IPAC BULLETIN

October 2016

QUARTERLY UPDATE OF THE IMMUNIZATION PRACTICES ADVISORY COMMITEE

Volume 2, Issue 3 **WORLD HEALTH ORGANIZATION**

A note from the Chair:

Dear IPAC members and observers,

Welcome to the October IPAC Bulletin! I was very sorry to have missed the October SAGE meeting (personal matters kept me in Australia) and I'm very grateful to Jean-Marc Olivé and Nora Dellepiane for representing IPAC in those discussions so well. Once again, a lot of programmatic implications in what was discussed at SAGE, and it's great to have Jean-Marc's reflections on this meeting.

I'd like to mention three different aspects of how a committee like IPAC can support WHO's global coordination of immunization, and of routine immunization in particular. **Firstly, there is IPAC's role in responding to SAGE recommendations,** both those expressed in their discussions, and those seen in the updates to vaccine position papers. One clear example is the implementation of vaccination against hepatitis B, especially the birth dose that requires monovalent hepatitis B vaccine provision within 24 hours of birth. This is a tough programmatic ask of those countries that commit to this schedule as a means to interrupt perinatal transmission. In response to the 2009 SAGE recommendation for birth dose vaccination, IPAC supported WHO in reviewing international practices that had proven successful in supporting birth-dose coverage, reviewed the eventual publication (WHO IVB 12.11), and IPAC also provided significant contribution, along with many in CDC, WHO and independents, to the 2015 Guide for Introducing and Strengthening Hepatitis B Birth Dose Vaccination(ISBN9789241509831). IPAC has also provided significant support, through past meetings and now through the Controlled Temperature Chain (CTC) working group, to WHO's efforts to find a safe, feasible and sustainable way to interpret and implement SAGE's past recommendations on the potential to manage hepatitis B vaccine outside of the standard cold chain.

In both examples, the role of IPAC expertise was to consider **how to help WHO to develop usable trustworthy guidance** that expands upon the relatively small number of words that form a SAGE recommendation, and adds 'real-world' understanding to the controlled environments that characterize the research under-pinning these recommendations. Programmatic expertise to do this is necessarily diverse, across those with experience of: field-work at all levels; regulatory, accreditation and manufacturer viewpoints; what constitutes credible and acceptable implementation evidence; and of how new delivery technologies can change service delivery. Thanks to those in IPAC more broadly, and those in the CTC working group, who have given time so far to review how to balance uses outside the standard cold chain

Cont'd on page 2

Inside this issue:

A note from the Chair (cont'd from page 1)

with the need to advance the on-license CTC usages of vaccines. I understand this was one topic of discussion at SAGE, in relation to hepatitis B vaccine, and I'm very grateful to those who supported the IPAC position statement in those discussions. It seems clear that there is more work to be done to support WHO in providing the most useful and feasible advice to countries on deployment of thermo-stable vaccines. I feel it is important that we pursue this in a way that does not complicate routine programmes unnecessarily, that takes account of the messy context of immunization in resource-constrained settings, and that does not discourage manufacturers from pursuing CTC certification. I hope that all IPAC members and others with programmatic expertise will support us in the work to come on this.

Secondly, IPAC has a role in ensuring that programmatic realities inform the application of new technologies to immunization. Of course, this is a role we share with many in WHO and other immunization partners, including those developing new technologies or strategies. I'd like to mention two examples that I have come across in recent months. WHO and PATH's joint work on microarray patches (Microarray Patches for Vaccine Delivery) included a TechNet discussion and other implementation research into how feasible and acceptable this delivery system would prove in the field. The Communicate to Vaccinate initiative (COMMVAC) has been working for some years now to support not only the development of new approaches to provider-parent communications, but to also develop solid frameworks for measuring whether new approaches work in low- and middle-income countries. Both represent significant advances that in different ways are likely to have an impact on how immunization programmes run in the future.

Thirdly, IPAC and others with programmatic interest, have a role in promoting the testing of new approaches to implementation, especially immunization service delivery. The interest in integrated health services that many of us share is a clear example of this, but I wanted to close with a different instance. Several years ago, IPAC was presented with work to develop an **immunization session checklist** that captured on one page the essential steps before, during, and after an immunization session that are needed to provide a safe, acceptable and effective service. This checklist is now included as part of Immunization in Practice – you can see it at the end of module five in the 2015 update (IIP) We (at Burnet Institute in Myanmar) are currently testing the introduction of this checklist as a means to improve service delivery in hard-to-reach villages in rural Myanmar. With a wrinkle: at the same time as introducing it to first line clinical settings to improve quality of service provision, we are also using it as mechanism to educate village health committees and families with young children in what a quality service looks like. We're at the mid-point of this formative evaluation funded by Gates through 3ie. We have a clinic checklist adapted to the Myanmar immunization programme, and also have a prototype community checklist that local community members are willing to try. We will let you know how it goes. Many in WHO and their partners are engaged in generating this type of evidence: which takes research findings and goes beyond to examine how they apply in routine practice.

Given that so many of the adverse events that are considered by GACVS and other safety review groups each year relate to programmatic error, I feel it is crucial that we support expansion of work to study and carefully document new ways to implement immunization programmes.

Make sure you check into TechNet21 to see what others are doing in this space. And, if anyone has experiences or comments to contribute to this bulletin – please do contact Anna-Lea Kahn, our indefatigable focal point.

Thank you for sharing in this work.

Kind regards,

Chris Morgan

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From the Working Group frontlines

Update from the Secretariat of the CTC –WG

The Controlled Temperature Chain Working Group (CTC-WG) convened for the first time in August 2016, tasked by EPI and IPAC to draft a concise position statement on the use of vaccines out of the cold chain and how this compares to use of vaccines in a controlled temperature chain (CTC). Through multiple teleconferences and discussion on the TechNet21 forum page dedicated to this group, consensus was reached on a statement that was approved by IPAC earlier this month. This was then shared with SAGE members prior to their October meeting and made publicly available on the IVB webpage for IPAC. The statement addresses the recognized need to clarify the distinction between OCC and CTC practices and to confirm the programmatic preference for the latter. However, as is mentioned in the statement, IPAC nevertheless recognizes that some countries may choose to pursue a strategy of delivering vaccines out of the cold chain, representing off-label use. Therefore there was a need to define the conditions around which this might be acceptable and render the practice as safe as possible, while still effective.

The official statement is as follows:

Statement on Controlled Temperature Chain (CTC) and Out of Cold Chain (OCC) vaccine usage

The WHO Immunization Practices Advisory Committee (IPAC) recommends that countries store, transport and distribute vaccines at temperatures above 8°C only if these products have been licensed for use in a Controlled Temperature Chain (CTC). IPAC further calls for acceleration of vaccine licensing and labelling consistent with CTC usage. The committee recognises that manufacturers, regulators, national programs and immunization partners consider that on-label indication of temperature storage conditions will enhance communication of correct handling and maintenance of the quality of vaccines above 8°C.

Nevertheless, IPAC recognizes that under special circumstances such as emergency situations, countries may consider delivering certain vaccines out of the cold chain (OCC) for public health benefit especially for otherwise unreachable populations. Should a country choose to use a vaccine OCC, this should only be an interim short-term step while licensure and labelling consistent with CTC is sought for the vaccine. Further, IPAC recommends that countries observe the following five conditions:

1. *Understand that any associated liability with OCC off-label use must be accepted by the country, irrespective of WHO guidance;*
2. *Apply the OCC strategy **only** to:*
   a.) a specific vaccine product, not to a class of vaccine products, where stability data suggest thermostability appropriate to the country's climate. Due caution is necessary with live attenuated vaccines in particular and adequate provision of cold chain management of reconstituted vaccines at the vaccination sites is essential.
   b.) a vaccine product fitted with a vaccine vial monitor (VVM);
3. *Set and monitor explicit time and temperature limitations on the use of the specific product OCC;*
4. *Ensure adequate vaccine handling training of health workers; and*
5. *Use appropriate temperature monitoring tools in addition to VVM, such as peak temperature threshold indicators*.

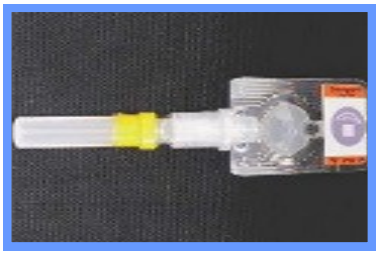
The CTC-WG continues to have a full and ambitious agenda ahead, including the notable task of defining a priority vaccine roadmap for CTC, and so will resume meeting by teleconference every two months but is also planning a face-to-face meeting on February 13th, just prior to the IPAC meeting scheduled that same month.

From the Working Group frontlines (cont'd)

Update from the Secretariat of the DT–WG

2016 is the mid-point of the Decade of Vaccines Global Vaccine Action Plan (GVAP), and as such, the delivery technologies working group was asked to review and provide technical input into the progress report and future recommendations for one of the GVAP indicators: Indicator G4.2: Licensure and launch of at least one platform delivery technology. The report was drafted by the WG chairs (Darin Zehrung and Birgitte Giersing). Briefly, we were able to report substantial progress in advancing novel platform delivery technologies for vaccines, and that the G4.2 GVAP indicator is expected to be achieved by 2020. Two of the platform delivery technologies, the Tropis disposable-syringe jet injector (DSJI) and the ID adapter, are targeted for immediate availability in LMICs for polio outbreak control due to the limited supply of inactivated poliovirus vaccine (IPV), with PQ expected for both devices in 2016/17 and LMIC launch in 2017. These technologies offer means for dose sparing (fractional dose) by delivering the vaccine intradermally resulting in adequate immune responses at lower doses, and may have applications for other vaccines, such as yellow fever.

Blow-fill-seal is a filling and packaging technology that commonly used for packaging a variety of licensed pharmaceuticals, and is in development for vaccines. GSK is leading the vaccine field, and has invested in a pilot blow-fill-seal manufacturing facility in Boronia, Australia for Rotarix vaccine. GSK's Rotarix vaccine is expected to be available in blow-fill-seal containers as an improved product presentation in the South Asian/Pacific region in 2018 as well as for eventual UNICEF procurement. Additionally rommelag, a major BFS equipment company is developing a parenteral capable BFS design that is intended to meet the requirements for a compact prefilled auto-disable device (cPAD).



For both existing and new vaccines, their combination with a new delivery technology requires product development, potentially including substantial capital investment in new, manufacturing infrastructure. Understanding the likely vaccination strategy and potential market demand for novel delivery platforms across a range of vaccines in both high and low income contexts may help to justify these substantial investments and strengthen the commercial strategy for a technology that is unlikely to be profitable if limited only to LMIC immunization programs. In addition, the clinical and regulatory strategy to achieve to achieve licensure, and ultimately policy recommendation and WHO prequalification is of novel vaccine/technology combinations is not clear, and needs to be delineated through consultation with regulators, as well as through understanding the programmatic needs and end user perspectives to ensure eventual implementation. Development of target product profiles for vaccines in combination with novel delivery devices, such as MR/MAP by IPAC's DT WG, has demonstrated value in guiding product developers and donors as to preferred product characteristics for low and middle income country contexts. Development of these documents for other delivery technologies, as well as mapping out the pathway to regulatory approval and WHO prequalification is encouraged so that development costs, risks and programmatic requirements are considered during the product development process, and assist manufacturers and developers in their planning. These activities would support the robust assessment of these technologies to meet GVAP goals and objectives going forward.

With a variety of novel vaccine presentation and delivery technologies emerging, there has been an increased desire for tools that will enable evaluation of the trade-offs between potential higher vaccine and delivery technology prices due to product innovation versus the potential programmatic impacts and systems cost savings. Ideally, such tools would facilitate the prioritization of public and private sector investments in key platform and delivery technologies applied to specific vaccine products. With this in mind, PATH in collaboration with WHO and the BMGF are developing a qualitative vaccine/delivery technology prioritization framework, as well as a quantitative vaccine technology impact assessment (V-TIA) tool that aims to provide a method for policy makers, technology developers, vaccine manufacturers and procurement agencies to evaluate potentially transformative vaccine technology combinations. We will be working with the DT WG over the coming weeks to evaluate the model, in preparation for a workshop in December. Many of the DT WG members will attend the workshop, which we expect will help to inform and optimise the technology impact assessment model.

Highlights from the October 2016 SAGE Meeting

By Jean-Marc Olivé

On behalf of the IPAC Chair, I attended the SAGE meeting, assisted by Nora Dellepiane for the hepatitis B (HepB) session.

One topic relevant to IPAC related to the fractional use of inactivated polio vaccine (IPV) and yellow fever (YF) vaccine to address supply shortages (the minimum effective dose administered as a fraction of the volume of the normal dose). For YF, the programmatic implication relates mainly to supply chains: needing to make available the correct injection equipment to support fractional dosing. For IPV, fractional dosing requires intra-dermal (ID) injection, requiring close attention to correct technique, particularly during mass campaigns. There is now increasing country experience with fractional ID delivery of IPV and new equipment available: a syringe adapter for 0.1 ml AD syringes and a needle-free injector.

For HepB vaccination at birth, SAGE considered a number of programmatic topics related to the accessibility problem posed by the high proportion of home deliveries in highly endemic countries. One point of discussion related to terminology and practices around the possibility of a "birth dose" received during the first contact with health facilities at any time between birth and the first primary schedule dose; noting the need to ensure a minimum interval of four weeks between each dose.

SAGE also reviewed approaches to increase reach by deploying the vaccine outside of the standard cold chain. Preliminary data on the thermo-stability of several HepB vaccines was considered, with significant discussion on the best way to support progress towards standardized approaches for usage outside of the cold chain. It is clear that continuing work on this, including by IPAC's controlled temperature chain (CTC) Working Group, is increasingly important: to incorporate more of the evidence base relevant to field usage; to elaborate more fully the most useful operational guidance; and to promote further efforts in support of CTC licensing.

Another topic of discussion was the long-awaited resolution on the addition of a routine second dose of measles-containing vaccine (MCV) to national immunization schedules in all countries regardless of MCV1 coverage. For countries that meet the criteria for introduction of rubella-containing vaccine, the potential of using measles and rubella containing vaccine was considered. SAGE recommendations on these matters will contribute to the conceptualisation of a second year of life platform (2YL) that includes vaccination and potentially other preventive health care. The implementation of the 2YL platform is a topic of great interest to IPAC and is likely to be circulated as a topic for members to discuss and review in coming months.

SAGE also discussed the implementation requirements needed to secure life-time protection from tetanus, covering the mix of vaccines that should be administered; a mix that requires programmes to reach children, not only in infancy but also through boosters during childhood and adolescence.

Regarding the prevention of cervical cancer and other diseases caused by the human papillomavirus (HPV), SAGE discussed the first introduction of the vaccine into national schedules. Major programmatic implications relate to the organization of a catch-up vaccination for girls 9-14 years of age, with, if resources are available, consideration of extending the target age-range to 18 years. This intersection with school health programs and other adolescent vaccination efforts is likely to also lead to significant new practice challenges for national immunization programmes.

Members are encouraged to review the documents provided on the SAGE WHO website, which includes background reading materials and presentations made at the October 2016 SAGE meeting, as well as a brief summary of the meeting:

www.who.int/immunization/sage/meetings/2016/october

Other immunization news:

Update on Second Year of Life (2YL) Progress

In the October 2015 IPAC meeting, WHO presented an overview of work towards promoting the establishment of a second year of life (2YL) healthy child visit for immunization and other health interventions. IPAC expressed interest in staying up-to-date on the five activity areas presented (shown below) and in contributing to guidance that will be developed. Regarding a 2YL workgroup (Activity #1), it was decided that a 2YL-specfic workgroup would not be formed but rather use an existing Measles & Rubella Initiative (M&RI) Routine Immunization Workgroup to seek input on measles and rubella-related aspects of 2YL and IPAC for broader input. Guidance and input has taken place in various other forums including the March 2016 Global Vaccine and Immunization Research Forum in Johannesburg, the April 2016 SAGE meeting in Geneva, the June 2016 Global Measles and Rubella Meeting in Geneva, and the September 2016 M&RI RI WG in Atlanta. The landscape analysis has been completed by UNICEF and rich experiences are being drawn from the WHO/BMGF-funded projects in Senegal and Zambia and an extensive CDC 2YL project in Ghana. John Snow International is assisting with drafting global guidance with the aim of having a draft ready for IPAC review in November.

2YL Project, 2015-2017

1	**2YL WORKGROUP - oversight** (pending)	2015
2	**LANDSCAPE ANALYSIS** (WHO & UNICEF)	2015
3	**COUNTRY PROJECTS** (WHO & CDC)	2016
4	**DRAFT GUIDELINES**	2017
5	**IMPLEMENTATION FEEDBACK & Finalize guidelines**	2017

Upcoming Meetings / Events:

⇒ October 21-22, 2016: Versoix, Switzerland – **Immunization Regional Advisers Meeting**

⇒ October 24-27, 2016: Buenos Aires, Argentina – **DCVMN Annual Meeting**

⇒ December 7-8, 2016: Geneva, Switzerland – **Meeting on Costing of Vaccine-Preventable Disease Surveillance**

⇒ December 12-13, 2016: Geneva, Switzerland – **WHO / PATH workshop on optimal vaccine presentations**

⇒ December 14-15, 2016: Geneva, Switzerland - **WHO Workshop on Vaccine Technologies Impact Assessment (V-TIA)**

A final word from the IPAC Secretariat

I would like to inform you that due to popular demand, these IPAC Bulletins are becoming publically available on the IPAC webpage of the WHO/IVB website. Originally designed to be an internal communications tool limited in circulation and primarily targeted to the Committee members and observers in order to keep everyone abreast of relevant activities and issues, our Bulletins have gained a broader readership and demand. In view of the recent calls for increased visibility of IPAC (through the 2015 IPAC Evaluation and reiterated in the recently completed 2016-2018 IPAC Operational Strategy), it was decided within IVB to render the Bulletins available online. We therefore encourage you to share this and prior issues, should you wish to.

You will note that other outputs such as the OCC/CTC Position Statement are also now available on that IVB/IPAC webpage and we welcome your participation in efforts to get the word out on activities and outputs of this Committee.

As you know, we are gearing up for a Face-to-Face IPAC meeting early next year. We are currently working on shaping the agenda and appreciate any inputs. As a reminder, the dates for that meeting are 14-16 February 2016 and you can confirm your attendance on the dedicated meeting page attached to our IPAC TechNet Discussion group.

The IPAC Secretariat Team