. It was thus important to assess the intended use of the vaccine, how many antigens needed to be tested in order to fulfil these criteria, and whether the interaction data were valid in a specific country setting. Further, since vaccines from different manufacturers differ in terms of interaction with other vaccines, these data would need evaluation and consideration as well. It was suggested by IPAC members that due to the importance and variability of these criteria, a separate clinical trial committee should be commissioned to deal with clinically significant interactions. These points were considered noteworthy by WHO.

### 4.4.2 Other considerations

It was suggested by IPAC that in revising tertiary and secondary packaging criteria of vaccines, a correspondence between amounts of diluent to the dose of that vaccine should be considered.

IPAC members questioned whether -20$^{o}$C was too low a temperature to be considered a mandatory characteristic for PQ of vaccines, considering that most vaccines were stable at much higher temperatures, and many developing countries lacked cold chain infrastructure. A member suggested that it should be mentioned specifically that the criteria of temperature control for storage of vaccines is applicable at the peripheral level or the health centre level, and not at the central storage level. For example, oral polio vaccine should be stored at -20$^{o}$C at the central storage facilities. However, in the health centres, it can be safely stored between +2 $^{o}$C to +8$^{o}$C. IVB clarified that the mandatory requirement made any vaccine that *required storage at lower than -20°C* as un-prequalifiable.

The role of countries in making a PQ decision for vaccines of their choice was questioned by IPAC. Dr Woods replied that WHO would advise countries about PQ of certain vaccines. However, the issue about countries' choice would be discussed in the future when the regulatory technical advisory group has a meeting. At that time, countries will have an opportunity to reflect on, and state, their individual choices.

During the discussion, other representatives of vaccine manufacturers expressed their concerns about this area of work. To avoid wasting of time and effort, to avoid duplication of work, and to streamline the process, the guidance on programmatic suitability of vaccines should be sought long before PQ procedure is started, in discussions between PSPQ and the manufacturers. Linkages of the PSPQ to other policy development, such as the revision of MDVP, should be taken into consideration, and it should be foreseen that revisions of the PSPQ characteristics would take place once these policies have been finalized.

### 4.4.3 Next Steps for PSPQ policy revision

The next steps for PSPQ Standing Committee included participation of IPAC members in the committee meetings once Terms of Reference were confirmed, and the PSPQ Standing

Committee convened. It was discussed that a teleconference meeting would be held for focused discussions with IPAC's MDVP revision subgroup. However, members requested more time to review the White paper in detail, before forming a subgroup.

# 5 Hepatitis B birth dose delivery

The objectives of this session were discussion of practical aspects of the ongoing Hepatitis B (HepB) birth dose programme, inviting IPAC's comments and recommendations for new approaches.

## *5.1 Overview of HepB birth dose programme*

Dr Steven Wiersma from WHO Geneva, presented this session. He explained that chronic Hepatitis B Virus (HBV) infection was an important cause of morbidity and mortality worldwide. In terms of disease burden, a large majority of deaths resulted from HBV infection acquired in early childhood whereas infection acquired after five years of age account for a minority of deaths. Preventing HBV infection can primarily prevent HepB.

There was moderate quality evidence to support effectiveness of HepB vaccine administration within 24 hours, and even within 7 days of birth, to prevent chronic infection. Based on these data, in November 2008, SAGE recommended that all countries, especially those with high endemicity, develop disease control goals for Hepatitis B appropriate to their epidemiologic situations. In April 2009, SAGE advised that all infants throughout the world should receive the HepB birth dose as soon as possible (less than 24 hours), after birth. This should be followed by two or three doses to complete the series. In the event that this is not possible, then the first dose should be given as soon as possible. SAGE also recommended that immunization programmes should work with maternal and child health programmes to promote the administration of the HepB birth dose, stating that its timely delivery (i.e. within 24 hours of birth) should be a performance measure for the immunization programme. These recommendations were endorsed by WHO.

## *5.2 Challenges and next steps*

Dr Wiersma listed some of the challenges for the HepB birth dose programme. Since it was important to immunize early to prevent late infections, it was important to also carry out immunizations in non-EPI settings, like rural homes where births take place, and where there may not be skilled health workers or appropriate facilities, like cold chain. Although in many countries, Hepatitis B vaccine was part of a pentavalent combination vaccine (with DTP and Hib), for the birth dose, a monovalent hepatitis B vaccine was required. A major problem was spurious Adverse Events Following Immunization (AEFI) against a background of high neonatal mortality, creating a risk for the programme to be unnecessarily suspended. In addition, monitoring may be difficult since the goal is stated in hours but vaccine doses are usually recorded in days.

Dr Wiersma mentioned that the next steps for the HepB programme included documentation of best practices and developing standards for implementation of the birth dose. A consultation has been planned in mid-October 2010 with WHO programme collaborators such as Burnet Institute, Victorian Infectious Diseases Reference Laboratory, and Division of Viral Hepatitis, US CDC.

## *5.3 Status of HepB adoption and country-specific examples from WHO WPRO*

Dr Karen Hennessey, from the WHO Western Pacific Region (WPRO), presented WHO's experiences with implementing HepB birth dose in WPRO.

Her presentation covered WPRO (with 37 countries and areas) and country approaches to HepB birth dose implementation. WPRO bears a disproportionate burden of HBV-related morbidity accounting for almost half of chronic infections worldwide. Therefore, HepB control

has been a public health priority, as demonstrated by the rapid introduction of HepB vaccine in all countries by 1996, and the goal for accelerated HepB control in the region adopted in 2005. However, fully integrating HepB vaccine into routine immunization systems and implementing birth dose vaccination has occurred over some time with a variety of experiences, challenges, and responses across WPRO countries. Some of these challenges are lack of infrastructure, home births with unskilled birth attendants, lack of awareness about importance of vaccinating in 24 hours, and a lack of financing.

By 2007, all countries in the region adopted policies for routine and HepB birth dose vaccination, except for Japan, which provides HepB vaccination using a targeted approach. Dr Hennessey covered country experiences with HepB birth dose implementation including successes in China (by increasing number of hospital births), challenges in Lao PDR and Papua New Guinea, as well as steady gains in Cambodia. She also described activities undertaken by the Philippines in response to late adoption of a national birth dose policy, and by Viet Nam in response to declining birth dose coverage after AEFI reports in 2007.

In addition, highlights from WPRO's 2006 Operational Field Guidelines for the Delivery of the Birth Dose of Hepatitis B Vaccine were presented in this session. This included a review of key messages, core and site specific guidance for developing national operational plans for HepB birth dose implementation, and special topics such as HepB vaccine options including the Uniject presentation, out of cold chain vaccine delivery, and the importance of recording and reporting the birth dose.

Dr Hennessey said that supporting countries that have not yet achieved birth dose coverage targets was a priority for WPRO. A key activity would be to assist with developing and implementing detailed operational plans, and a key strategy would be to include joint planning with Maternal and Child Health services.

## *5.4 Discussion and IPAC recommendations*

### 5.4.1 Expectations from IPAC

Dr Eggers suggested IPAC provide a global recommendation on practices by taking into account the recommendations by SAGE and the experiences of WPRO. IPAC would be required to help with programmatic issues, such as advising WHO about how to properly operationalize the HepB birth dose programme. Dr Eggers suggested the following four areas of further discussion by IPAC-

1. Service delivery: Operational challenges of delivering the dose; where the vaccine would be administered (home, hospital), private versus public sector delivery, and who delivers it (e.g. health care provider, trained birth attendant or community member) etc.

2. Vaccine: This would include discussions revolving around the vaccine and its presentation; whether it should be part of the cold chain, the vaccine costs and funding issues, the mode of administration, whether using Uniject was better than bundled single dose presentations, and the necessity of using monovalent preparations in the programme.

3. Monitoring: Operational part of vaccine coverage and challenges for data recording.

4. AEFIs and communication: Intervention and communication around incidental adverse events; examining temporal versus causal issues according to importance.

### 5.4.2 Concurrent administration of other neonatal health interventions

Several IPAC members pointed to the opportunity of combining HepB vaccination with other neonatal health interventions that should be given as a "package" within the first day of life. However, there were concerns raised over possible interactions of HepB with other vaccines like BCG, which were administered at birth. Dr Wiersma replied that at the moment, no possible interactions with concurrent administration of BCG had been observed. However, concerns were also raised about feasibility of co-administering HepB with other vaccines at birth, in terms of safety and cost for countries.

### 5.4.3 Issues around "birth dose"

IPAC members suggested that "birth dose" should be defined in terms of time limit, by appropriate scientific advisory bodies. WHO secretariat took note of this point for mention in the HepB position paper.

Also, IPAC considered it important to reconsider the data to define the upper age limit for administering a birth dose, which may have an influence on safe co-administration of other vaccines along with HepB, or on dosing intervals for subsequent vaccines.

The SAGE April 2009 meeting considered the exact number of later doses to be administered, and the time interval between HepB birth dose and other doses, along with GACVS. This information would have to be conveyed to the doctors, nurses, and health workers, in guidance documents.

### 5.4.4 Operational Issues

IPAC members also suggested involving paediatricians as key advocates and stakeholders in operationalizing the programme, as in some countries doctors rather than health workers administered vaccines. In addition, IPAC recommended considering appropriate HepB birth dose recommendations for premature children.

Several IPAC members concurred that HepB was a very heat-stable vaccine and suggested that it would be appropriate to discuss taking HepB out of the cold chain. This would benefit remote areas where cold chains were not available. It was suggested that this topic be discussed in the next IPAC meeting.

IPAC agreed that immunization at home and in hospitals was the key issue to consider, since it posed huge operational challenges. It was suggested that guidance documents from WHO should explicitly describe how data must be recorded for the EPI.

Some IPAC members recommended that an advocate at country level might be useful to effectively frame and package the operational problems for the national pediatric board to consider.

### 5.4.5 IPAC focal point for HepB working group

Dr Robin Biellik volunteered to participate in the HepB working group and act as a liaison between the two committees – IPAC and HepB Standing Committee, which was scheduled to meet in the fall of 2010.

# 6 "Routine" vs "Supplemental" - definitions and issues in data recording and analysis

The main objectives of this session were to draw attention to different strategies being used to increase immunization coverage, and to highlight key challenges for data recording and use. Furthermore, this session aimed to raise awareness about the scope of problems relating to routine versus supplemental doses, achieving agreement on definitions, and standardization of terminology. IPAC members were asked to volunteer to play a leading role for this initiative.

## *6.1 Routine versus Supplemental doses and delivery strategies: definitions and challenges*

Ms Tracey Goodman from WHO Geneva presented this session. She mentioned that routine delivery of immunization services to deliver routine doses remain the cornerstone of immunization in countries throughout the world. However, a variety of other delivery strategies have been employed to protect children from vaccine-preventable diseases as early in life as possible, and to control/ eliminate/ eradicate vaccine preventable diseases. She said that this diversity has led to some confusion in terminology because different approaches to delivering "routine doses" are used to boost immunization coverage.

Ms Goodman mentioned that previous distinctions between immunization campaigns/supplemental and routine delivery strategies for immunization have become blurred in recent years as events such as Child Health Days (CHDs), Maternal Child Health Weeks, Immunization Weeks, and other strategies are being increasingly used occasionally to boost routine immunization coverage, raise awareness of the benefits of immunization, and provide other high-impact health interventions. Collectively, these activities have been termed "Periodic Intensification of Routine Immunization" or PIRI. In 2008, more than 100 countries around the world conducted PIRI activities. However, the data recording and analysis practices differed from country to country. Consequently, performance monitoring of PIRI activities, and inclusion of the doses in national routine coverage calculations are inconsistent.

Ms Goodman emphasized an immediate need to offer guidance to countries on PIRI in order to ensure efficient data coverage and standardization of data reporting.

Before best practices for data recording and analysis can be developed, IPAC was asked to review proposed working definitions of types of immunization activities to be used as a global reference to standardize terminology. The definitions and the summary table are attached in Annex 1 on page 17.

## *6.2 PIRI- Challenges for data recording, collection and use*

Ms Rebecca Fields from AED presented this session. Unlike SIAs, screening of individual children during PIRI activities for age and vaccination history is critical because it determines which doses the child should receive during the activity. The presentation highlighted the need to calculate PIRI targets for children due or overdue for routine doses in order to measure achievements, and forecast vaccine supplies and equipment. To set these targets, both microplanning guidelines and the judgment and decisions of local managers are required.

Citing country-specific examples of promising practices for PIRI, Ms Fields mentioned that the organization of vaccination sites and good crowd management are important for promoting accurate screening and recording of doses administered. During a PIRI activity, the child health card should be used both for screening the child and recording the doses given. Tally sheets and registers should also be used to record doses, but both present certain operational challenges; e.g. the clinic-based register can only remain in one place at a time, making it difficult to capture all doses given at the many outreach sites typically used during a PIRI activity. Other good practices to enhance screening, recording and reporting of PIRI doses were presented, including communicating in advance with community members about the need to bring the child health card to the vaccination site. The importance of training, including skill practice on screening and recording, and timely supervision during PIRI activities were also discussed.

For effective data analysis following PIRI, sub-national specific trends need to be identified using pre and post-PIRI data. In addition, forums need to be arranged to review findings and provide feedback to the operational level. Planning and guidelines need to be revised accordingly and experiences need to be documented in the form of a publication. Further, including a session in EPI managers' meetings to exchange experiences on PIRI was suggested.

IPAC was asked to discuss various issues regarding screening, recording and reporting of PIRI. These issues included discussion on what kind of targets should be set for routine doses during CHDs and whether any registers, tally sheets, or special event-specific tally sheets should be used during PIRI events. IPAC members were also asked to discuss the challenges and possible solutions for analysis of data from PIRI.

An observer expressed reservations about the "supplemental" terminology applied to campaigns, observing that in general, the campaigns' main objective is to get high immunization coverage, not to give supplemental doses, as could occur in situations of waning immunity.

A key discussion point that remains to be resolved was about the distinction of "programme" and "doses" in describing routine or supplemental activities - there remains some confusion

between routine/supplemental doses and the delivery strategies, as both kind of doses can use same delivery strategies depending on the environment to reach their different objectives.

## *6.3 IPAC discussions and recommendations*

### 6.3.1 Working definitions

Overall, IPAC agreed that there was a need for definitions in order to standardize the terminology. There was consensus/support for the typology or definitions that proposed two categories of immunization and doses: (i) routine immunization/routine doses, and (ii) supplemental immunization/supplemental doses. However, there was no consensus on the actual proposed definitions. (see details in Annex 2). In addition, there was some agreement that PIRI was a subcategory of routine immunization. There was also a request for greater clarity when discussing PIRI, so as to distinguish the role of PIRI in the short term to boost vaccination coverage versus the potential role of PIRI to strengthen the capacity of the routine immunization system to predictably deliver timely and effective services of good quality. There was also a submission on the need to provide guidance to countries on the uses/purposes of PIRI and what kind of balance needs to be maintained between PIRI and with the routine immunization system.

### 6.3.2 PIRI, data coverage and recording

A need for offering WHO/EPI recommendations and guidance on best PIRI practices for data recording and analysis to countries was acknowledged by IPAC. This would help countries conducting PIRI activities to address data management issues effectively, promote monitoring and evaluation of PIRI, and better use PIRI as a strategy to strengthen routine immunization performance.

### 6.3.3 IPAC focal point for data analysis subgroup

Drs Vance Deitz and Folake Olayinka volunteered to serve as IPAC focal points for this topic.

# *7 Future considerations for IPAC*

Dr Michel Zaffran from Project Optimize discussed issues regarding Controlled Temperature Chain (CTC) with IPAC, for future deliberations.

CTC is an important factor to reach more people (where cold storage infrastructure is lacking), to reach right groups of people at the right time, decrease the risk of freezing of vaccines, and would become more conducive to integrated supply chains whilst decreasing reliance on specialized equipment.

WHO, in collaboration with PATH, was coordinating vaccine related activities to develop an acceptable requirement pathway for vaccines, to ensure that CTC was put into practice. In terms of technology, studies were ongoing to work out heat stability of vaccines, storage, threshold indicators, and VVM utilization. It was important also to generate guidelines to help countries and operationalize CTC at country level.

Dr Gastineau indicated that industry should be involved in this topic.

Dr Jules Millogo from IPAC volunteered to participate in the CTC subgroup.

## *7.1 Document for future IPAC consideration*

In the second part of the session, Dr David Wood presented a document ("Model requirements for the storage and transport of time and temperature-sensitive pharmaceutical products") for IPAC consideration in the future. The document, currently posted on WHO website[5], was

[5] http://www.who.int/immunization_standards/model_requirements_v2b.pdf

complementary to Dr Zaffran's description of CTC needs, and was in a mature stage of development. The document describes model requirements for storage and transport of temperature-sensitive products and biologicals, and defines regulatory considerations for oversight for pharmaceutical products. It would be presented to two expert committees for approval in October 2010.

Dr Wood requested IPAC members to go through the document and provide their comments. It was decided by IPAC members that the September teleconference would also include this item in the discussion agenda.

## *7.2 Administrative issues and Planning*

Dr Rudi Eggers discussed administrative issues in the last part of the meeting.

It was mentioned that, since this IPAC meeting was essentially paperless, all supporting documents and presentations would be present on the SharePoint website. However, it was suggested and agreed by IPAC, that an email would be circulated along with attached documents.

Dates were discussed for the teleconference, which was scheduled for the first week of September (tentatively 6 September 2010). It was decided that the second IPAC meeting would be held a week before the SAGE meeting, which was scheduled to be held from 9-11 November 2010. Due to several considerations, it was decided that the second IPAC meeting would be held on 4-5 November 2010.

IPAC members requested that pre-reads be distributed within a significant timeframe before IPAC meetings, so that members have enough time to review them. Dr Eggers agreed that pre-reads would be sent at least two weeks prior to meetings.

In addition, IPAC members were asked for their feedback on the first IPAC meeting. It was discussed that future IPAC meeting agendas should include additional pending topics from TLAC. In addition, IPAC members could suggest relevant issues to be presented for the future agenda. The IPAC chairperson, Dr Shelley Deeks, was the focal point for bringing in new topics that could be placed on the agenda.

Finally, IPAC members requested WHO secretariat that the email containing the meeting agenda should include annotations that described the purpose and the expectations for each session, along with the title of the background document and corresponding weblink.

# 8 Annex 1: Initial terms of service for IPAC members

| IPAC member | Start | End |
|---|---|---|
| Shelley Deeks (chair) | 2010 | 2013 |
| Robin Biellik | 2010 | 2013 |
| Xavier Bosch-Caplanch | 2010 | 2011 |
| Francois Gasse | 2010 | 2013 |
| Najwa Khuri-Bulos | 2010 | 2011 |
| Sanath Lamabadusuriya | 2010 | 2012 |
| Jules Millogo | 2010 | Resigned |
| Pieter Neels | 2010 | 2011 |
| Folake Olayinka | 2010 | 2013 |
| Jane Soepardi | 2010 | 2012 |
| Robert Steinglass | 2010 | 2012 |
| Pierre Van Damme | 2010 | 2012 |

# 9 Annex 2: Definitions of Types of Immunization as presented to IPAC

The Global Immunization Vision and Strategy (GIVS) is comprised of four major strategic areas, of which the first is "reaching more people in a changing world." Routine immunization services remain the cornerstone of immunization in countries throughout the world, but a variety of service delivery strategies can and are employed to protect children from vaccine-preventable diseases as early in life as possible. This diversity of approaches can lead to some confusion because different approaches to delivering routine immunization services are used to provide routine vaccine doses. The following text clarifies the different categories of service delivery strategies, with particular attention to the characteristics of the vaccine doses administered through each approach.

Routine immunization refers to vaccination services that are planned and provided continuously throughout the year. The target group for routine vaccination are those children (and women, for tetanus toxoid) who are of eligible age to receive vaccination according to a national immunization schedule. All types of delivery strategies can be used for routine immunization, including fixed-site, mobile, outreach, and campaign. The age of the child is determined, vaccination history is obtained from card or mother's recall, and this information is used by the vaccinator to decide which vaccinations should be given (this is called screening). Children younger than the recommended age of vaccination (per the national schedule) are not vaccinated. Older children who have delayed or missed vaccinations are vaccinated. For every child vaccinated, the vaccination/dose and date is recorded on the child's health card, clinic registry, and clinic tally sheet. The caregiver is told when the child needs to receive its next vaccination. Likewise, women of childbearing age are screened and vaccinated with tetanus toxoid, with doses recorded in a similar manner.

Periodic Intensification of Routine Immunization (PIRI): A special, time-limited (i.e. not year round) effort that is conducted periodically (this may be annually, semi-annually, or several times a year) with the objective to improve/boost routine immunization coverage. PIRI activities may be designed to focus on missed or hard-to-reach children, special groups (immigrants, nomads etc.), or simply all children. The population for PIRI does not have to be the same each time, and may change depending on need or priorities. It is also possible that the PIRI target may vary sub-nationally (i.e. be different in different places). Regardless, the objective and target group for PIRI remains the same- to vaccinate children who are of eligible age to receive vaccination according to a national immunization schedule. Most PIRI activities also serve the purpose of creating or revitalizing demand for routine immunization services.

Globally, there is a wide range of PIRI strategies, including for instance, intensified advocacy/communications (European Immunization Weeks), where populations are encouraged to attend fixed-site facilities for vaccination and some focused additional vaccination activities are carried out; integrated Child Health Weeks (campaigns); and Quarterly Pulse Outreach. In all PIRI strategies, it is intended that children are screened for age and vaccination history is obtained from card or mother's recall; this information is used by the vaccinator to decide which vaccinations should be given. Children younger than the recommended age of vaccination (per the national schedule) are not vaccinated. Older children who have delayed or missed vaccinations are vaccinated. For every child vaccinated, the vaccination/dose and date is recorded on the child's health card, and a tally sheet in an age-appropriate column (disaggregating data for those under 1 years of age, and doses given to those over the age of one year). Depending on the type of PIRI strategy used, it may not be possible to record the doses given on a clinic register. The caregiver is to be told when the child needs to receive its next vaccination. All vaccinations given to children under one year of age through PIRI strategies should be included in the routine administrative data collection systems. These doses should then be included in the "Administrative Coverage" section of the WHO/UNICEF Joint Reporting Form (JRF).

Supplemental Immunization refers to vaccinations that are given irrespective of prior vaccination history, to boost population-level immunity and achieve a particular disease control objective, e.g. Polio National Immunization Days (NIDs). These doses are "supplementary" (i.e. additional and extra) and do not count towards the routine vaccination doses that are required per the national immunization schedule.

Supplementary immunization activities are periodic and time-limited. All types of delivery strategies may be used including fixed-site, mobile, out-reach, and campaign. The target population is a defined age group of infants/children/adults, susceptible and known epidemiologically to be important to the transmission of the disease. Vaccinators screen children/individuals for eligibility by age, but prior vaccination history is irrelevant to the decision to vaccinate. All individuals of eligible age are vaccinated regardless of the number of doses they have received previously. Caregiver is to be reminded when and if subsequent supplemental vaccination will occur (e.g. 2nd round). Messages about when and where to return for the next routine immunization session should also be given.

All supplementary doses are recorded on a tally sheet, which disaggregates doses given by age. Usually supplementary vaccinations are not recorded on child health or vaccination cards or clinic registers. However, if they are, then they should be recorded in a separate place on the card/register, and clearly date indicated as "Supplemental doses". Supplementary vaccinations should not be included in the routine administrative data collection systems, but should be reported separately. They should be reflected in the section of the WHO/UNICEF JRF on "Supplementary Activities".

**Different Types of Immunization Activities**

| | Vaccination given according to National Immunization Schedule | Frequency of activity | | Decision to vaccinate based on screening for | | Delivery Strategies | | | | Recording of vaccines given | | | Caregiver told when next routine doses are due | Doses Included in Routine Administrative Data Collection System |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Continuous throughout year | Periodic, Time-limited | Eligible age | Prior Vaccination History | Fixed Site | Mobile | Outreach | Campaign | Immunization Card | Register | Tally sheet | | |
| **Routine Immunization** | ✓ | ✓ | X | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| • **PIRI*** | ✓ | X | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | Not always | ✓ | ✓ | ✓ |
| **Supplementary Immunization** | X | X | ✓ | ✓ | X | ✓ | ✓ | ✓ | ✓ | Usually not; if yes must indicate "supplemental dose" not routine | X | ✓ | Next supplemental dose due; should give message about routine immunization services | X |