1 Opening and Introduction

Dr Shelley Deeks (chair) opened the meeting and welcomed all of the participants. Dr Pierre van Damme resigned as a member of IPAC. His vacancy will be filled through a public call for nominations. Prof. Jonathan Colton from Georgia Institute of Technology, Atlanta, USA and former TLAC member was welcomed as new IPAC member. Pieter Neels and Jane Soepardi were unable to attend this meeting, and Francois Gasse was not been able to attend the second day.

The minutes of the previous IPAC meeting were approved unanimously, without changes.

1.1 Feedback from SAGE meeting, April 2011 (Shelley Deeks, IPAC chair)

SAGE will focus in 2011-2013 on twelve priority cross-cutting and strategic issues which include the use of vaccine in humanitarian emergencies; accessibility to affordable vaccines and WHO’s role; reinforcing surveillance networks; communication methods for vaccine-hesitant populations; validation of coverage figures; use of vaccines in immune-compromised populations; optimizing immunization schedules; impact of introduction of new vaccines on strengthening of immunization and health systems; maternal immunization to enhance the protection of mothers and infants; involvement of the private sector; and, strengthening of NITAGs. A number of these issues are also of importance to IPAC.

Priorities for vaccine-specific recommendations and updates were also identified and include pneumococcal conjugate strain replacement (Nov 2011), rotavirus vaccines, TB vaccines, measles eradication, optimizing immunization schedules (RV, Pneumo, Hib), Polio (bOPV and post eradication), hepatitis A (Nov 2011), seasonal and pandemic influenza, yellow fever, varicella and zoster, JE, HPV, Malaria, and Dengue vaccines.

Some of the topics discussed during SAGE have implications for IPAC including the sessions on polio, rubella and meningococcal vaccines. SAGE will be developing recommendations on routine IPV use in low income setting in the post-eradication era, including considerations of fractional IPV (intra-dermal), which will have implications inter alia for IPAC’s visual cues discussions. In addition the working group is assessing the utility and feasibility of type 2 OPV
cessation in the pre-eradication era and considers planning for cessation and switch from trivalent to bivalent OPV. This may also have programmatic issues. Recommendations are expected at SAGE in April 2012.

The WHO position paper on rubella vaccine from 2000 is being updated. It was recognized that rubella control will benefit from the increased use of the measles platform and that measles elimination activities provide an opportunity to introduce rubella containing vaccines.

Finally the session on meningococcal vaccines also had programmatic issues including mass vaccination of adolescents/young adults with MenAfriVac, a group who may be challenging to reach, as well as the impact of the program on the immunization and health care system.

The interaction between SAGE and IPAC has been limited to the attendance of the Chair of IPAC to SAGE and providing feedback to SAGE on areas of interest/relevance. It was agreed that the chairs of the various advisory groups who attend SAGE will identify items of relevance for their committees and feed these back to the advisory committee, as well as the Chair of SAGE.

2  **Hepatitis B birth dose implementation**

2.1  **Overview of technical document on the implementation of the Hepatitis B Birth Dose. (Steve Wiersma, WHO)**

Worldwide, over two billion individuals are infected with hepatitis B virus (HBV). Four hundred million of them remain chronically infected. Early infection, especially perinatal infection (21% of HBV infections), substantially increases lifetime risk of chronic liver disease, including cirrhosis, and hepatic cancer which is the third most common cause of cancer mortality globally. Delivery of the first dose of a course of hepatitis B vaccine as a birth dose (BD, given <24 hours after birth) is the most efficient way to prevent perinatal transmission.

When SAGE made a global recommendation to implement the BD in 2009, WHO published a position paper which stated that all infants should receive the first dose of hepatitis B vaccine as soon as possible (<24 hours) after birth in all regions of the world. It was recommended that this should be followed by two or three doses to complete the series. Immunization programmes should work with maternal and child health programmes to promote the administration of BD, and the timely delivery of a BD should be a performance indicator for all national immunization programmes.

At present, 178 out of 193 member states have introduced hepatitis B vaccine, 89 of them also introduced BD; however, the coverage of BD (the proportion of live births that receive BD) is currently only 26% worldwide. Weak immunization programmes and primary health care services in some countries create challenges to birth dose delivery and achievements of hepatitis B control goals.

The technical guidance document, based on literature review and a WHO consultation held in Melbourne in December 2010, reviews the current evidence for best practices and needs for delivery and monitoring of BD. Varied approaches are required according to the place of birth (health facility or home), the availability and capacity of vaccination staff and their other duties (childbirth care, newborn care, routine immunization), the vaccine supply, the vaccine presentation, distribution and storage, and the level of community understanding, demand and utilization of childbirth or newborn care services.

In this document, it is suggested that the need for further guidance be provided in the following formats are: a short policy brief for use by national programme managers advocating for introduction or better integration of BD; a short ‘job-aid’ for programme managers, covering issues to address when integrating birth dose vaccination into maternal and newborn care; a short problem-solving guide, for settings with low coverage among births in health facilities or at home; and a longer management manual that consolidates documented experience with best practice suggestions, building on the WHO WPRO model. Further, there is need for a coordinated and systematic approach to integrate appropriate clinical guidance on
BD into global and national clinical protocols for care at childbirth or in the immediate newborn period and for formal position paper on ‘minimum standards’ as part of the WHO Making Pregnancy Safer series.

Discussion

A major concern to increasing BD coverage is funding. Although GAVI supports immunization of children for hepatitis B vaccine as part of pentavalent vaccine combined with DTP and Hib, GAVI does not provide funding for BD monovalent vaccine. Therefore, countries should be creative and look for innovative mechanisms to fund monovalent.

As the early neonatal period is fraught with risks, a coincidental adverse event incorrectly associated with BD vaccination may have a very negative impact on the credibility of vaccinators and the vaccine in the community. It has been suggested that initially hepatitis B BD should only be administered by vaccinators or trained midwives and thereafter to follow a step-by-step approach in extending this role to other cadres.

It is important to address the misconception that children with unstable conditions, and/or low birth weight are not eligible or are contraindicated for BD.

Hepatitis B vaccines from different manufacturers vary in their thermostability profiles, and this variation has implications for policy guidelines for the controlled temperature chain (CTC). A review of ongoing work and results from the Project Optimize will be provided to IPAC in September 2011.

It is necessary to create synergies with other health interventions given at birth. Clearly, interventions in the early neonatal period are more MCH-driven than EPI-driven and are focussed on high priority acute life-saving and life-preserving needs such as adequate ventilation, warmth and breastfeeding; the administration of the hepatitis B BD is less urgent than these acute care needs, and should therefore be instituted once the other interventions have stabilize the infant. It has been suggested to finalize the flowchart for newborn care in order to include the optimal time for administering the BD within the first 24 hours of life. The BD as part of an integrated package of services should be requested to be endorsed by professional associations.

WHO supports the compact prefilled auto-disable devices (CPADs), for example, Uniject™, as a valuable delivery technology for BD administration worldwide. The Uniject™ auto-disable injection system can be used by everyone after less than two hours of training. It cannot be reused, and it is precisely prefilled by the pharmaceutical producers with a single dose. The cost of a devise prefilled with hepatitis B vaccine is still relatively high, but bulk prices of prefilled devices have not yet been accurately costed.

It was suggested that more experience from African countries should be included in the document.

It was pointed out that the report had several methodological limitations and that the analyses, as presented, could not provide light on the implementation issues of BD introduction.

2.2 Overview of Melbourne Statement on the implementation of the Hepatitis B birth dose (Robin Biellik, IPAC member)

World Health Assembly resolution number 63.18 provided WHO with the mandate to accelerate the implementation of a birth dose (BD) of hepatitis B vaccine. To identify strategies to maximize coverage with the BD, WHO organized a consultation in Melbourne, Australia, in December 2010. The Melbourne Statement that was generated during the consultation recommends the implementation of the following strategies:

- Birth dose should be an integral part of Decade of Vaccines vision and implementation, contributing to global elimination of HBV transmission;
• Birth dose should be delivered as part of an integrated package of maternal and newborn care;
• Birth dose delivery should be coordinated with national immunization schedules;
• Expanded funding should be secured;
• Maximize the demand for birth dose;
• Provide funding support for monovalent HepB vaccine for poorest countries, for example by lobbying GAVI Alliance to reconsider inclusion of monovalent vaccine in its portfolio of new and under-utilized vaccines;
• Increase proportion of births occurring in health facilities;
• Ensure that infants born at home receive integrated package of maternal and newborn care, including birth dose;
• Promote the use of heat-stable vaccines through controlled temperature chain (CTC) in low-resource settings;
• Assess available alternative vaccine delivery options for use in low-resource settings, such as compact prefilled auto-disable devices (CPADs), for example, Uniject™;
• Pursue future innovations; and
• Address residual professional concerns regarding safety and effectiveness of birth dose delivery.

Hepatitis B (HBV) infection is a global public health problem. Significant migration between regions has resulted in pockets of population with high rates of chronic HBV infection occurring almost everywhere. A coordinated global effort to provide a dose of hepatitis B vaccine BD to all newborns within 24 hours of birth is urgently required. The achievement of high BD coverage would contribute to the eventual elimination of hepatitis B infection.

IPAC was requested to support the Melbourne Statement and to call upon WHO to support the Statement.

Discussion

Clearly, the Melbourne Statement is an outcome of a specific meeting with specific participants, and thus has a standing on its own. IPAC should focus on its advisory mandate to develop the best practices in birth dose implementation, and within that context may endorse the Melbourne Statement as is. However, some limitations to the Melbourne Statement were noted such as the absence of any mention of monitoring and evaluation.

Concern was expressed that BD may not receive enough attention in the MCH community because it does not contribute to infant and under-5 mortality reduction. It has been proposed to change the definition of the fully immunized child to include BD. Although the widespread introduction of pentavalent vaccine is a major step forward, it is also essential to maintain monovalent hepatitis B vaccine for BD.

2.3 IPAC recommendations and decisions

• IPAC recommends that WHO actively engage with countries through regional and global fora to anticipate the programmatic considerations and to assist with the effective implementation of SAGE-recommended universal introduction of the hepatitis B birth dose.

• IPAC acknowledges the value of, and has provided expert input on, the draft WHO document entitled “Best practices and needs for the delivery and monitoring of the hepatitis B vaccine birth dose,” and members will review an updated version for decision at the Sept 2011 meeting. However, methodological issues need to be addressed.

• IPAC recommends that WHO produces appropriate hepatitis B birth dose vaccination guidance materials/documents within one year.

• IPAC recommends that WHO develops a coordinated and systematic approach to clinical and preventative interventions at the time of birth. WHO should promote inter-departmental collaboration and coordinate between EPI and Maternal, Neonatal, Child and Adolescent Health (MNCAH) departments, as well as inputs from external stakeholders.
• IPAC envisages that monovalent hepatitis B vaccine will increasingly be required for hepatitis B birth dose. While short-term supply (until the end of 2012) is sufficient to meet UN demand, IPAC wishes to signal to manufacturers that for the longer-term demand scenarios may increase, and recommends that manufacturers prepare to meet this demand for preserved multi-dose and single-dose vials as well as compact prefilled auto-disable devices (CPADs).

• IPAC acknowledges the importance of the initiative articulated in the "Melbourne Statement on the Prevention of Perinatal Transmission of Hepatitis B virus: a call for the consideration of all available strategies."

3 Visual cue

3.1 Final report of the Synovate focus group assessment of the visual cue in Uganda, Cambodia and Peru. (Melissa Moodley, Synovate)

Results from the study conducted in Uganda and Cambodia were presented to the previous IPAC meeting. This presentation provided feedback on the results from Peru as well as general findings and recommendations. The initial samples included at least 100 health workers per main-stage interviews and on A4 size paper during follow-up interviews. For these follow-ups, random structured samples included at least 30 health workers per market from both rural and urban regions. A follow-up study was performed two weeks later. Samples were structured by region setting (urban, rural, peri-urban) to be aligned with the initial sample. The study evaluated the most preferred visual cues, spontaneous understanding, ease of communication, as well as long-term recall of the visual cues. Health workers were presented with five pairs of visual cues selected for testing (figure 1). These cues were presented to health workers on vaccine vials (both with and without VVM) during main-stage interviews and on A4 size paper during follow-up interviews.

Figure 1: Icon pairs

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Icon A" /></td>
<td><img src="image2" alt="Icon B" /></td>
<td><img src="image3" alt="Icon C" /></td>
<td><img src="image4" alt="Icon D" /></td>
<td><img src="image5" alt="Icon E" /></td>
</tr>
</tbody>
</table>

In assessing suitability in all three countries, overall, pair A (Figure 1) was deemed appropriate for all markets. Visual cues using familiar symbols (such as clock, watch, and calendar) are most likely to intuitively communicate the correct discard message. In all countries, pair C is most likely to be correctly identified for the 6 hour message. Additionally in Uganda and Cambodia, pair B also achieves a high level of correct recall. Pair A is mostly likely to be correctly identified in Uganda and Cambodia for the 28 day message. Additionally in Cambodia and Peru, pair B is also accurately identified. While these countries have similar levels of spontaneous recognition, patterns for overall preference for visual cue differ: Uganda consistently favours pair A (clock and calendar) on all parameters. Cambodia and Peru however do not have a strong preference for one pair. Pairs A, B, C, and E (for Cambodia) score well on all metrics tested and are ranked 1st or 2nd overall by a similar number of respondents. This suggests that pairs A, B, and C are all feasible for Cambodia and Peru. The follow-up study is also consistent with the above results: Uganda is most likely to correctly recall messages based on pair A while the majority of respondents in Cambodia and Peru correctly recall the messages based on pairs A, B and C. pair A causes the least amount of confusion in Uganda, while pair B and C cause the least confusion in Peru and Cambodia. It is important to note that option E is the least intuitive and most likely to cause confusion because there is no indication of time in the picture.

Different pair combination options have been considered, but these were not tested because only 25% of the sample population preferred to make a new combination. The written report from Synovate will be available the end of April and will be copied to IPAC.
It was pointed out during the discussion, that the way data were presented did not allow assessment of the magnitudes of the differences observed. There was also a discussion on which of the criteria assessed in the study should prevail in the interpretation of superiority of a pair.

3.2 **Reflection on the previous visual cue decisions made in IPAC and TLAC (Rudi Eggers, WHO)**

This is the sixth meeting to discuss the visual cue. TLAC-MDVP sub-group decided on 25 May 2009 that placement of the VVM alone is insufficient as a visual cue for the MDVP. The VVM will continue to be used as an additional cue and default position would be that without a VVM, the product must be discarded at the end of a session. It was decided that visual cues should be professionally designed icons or symbols, and tested through empirical data gathered from multi-cultural focus group.

During the TLAC-MDVP teleconference of 26 June 2009, it was agreed that the visual cue should be an additional symbol on the label of the vaccine. It was also agreed that visual cues should be pairs of markings presented, not single markings. In addition, the visual cue should not be colour based. All of the proposed coloured icons and labels were removed from consideration, leaving only black/white options.

TLAC recommended in September 2009 that field-testing should be performed at the peripheral health-centre level in various cultural and linguistic settings on three continents and that this work should be designed and conducted by professionals experienced in market research, product image recognition, and consumer assessment. Five pairs were recommended, of which four were accepted by WHO, and one replaced with an alternative, (pair E). The options relying on a coloured, serrated or marked border would not be acceptable.

Visual cues also were presented and discussed at the two previous IPAC meetings.

WHO would clearly recommend that all multi-dose vaccines, whether pre-qualified or not, comply with the visual cues standards to avoid confusion.

3.3 **IPAC recommendations and decisions**

- IPAC recommends that a visual cue is placed only on multi-dose vials and on those single dose vials that can (as fractional doses) be used as multi-dose vials. Visual cues are **not** required on single dose vials.

- Legibility: IPAC finds that the visual cue icons are sufficiently clear to distinguish among them.

- Adaptability: IPAC recommends that the visual cue should be chosen to allow for adaptability (i.e., future additional discard time categories).

- IPAC recommends that the icon pair A (timer and calendar) is the visual cue pair chosen to be piloted.

- IPAC further recommends that pair A should be reviewed and refined by a professional designer, with appropriate input from industry, to ensure the maximum readability and feasibility of print by end of June 2011.

- IPAC recommends that the chosen visual cue pair is piloted based on a protocol reviewed and agreed to by the VCSG. A final decision on the global roll-out should be taken after the pilot.

- IPAC will provide guidance to WHO on the purpose/objectives of the pilot, types of country(ies) and vaccine(s) that should be chosen as pilot.
4 Vaccine safety update

4.1 Outline of vaccine safety issues presented to the Global Advisory Committee on Vaccine Safety (GACVS) in the last year. (Najwa Khuri-Bulos, IPAC member)

Two GACVS meetings took place in 2010. This feedback is from the most recent GACVS meeting held in December 2010 where four major topics were discussed:

Rotavirus vaccine and risk of intussusception.

The first commercial rotavirus vaccine, (Rotashield, manufactured by Wyeth) was associated with an increased incidence (1/5,000,000-1/10,000) of intussusception, an uncommon form of bowel obstruction. The two rotavirus vaccines available on the market now are Rotarix (by GSK Biologicals) and RotaTeq (by Merck & Co, Inc.). Large pre-registration clinical trials for both vaccines did not show evidence for increased risk of intussusception. Nonetheless, WHO recommended that post-marketing surveillance for this adverse event should continue whenever these vaccines were introduced on a wide scale in new population groups. Post-marketing surveillance was conducted in two large countries in South America, Mexico and Brazil. In Mexico an increased risk of intussusception of 1/50,000 to 1/100,000 was found, occurring within 1-7 days after administration of a first dose, but a similar study in Brazil did not find this effect. After review of evidence from other countries including Australia and the USA, GACVS concluded that postmarketing surveillance indicates the possibility of an increased risk of intussusception shortly after the first dose of rotavirus vaccine in some populations. However, the benefit (estimated to prevent 700 deaths per year in Mexico), still substantially outweighs the risk. GACVS will continue to monitor post-marketing surveillance data on rotavirus vaccines.

Yellow fever (YF) and HIV infection

Administration of yellow fever (YF) vaccine is contraindicated in immune-compromised persons. However, the mass scale of vaccinations, showed that most of the reported serious adverse events following immunization (AEFI) were not related to a positive HIV status. GACVS confirms that individuals known to be severely immunocompromised should not receive yellow fever vaccine; the available data do not identify a significant problem with mass vaccination in populations where a moderate proportion of individuals are HIV-positive.

Meningococcal type A conjugate vaccine

Meningococcal type A conjugate vaccine has been administered to more than 1,000,000 people in several African countries in the meningitis belt. Surveillance detected 215 cases of AEFI, only 34 of them severe. Based on a review by experts, one of the severe cases was classified as anaphylaxis. In addition, GACVS concluded that there is no evidence to support the current recommendation of withholding meningococcal vaccine in pregnancy and lactation and recommends instead its use in pregnant and lactating women. Finally since current surveillance is passive in nature and may not fully capture all AEFIs in African countries, efforts are needed to improve post-marketing surveillance GACVS will continue to monitor the situation.

Safety of H1N1 vaccines

Data from Finland suggest that the risk of narcolepsy among people aged 4-19 years old who had received pandemic influenza vaccine was nine times higher than that among those who had not been vaccinated. This translates into a risk of about 1 case of narcolepsy per 12,000 vaccinated in this age group. No increased risk has been seen in younger or older age groups. Narcolepsy is a rare sleep disorder which is genetically linked with a specific HLA genotype. A report on this subject will be published shortly after data from other European countries have been examined.

1 Weekly Epidemiological Record, No. 5, 28 January 2011
4.2 Programmatic consequences of the rotavirus dose timing limitations (Jhimil Bahl, WHO)

Both Rotarix™ and RotaTeq™ are live liquid vaccines, presented in single-dose vials. Both can be co-administered with pentavalent and several other vaccines. The number of doses needed for full protection for Rotarix™ is two doses and for RotaTeq™ are three doses. There is a VVM available for Rotarix™, but not yet for RotaTeq™.

WHO recommends that the first dose of either RotaTeq™ or Rotarix™ be administered between ages 6 and 15 weeks because cases of intussusception are more likely to occur in infants aged >15 weeks than in younger infants. The maximum recommended age for administering the last dose of either vaccine is 32 weeks. A flowchart to determine eligibility for rotavirus vaccination is available in Annex 2. If outreach services are delivered at intervals of more than 10 weeks some children will be ineligible for Rotarix™ vaccination as children 5 weeks old at the time of the outreach would be too young to receive the first dose of vaccine, and 10 weeks later, when the next outreach is conducted, they will be too old to be eligible, thus missing all doses. For RotaTeq™, with a three dose schedule, outreach should occur at regular intervals of less than 9 weeks to limit the number of children to be ineligible for RotaTeq™ vaccination.

IPAC has been requested to provide guidance to countries about how to deal with the timing of the strict rotavirus vaccination schedule, and its programmatic consequences. Countries with a large proportion of outreach sessions need to undertake detailed micro-planning outlining session frequency in each area/village. Sessions need to happen at regular intervals throughout the year. Local mechanisms need to be strengthened to register and follow newborns.

Discussion

Intussusception occurs in all countries, with or without rotavirus vaccination. Where intussusception is temporally associated with rotavirus vaccination, it is a potentially severe AEFI and, therefore, monitored closely through post-marketing surveillance, including the recognition of early intussusception signs and symptoms.

AEFI can have serious negative impact on immunization programmes. It has been suggested to increase communication between GACVS and SAGE and to exchange minutes of the meetings. It was also suggested to share all reports of severe AEFI (also programmatic errors like toxic shock cases of Vietnam or deaths following use of wrong diluents for measles in India) to IPAC.

4.3 IPAC recommendations and decisions

- IPAC decided to form two new sub-groups. One group (including IPAC members Robin Biellik, Robert Steinglass, and regional WHO staff member Nadia Teleb) will focus on urgent programmatic issues for rotavirus vaccine introduction. The other sub-group (Najwa Khuri-Bulos and Shelley Deeks) will focus on safety, legislation and policy issues related to rotavirus vaccine timing.

- There should be regular feedback between IPAC and GACVS, including the sharing of each other's agendas prior to the meetings. The WHO secretariat should follow up internally to ensure that this occurs.

5 Vaccine labelling proposal

Debbie Kristensen from PATH presented on behalf of the Vaccine Presentation and Packaging Advisory Group’s (VPPAG). Two issues from experiences in country programmes were brought to the attention of VPPAG in May 2010: the expiry date format and the label legibility. Many

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2 Weekly Epidemiological Record, No. 23, 5 June 2009, page 235
non-English speakers have difficulties reading the month when written in English. When the month is in numerical form, there is confusion about which number represents the month and which represents the day (e.g., 02-04-12 = February 4th or April 2nd?). The text size on some vaccine labels is too small to be legible.

VPPAG conducted primary research on the topic and surveyed vaccine producers through the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) and Developing Country Vaccine Manufacturers’ Network (DCVMN) representatives about the issues. The group sought initial regulatory input through the WHO/QSS representative and developed a draft position paper on the labelling topics. VPPAG circulated a paper to constituents, incorporated their feedback, and prepared a consensus document for submission to WHO and IPAC for review.

VPPAG proposed further evaluation of the following vaccine labelling issues to IPAC:

**Content and language requirements:** Text legibility is directly related to the quantity of text. There are at present more label content requirements for WHO compared with US or EU. Multiple language requirements add to the challenge of excess content. A review of WHO’s minimum requirements for content and language is suggested. Some information might be better placed in the package insert.

**Standard generic names for vaccines:** Use of standard, generic names could create consistency and improve correct product identification and use. Brand names could also be included.

**Minimum font size and type:** As the same font size can be of very different legibility, it is recommended that WHO consider specifying both a minimum font size and type (or “x height”).

**Minimum viewing area:** It is important that the vaccine label does not obscure the ability of health workers to view the vial or container contents to conduct the shake test or ensure that a vial has been fully reconstituted. Specifying a minimum viewing area might assist in this regard. Specification could differ by type of vaccine and number of doses per vial.

**Expiry Date format:** An all-numeric format is recommended for expiry date: MM-YYYY, meaning that the product expires at the end of the month.

**Discussion**

The label content text is formal requirement, although studies have shown that many health workers tend not to read the information available on the label. It is indeed good to rethink what needs to be on the label. As labelling is a country-specific national regulatory requirement, the minimum requirement proposed here should be appropriate for all countries.

The programmatic benefits need to be considered before the introduction of changes.

Brand names on the label are important for product identification (e.g., to differentiate between a brand that is a two dose regimen and one that is a three dose regimen) and also for safety issues. The lot number has to be present on the label.

Consideration of the use of graphic standards was suggested – that is a standard layout where the same information is consistently placed in the same location on all labels.

There was discussion about adapting to an expiry date format of MM-YYYY. An added benefit could be that this format would help with stock management – as stock could be reviewed at the end of each month and expired products could be discarded. There was some discussion about the interpretation of the month: whether does the vial expire at the end or at the beginning of the month, and the potential for confusion The products would still be 100%
effective at the end of the month listed as the expiry date. The risk is in the right direction as a misinterpretation would lead to early discard rather than late discard. The final decision needs to balance risk against wastage. Changes in labelling also have a programmatic issue, requiring communication to the field.

It would make sense to also review the concept of adding RFID/bar codes to vaccine labels at the same time as reviewing other label content requirements.

5.1 IPAC recommendation and decision
IPAC agreed on the following recommendation:

• From a programmatic perspective, IPAC recommends that WHO/QSS consider the VPPAG proposal entitled “VPPAG Position on Labels for Vaccine Containers.”

WHO/QSS may request further feedback from IPAC and VPPAG members as they move this scope of work forward.

6 Request for proposal: Impact of measles activities on routine immunization

6.1 Purpose of the RFP (Emily Simons, WHO)
As momentum has been building towards achieving worldwide measles elimination and possibly even eradication, so too has the recognition that strong routine immunization (RI) and surveillance systems are critical to achieving and sustaining the gains in measles control. Special measles control and elimination activities, such as supplementary immunization activities (SIAs), can have positive or negative effects on routine immunization services and the broader health system. Studies indicate that the effects are more likely to be positive in stronger health systems and negative in weaker ones. Yet it is the weaker systems that have the greater need for SIAs. Because it is still unclear how to minimize negative externalities or to promote the uptake of best practices, WHO launched a RFP.

The objective of the proposal is to identify opportunities and practical methods in which member states can use activities focused on controlling or eliminating measles to also strengthen routine immunization/surveillance system performance for mutual advantage. The deliverables include guidelines for SIAs and surveillance that:

• Describe practical actions to strengthen routine system capacity or performance when implementing measles activities;
• Present human resource requirements, financial and material costs needed to carry out these actions; and
• Provide potential quantitative process indicators to monitor how measles activities influence determinants of routine immunization and surveillance system capacity or performance at the national level.

• The revised timeline is 1 May 2011 to 31 May 2012, and the budget: US$ 150,000

The main challenge will be to provide indicators to measure the influence of measles activities on routine systems. It is difficult to develop valid, reliable and useful indicators. Process indicators are more applicable to “best practices”, but are not direct measures of the impact of measles activities on systems. Attributing changes in indicators of health system strength to a single intervention such as measles is extremely difficult, as there are multiple contributing factors to changes in the health system performance. Inaccurate data (e.g., population) diminish reliability of indicators. Uneven changes in data quality between various sources (e.g., surveillance and human resources data) over time inhibit meaningful comparisons and infrequent data collection outside of immunization may prevent regular monitoring of indicators relating to broader system. The time available for data recording/management is very limited, so commitment to calculating and monitoring new indicators may be low.
6.2 Awarded JSI Proposal (Robert Steinglass, John Snow Inc.)

The tender was launched in February 2011. Two proposals were received and the proposal of John Snow Inc (JSI) was selected for funding.

JSI will deliver a report about the positive and negative aspects of single disease efforts on routine immunization and the estimated additional costs to reap benefits. JSI will also provide two guideline documents for actions to strengthen RI (and indicators) and for actions to strengthen routine surveillance (and indicators). Further, they will develop prototype advocacy materials that reframe measles control as a development challenge instead of isolated activity.

The methods proposed to reach the objective are examination of literature to guide the field work and review of experience in three countries. The project concept will be discussed with selected CDC, UNICEF and WHO regional staff. A small advisory panel comprising respected experts in the areas of measles epidemiology, surveillance, and programme monitoring will be assembled.

The review literature will include comprehensive multi year plans (cMYPs), plans of action, SIA plans, reports, and planning tools, and other documents to become familiar with the costs and management of SIA, routine immunization, and surveillance.

One country each from the AFR, EMR and SEAR will be selected in conjunction with WHO. Three districts per country will be visited and will include both urban and rural sites with higher and lower routine immunization performance that have participated in SIA. Country visits will take approximately two weeks, and local counterparts will be requested to participate in the field visits. Two to three days will be spent at national level for interviews and data review. Visits to each of the three districts will also take two to three days. This will be followed by a working session at national level with MOH/EPI, WHO, UNICEF to discuss findings, identify/agree on ways that measles-specific activities can support routine immunization and surveillance, cost implications and possible indicators.

Discussion

Some members were concerned about potential conflict of interest, where an IPAC member was also the primary recipient of an RFP, and that the awarded proposal was further discussed during the IPAC meeting with the successful recipients present. Rudi Eggers and Peter Strebel explained that potential perceived or actual conflict of interest was mitigated in the following ways:

- The original draft RFP was shared for comments only with IPAC members who had indicated that they would not be bidders to the proposal. Any IPAC members that commented on the draft RFP could not be bidders;
- The RFP was published widely and publically - in addition to it being sent to all IPAC members. There was thus no preferential access of IPAC members to the RFP;
- The selection of the best proposal was done by the WHO secretariat for the RFP based on scoring by independent external reviewers who were not affiliated with IPAC;
- The award was made and announced without input or interaction with IPAC or any of its members; and
- IPAC was requested in this presentation to provide their experienced inputs into a proposal that had already been successful.

A summary of the selection process will be made available.

It was suggested that the impact of incentives in measles SIA on immunization coverage and its effect on sustainability be studied. It also was suggested that the influence of donors on prioritizations in country be studied. Support for routine immunization from political leaders as well as from NGOs and sustained interest in community mobilization are important to maintain elimination. The measles control/elimination approach includes more than just SIA. It builds
on a comprehensive approach of routine scheduled fixed services, outreaches, surveillance as well as the SIAs. There are efforts to consider the inclusion of a routine second dose.

WHO Regional Offices will be consulted to identify an appropriate country for conducting the field work in each of AFR, SEAR, and EMR. The relative advantages of some countries such as India, Bangladesh and Nepal were discussed. It has been suggested to do the field visit in Nepal or Bangladesh instead of in India. However, India may be a good choice because several strategies, including the introduction of a second routine dose and SIAs are being implemented, which would enable a more comprehensive analysis of all measles vaccination options.

There were some comments about how to differentiate the effect of measles activities from others (like GAVI HSS support) on the improvement of routine immunization and the difficulty to trace results in countries working towards the elimination goal over a long period of time. A question was also raised on whether two weeks per country visit be sufficient to collect all necessary information. The main purpose of the work is not to examine historical information to assess whether the package of measles activities strengthened the routine immunization program, but to identify opportunities to deliberately leverage improvements in routine immunization while mitigating any negative effects.

### 7 Programmatic Suitability of vaccine candidates for WHO Prequalification (PSPQ)

#### 7.1 Update of proposed modifications to PSPQ criteria and process. (Rudi Eggers, WHO)

The PSPQ document was drafted collaboratively by the PSPQ working group, in early 2010 and presented at SAGE in April and November 2010. The corrections and clarifications asked for at the previous IPAC meeting have been taken into account and were now presented for decision (page references refer to pages in the draft document dated 4 Apr 2011). The following changes to the criteria were proposed:

1. Lack of **dose volume specification for oral vaccines** was left as a preferred criterion, the dose volume should be as small as possible (p12).
2. Specifying quantity of **diluents corresponding to the vaccines** in secondary packaging has been incorporated in the preferred characteristics (p12).
3. Preservatives would be unable to "prevent" contamination has been reworded to "control" contamination (p.10).
4. Application of the **visual cue** to multi-dose or single-dose vials will be decided during the visual cue discussion.
5. The **scheduling criteria** have been specified to limit the introduction of existing visits in the vaccination schedule (pp. 8-9 draft): If the proposed vaccine is for use in children under five, it should be recommended to be given at one or more of the following immunization visits: within 24 hours after birth; at three visits, 4 to 8 weeks apart, with the first visit at or after 6 weeks of age and the third visit at or before 6 months of age; one visit between 9 and 12 months of age; one visit between 18 and 24 months of age; one visit in the fifth year of life. If the proposed vaccine is designed to be given to adolescents aged 9 to 15 years, it should require no more than four contacts through health service or school-based immunization programmes. The vaccine also will be qualified if the proposed vaccine is given as a single dose and designed exclusively for use in reactive campaigns, if the vaccine is given post-exposure or if the vaccine requires no more than one dose to be administered within a two week period. If the vaccine does not fit into one of the above criteria, it must be reviewed by the PSPQ Standing Committee. (WHO EPI). In the discussion, the scheduling criteria remained unclear: the intent of this criterion was to maintain the established number and timings of visits to get vaccinated, assuring that new vaccines presented for pre-qualification would fit into the existing schedule. The new articulation of the criteria in this draft had
become too complicated, and concern was raised to state the criteria in more understandable terms.

6. The secretariat suggested re-wording of **VVM characteristics** as proof of feasibility and intent to apply a VVM to the proposed vaccine (p9 draft): The vaccine presented for prequalification presents data confirming that it has a thermo stability profile that will enable it to be matched to a current WHO approved VVM type (VVM2, VVM7, VVM14 or VVM30) or a future VVM type approved by WHO (WHO/V&B/99.18, WHO/IVB/07.04). A signed declaration, as part of the cover letter, should be submitted along with the file for prequalification confirming that the manufacturer will apply a VVM to the vaccine and has the technical capacity to do so, if requested to do by the purchasing specifications.

7. Concerns about inflexibility of the procedure regarding **inadequately preserved multi-dose vials**: The flowchart for PSPQ (in annex) has been modified to be less restrictive by adding a third criterion: If multi dose vials vaccines are not live attenuated and do not meet either antimicrobial preservative or antigenic stability requirements and are in ready to use (no reconstitution) presentation, then the vaccine cannot proceed with PQ assessment.

In respect of the procedure, the following clarifications were made:

**Clarification of procedure** as it relates to the criteria that require in-depth analysis: Criteria indicated in yellow boxes in the flowchart will be superficially reviewed at the initial point of screening prior to the PQ assessment. If, during the more thorough review during the PQ assessment, an issue is raised in relation to these criteria, then the PSPQ SC will be requested to review the vaccine again.

**Clarification of timeline and deadlines**: Any new submissions for pre-qualification made on or after January 1, 2012 will be required to conform to the PSPQ guidelines as part of WHO’s pre-qualification process. Any applications that have been submitted to WHO for pre-qualification prior to or on December 31, 2011 are exempt from being immediately required to adhere to the PSPQ guidelines. However, these products will be screened by the PQ Secretariat, and manufacturers will be informed of any issues of non-compliance with the mandatory or critical criteria. Addressing any non-compliant characteristics prior to pre-qualification is voluntary, but if these changes are not feasible to implement prior to pre-qualification, then a one-on-one discussion with the PQ secretariat will be held in order to agree on a process and timeline to address them.

The **PSPQ process and criteria** will be reviewed at minimum interval of every three years by the PQ secretariat, in consultation with the PSPQ standing committee, IVB team, and the regional offices. Expert input will be requested as needed. Any proposed changes will be presented to IPAC for endorsement, along with a proposed timeline for compliance with the new characteristics for both new and already prequalified products. The timeline for implementation will vary on a case by case basis, depending on the magnitude of the change. Changes will not come into effect until after they have received IPAC endorsement. However, should the criteria need to be changed to address issues of safety, the PQ secretariat reserves the right to implement these changes with immediate effect, without further consultation. Products that do not comply with changes to the PSPQ criteria implemented in order to address safety concern will have their pre-qualification status withdrawn with immediate effect.

**7.2 Progress with the establishment of the PSPQ Steering Committee (by Simona Zipursky-PATH)**

The mandate of the PSPQ Steering Committee is to provide, on request, recommendations and technical advice on the programmatic suitability of vaccine candidates that are non-compliant with critical characteristics or that present with unique and innovative characteristics. The steering committee can advise to accept or to reject the application. The PSPQ standing committee is an independent entity, and does not report to IPAC; instead, it reports directly to the PQ secretariat and the Director of IVB. The chair of the committee will be an independent
public health immunization expert. The committee will consist of five members: three IPAC members (Robin Biellik and Jane Soepardi have already been nominated, a third IPAC member will be selected) and one regulatory expert with focus on developing countries.

A call for nominations for the two non-IPAC members of the Standing Committee will be posted by May 31, 2011 in the Global Immunization Newsletter, the TechNet e-forum and website, and partners and will be emailed to IPAC members, IVB staff, WHO & UNICEF regional offices, SAGE & IPAC attendee lists, VPPAG and CCL. Deadline for submissions is July 1, 2011, and the applications will be reviewed by July 30th by a selection panel that will be established the end of June 2011. The selection panel will convene for review July 20 and the standing committee members will be appointed by the Director, IVB by July 31, 2011. Standing Committee will do trial reviews with three existing pre-qualified products between Sept-Dec, 2011 to "learn the ropes" and will be fully operational by January 1, 2012. The Committee will be informed of requests for input by PQ secretariat within two weeks of each PQ application submission deadline and will have three months to deliver its report.

Discussion:

There are currently 115 pre-qualified vaccines: It is estimated that about fifteen of these are PSPQ non-compliant products. For non-compliant products (i.e., those that do not meet critical, mandatory or unique criteria) there will be one-to-one discussions between the PQ secretariat and the manufacturers. Some solutions can be found quickly but others will be more complicated; therefore there is no general timeline to solve the issue.

The representatives of manufacturers asked to be regularly informed of decisions of PSPQ and would like to receive minutes of the meetings.

Conflict of interest of members of Standing Committee needs to be taken into account for each product to be reviewed.

There was much discussion about the need to clarify the wording of the document in general and on the need to clarify the flow chart.

7.3 IPAC recommendations and decisions

Discussion on the modifications of the PSPQ criteria and process led the following recommendations:

- The minor changes to the document relating to the dose volume specification for oral vaccines, the quantity of diluents corresponding to the vaccines, the rewording of the preservatives section were agreed (items 1 - 4 above);
- The scheduling criterion (item 5 above) has been approved, with modification of wording to “up to three visits”. The adolescent age still needs to be specified;
- The VVM criterion (item 6 above) has been approved with the modification of wording replacing the second sub-bullet with: "Confirmation that the manufacturer has the technical capacity to attach a VVM and, if requested, will apply a VVM to the vaccine vial.”.
- The inadequately preserved multi-dose vial criterion (item 7 above) has been approved.
- Change in procedure: IPAC agrees in principle that PQ standing committee may have a role both during initial screening and during PQ in-depth evaluation process, should a vaccine match a critical or unique criteria;
- Clarification of timeline and deadlines: IPAC agrees to the timeline proposed including that currently pre-qualified vaccines will be reviewed and that the timeline will be negotiated on one-to-one basis for those vaccines that match a critical, mandatory, or unique requirement; and
- Procedure for changes to PSPQ process and criteria: IPAC agrees that PSPQ procedural changes go to IPAC to endorsement.

As the PSPQ document had been made available only a few days prior to the meeting, it was also decided that additional comments will still be welcome within ten days after IPAC, and that WHO will release a further draft within one month. Also agreed was that the last draft will be submitted to IPAC for approval at the Sept 2011 meeting.
8 Further IPAC recommendations

Recommendations related to a specific topic are presented at the end of the topic section. In addition, the following recommendations were made:

- **Pre-meeting materials**: The WHO secretariat should disseminate all reading materials to members at least two weeks prior to the meeting date. All draft recommendations to be voted upon during an IPAC meeting should be circulated in the pre-meeting materials.

- **IPAC member and observer attendance**: Members and observers commit to review meeting dates in advance and attend meetings in their entirety.

- **Agenda items**: All agenda items should be considered as topics on which decisions could be made (i.e. "For decision").

- **Rotation of IPAC members**: In line with the original term of service, three IPAC members (Najwa Khuri-Bulos, Xavier Bosch-Caplanch, and Pieter Neels) and are due for renewal after the second meeting in 2011. While there will be a formal exchange of letters to review renewal, these IPAC members are requested to indicate if they are agreeable to continue serving on IPAC for a further three years term.

- **Next meeting dates and potential future topics for IPAC**: The next meeting will take place on Wednesday, 28 Sept to Thursday 29 Sept 2011 in Geneva and is not aligned to any SAGE meeting. Potential topics will be an update on the Controlled Temperature Chain (CTC), the definition of Routine / Supplemental vaccination, rotavirus programmatic issues, and the finalization of PSPQ & Standing committee.

- **Future IPAC meeting dates**: (the actual dates of the meeting will be confirmed in the preceding meeting; however, IPAC members and observers should please note save these dates as likely future meeting dates:
  
  | First meeting 2012: | Tue 17 – Thu 19 Apr 2012 (after SAGE 10- 12 Apr 2012) |
  | Second meeting 2012: | Tue 2 – Thu 4 Oct 2012 (not aligned to SAGE dates) |

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Annex 1: PSPQ criteria flowchart
Annex 2: Flowchart to determine eligibility of Rotavirus vaccine

Doses of Rotavirus vaccine given

0 doses given

1 or more dose given

Child's age?

Doses of Rotavirus vaccine given already?

Less than 6 weeks

Between 6 and 15 weeks

More than 15 weeks

Make appointment for when child is older than 6 weeks.

Make appointment for second dose of Rotavirus vaccine after

Give Rotavirus vaccine together with other vaccines the child is eligible for

Explain to caregiver that the child could not get Rotavirus vaccine because he/she was brought late. Give appointment for other vaccines in the schedule.

Not eligible, too early for Rotavirus vaccine

Not eligible, too late, for Rotavirus vaccine give other vaccines as appropriate

Not eligible, too late, for Rotavirus vaccine second dose

Make appointment for when the interval with previous dose is more than

Give next dose of Rotavirus vaccine together with other vaccines the child is eligible for

Make appointments for other vaccines in the schedule and third dose of Rotavirus (if applicable)

Make appointments for other vaccines in the schedule

Make an appointment for second dose of Rotavirus vaccine after

Less than 32 weeks

More than 32 weeks

Interval with previous Rotavirus vaccine dose

Less than 4 weeks

4 weeks or more

Not eligible, too early for Rotavirus vaccine second dose

Not eligible, too late, for Rotavirus vaccine

Not eligible, too late, for Rotavirus vaccine, give other vaccines as appropriate