



**WORLD HEALTH ORGANIZATION
IMMUNIZATIONS, VACCINES AND BIOLOGICALS**

**IMMUNIZATION PRACTICES ADVISORY COMMITTEE
(IPAC)**

14-16 February 2017

Final meeting report and recommendations

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Opening and Introduction

The Immunization Practices Advisory Committee (IPAC) was convened for the 11th time on 14-16 February 2017 in Geneva, Switzerland to support and advise the Director and staff of the WHO Department for Immunization, Vaccines and Biologicals (IVB). The last IPAC meeting took place in October 2015. The Committee currently meets every 12 to 18 months, but the intention is to continue with annual meetings. The Committee remains active between meetings, using a virtual discussion group platform hosted on the TechNet-21 website, email and teleconferences. In addition to providing strategic guidance and feedback to various Expanded Programme of Immunization (EPI) initiatives and documents, key achievements since the last IPAC meeting include the establishment of two new working groups: the controlled temperature chain (CTC) working group and the delivery technology (DT) working group, each of which have yielded important outputs, including provision of key contributions to discussions held by the Strategic Advisory Group of Experts (SAGE) on Immunization in October 2016.

IPAC Members present:

Chris Morgan (Chair)
K.O. Antwi-Agyei
David Brown
Craig Burgess
Nora Dellepiane
Michael Free
Ian Gemmill
Masahiko Hachiya
Kelly Moore
Amani Mustafa
Adelaide Shearley
Carla Vizzotti

This IPAC meeting was formally opened by Dr Thomas Cherian, Coordinator of WHO/EPI, on behalf of Dr Jean-Marie Okwo-Bele, Director of WHO/IVB. Dr Cherian highlighted the fact that it had been almost three years since the launch of IPAC's new operating modality, with a more virtual way of operating and a departure from the previous format of two meetings per year. WHO/IVB has managed to stay abreast of the Committee's work through quarterly bulletins prepared by the IPAC Secretariat, but has not always taken best advantage of the support the Committee could offer. This was one of the

reasons that the terms of reference (TORs) of the Committee were to be reconsidered, with a view to better aligning them with the work and mandates of the other advisory committees serving WHO/IVB. Dr Cherian asked the Committee to discuss the next steps with respect to the IPAC TORs, in addition to the substantive advisory work of the meeting that included: technical input to and endorsement of second year of life guidance, as well as a data reference manual; guidance on programmatic issues concerning vaccine shortages; reflections on and technical input to the area of immunization supply chain logistics; and strategic feedback on prioritization and outputs of the DT and CTC working groups.

Dr Chris Morgan, the Committee Chair, welcomed participants, including six who were meeting the other Committee members in person for the first time. Dr Morgan also conveyed the regrets of Francois Gasse and Jean-Marc Olive, who were unable to attend and both will be reaching the end of their respective terms on this Committee at the end of June.

Session I. Immunization supply chain and logistics

A. Progress since the 2014 “call to action” on supply chains *(Patrick Lydon, EPI/WHO) – presented for information*

During 2013, the IPAC developed a “Call to Action” on immunization supply chain and logistics (iSCL) and presented this to SAGE during their November 2013 meeting, and later published as a WHO document in March 2014. The “Call to Action” draws attention to the fact that immunization supply chains are increasingly challenged by the growing size and complexity of immunization programmes, requiring new metrics to measure and monitor systems, as well as significant improvements to both address system weaknesses, and allow for innovations and better functioning. It was also recognized that the global community of partners has a role to play in supporting national iSCL systems, notably through increasing awareness and investments, and considering the implications of new immunization policies on supply chain logistics. Notable progress in response to these recommendations was presented to IPAC. Increased visibility of iSCL needs is seen at such meetings as the TechNet conferences and the Ministerial Conference on Immunization in Africa of 2016, or through publications such as a special issue of *Vaccine* on immunization supply chains. Likewise, there is increased country support on iSCL by partners through initiatives such as the Gavi Alliance Immunization Supply Chain Strategy, Bill and Melinda Gates Foundation (BMGF) investments, greater allocation of Gavi Health System Strengthening funds to iSCL improvements, the development of the Cold Chain Equipment Optimisation Platform (CCEOP) by the Gavi Alliance, and the establishment of the WHO/UNICEF Immunization Supply Chain and Logistics Hub. Other critical developments include the dashboard for immunization supply chains (DISC) with globally agreed key performance indicators that ensure better alignment of measurements.

Discussion

IPAC members welcomed the update on global work on iSCL since the 2014 Call to Action, and the increased attention paid by WHO, UNICEF, the Gavi Alliance and other immunization partners to this crucial area, with many country systems still not making

optimal use of modern logistics technologies and strategies. The Committee commended the contribution of the Effective Vaccine Management (EVM) Initiative to providing evidence for change. The Committee also supported the EVM 2.0 revision, particularly its focus on national and subnational supply chain improvement plans linked to country multi-year planning, as well as other new tools, including dashboards for timely information and the Cold Chain Equipment Optimisation Platform.

It was noted that there is a need for increased technical assistance to countries in support of the development of strong cold chain improvement plans, and a pressing need for countries to allocate domestic resources and plan for sustainability of supply chains. The Committee encouraged examination of ways in which immunization supply chain improvements can interact with broader health system strengthening, and seek integration with work to improve the supply of other life-saving health commodities.

B. Cold Chain Equipment Optimisation Platform sustainability (*Souleymane Kone, EPI/WHO*) – presented for information

Cold chain equipment (CCE) is an essential component of any immunization supply chain system. However, estimates by WHO/UNICEF in 2016 indicated that many health facilities in low- and lower-middle-income countries do not have a cold chain or are equipped with a suboptimal cold chain. It was found that more than 78% of health facilities were equipped with CCE that was either not functional, or that used obsolete technology, potentially exposing vaccines to excessive heat or freezing. Up to 20% of health facilities had no or insufficient CCE to store vaccines. The Cold Chain Equipment Optimisation Platform was created by the Gavi Alliance to support countries to improve their cold chain systems, with the main objectives being to:

- extend appropriate cold chain devices into health facilities which have no equipment, and potentially contribute to outreach activities being conducted from nearby facilities; and
- accelerate the upgrading of existing equipment through the deployment of higher-performing, innovative devices to health facilities.

Cold Chain Equipment Optimisation Platform support is provided through a joint investment mechanism, targeting 55 low- and lower-middle-income countries, to complement efforts to strengthen other supply chain strategy “fundamentals” and contribute to efforts to sustainably strengthen the coverage and equity of immunization. This is achieved through a service bundle which consists of procurement, installation, and training of users. After one year of implementation, the Platform had received growing interest from countries, but some challenges had been reported, including:

- Lack of experienced personnel to provide technical assistance in support of the development of country proposals (the generation of evidence to support applications to the Platform requires up to 15 consistent mandatory documents).
- Gavi health system strengthening grants have been reported as the sole source of funding for country joint investment. The use of country local resources remains marginal.
- Clarity of vision is required regarding the sustainability of the large-scale investments being requested. Most country proposals did not provide sufficient

indications of how savings from using high-performing and cost-saving CCE from the Platform will benefit the long-term sustainability of an investment.

- Significant delays had been reported between the approval of the applications and completion of procurement projects. The first approved proposals were still pending due to operational and organizational challenges. Clear steps to improve procurement of CCE and the related service bundle are required for the delivery, installation and commissioning of such equipment.

Discussion

While the Cold Chain Equipment Optimisation Platform was welcomed by IPAC members, the importance of in-country monitoring and sustainable maintenance was emphasized, along with the need for alignment with national strategic plans. Further guidance would be required to ensure appropriate country ownership and sustainability. To this end, the Committee encouraged more focus on systems and a long-term, sustainable approach to supply chains (not just 'once-off' fixed costs, but including ongoing running and maintenance costs), rather than a focus solely on the cold chain. It was further agreed that the weak components of immunization supply chain management as documented through EVM assessments should also benefit from further investments and stronger links to HR and financing aspects of the broader health system to reduce duplication and inefficiency between programs. It was emphasized that in view of the lack of experienced personnel, a major investment needs to be made into cold chain capacity building, integrated with efforts to strengthen health system.

Committee members suggested that the technical assistance required to ensure the long-term sustainability of the Cold Chain Equipment Optimisation Platform should include regional workshops for reviewing applications and the development and provision of simple checklists to guide countries on how to manage critical and weak/challenging areas, such as maintenance of CCE. It was further agreed that the Platform could benefit from a more formal linkage with the TechNet forum to enable more experts to contribute.

C. Update on development of a data reference manual (*Jan Grevendonk, EPI/WHO*) – presented for feedback

Along with more complex immunization systems, programme monitoring has become increasingly complex. Countries have adapted monitoring systems to accommodate changes such as new vaccine introductions, expanded target age ranges, and donor requirements for disaggregated reporting. These changes often multiply collection efforts, while data use sometimes lag behind. The need to collect more and more data also runs counter to the desire to integrate systems across health programmes and to rationalize the amount of data that is collected. At the same time, data quality is not always sufficient for programme management and accountability, and there is a perception that current approaches to improving data quality (like Data Quality Self-Assessments) are not having the needed impact. Instead, some immunization partners favour the introduction of new systems, often using more advanced information and communication technology, such as electronic health management information systems, electronic immunization registries, and logistics management information systems.

To respond to these challenges, there is a need to clarify best practices for monitoring, to strengthen methodologies for data quality assessment and improvement, and to provide minimal functional standards for the use of electronic systems. The Committee was provided with an update of the draft immunization programme data reference manual, noting the challenges of providing normative guidance across the range of needs and tools relating to routine data for immunization programmes. A framework to improve partner alignment when working towards common goals for data availability, quality, and use, which is at an earlier stage, was also presented.

Discussion

The Committee observed that improving data quality and usage is an essential but neglected support activity. Members of the Committee provided detailed feedback on the draft manual and were requested to continue doing so by email. They were also invited to review a draft framework for partner collaboration on immunization data and discussed matters raised through this review, noting the implications of introducing new vaccines, the increasing variety of vaccination settings, expanded age ranges, and including other work on vaccination of children in their second year of life and of older children. The Committee supported the review of definitions of “timely vaccination” and “fully immunized” to encompass these expanded requirements, and the need to reform paper-based administrative data collection in a way that prioritizes quality of recording over breadth of indicators.

After significant discussion, the Committee noted that some less time-sensitive indicators, such as gender and socio-economic status (or other equity markers), may need to be removed from administrative systems and monitored through periodic evaluations, such as surveys. When routine monitoring data systems are stretched, the emphasis should be on the routine data that is most likely to be used locally for identification of problems in service delivery. Discussions also raised the potential for electronic information systems to bypass difficulties encountered in using paper-based systems and to enable broader data capture with an acceptable burden on health workers, but noted the need for caution in their introduction to ensure that the necessary equipment and resources are sustainable by country programmes and remain user-friendly. Continued strengthening of paper-based recording and reporting systems remains a critical activity for the foreseeable future for many low- and middle-income countries that will require continued support from WHO, UNICEF and Gavi. Ensuring mechanisms are in place for user feedback will also bring value to this effort. The Committee asked for further iterations of both documents to be brought back for review as they develop, and invited focused questions to be brought to the group using its virtual discussion forums.

Clarifications, with increased level of detail, were flagged as needs with respect to timeliness and an indicator for data quality. The descriptions of EVM measures, with its global indicators, was highlighted as an illustration. The importance of better triangulation of data collected for quality improvement was also emphasized, as was the integration of LIMS with HIMS to build and sustain the culture of better data quality.

Session II. Global supply, shortages and implementation solutions

The ability to ensure an uninterrupted global supply of vaccines is a growing concern. Over recent years, countries across all WHO regions and in all income groups have reported vaccine shortages and stock-outs, sometimes causing critical disruptions of immunization programmes. Countries have adopted mitigation strategies, including postponing vaccine introduction, stopping vaccination, switching to alternative vaccine presentations and adapting schedules to use fewer doses.

Given these mounting concerns, the World Health Assembly adopted a resolution on “Addressing the global shortages of medicines and vaccines” in May 2016. Prior to the Health Assembly, the April 2016 SAGE meeting discussed the vaccines situation given the evidence from the WHO Model List of Essential Medicines that there are shortages or risk of shortages of 60% of vaccines, including BCG, yellow fever, acellular pertussis containing vaccines and inactivated polio vaccine (IPV).

This session brought together several interrelated topics such as global shortages of vaccines leading to shortages of some vaccines in countries, and how dose sparing and fractional dosing had been explored and tested in 2016 as a way to address the issue. The session began with a presentation on the global vaccine market and shortages affecting the timely availability of vaccines. The presentation focused on IPV and yellow fever shortages that in 2016 hampered global polio eradication efforts with the IPV “switch” and the ability of affected countries in the African Region to promptly respond to yellow fever outbreaks. To enrich the context, the evidence on stock-outs at country level for vaccines and for home-based records was presented before a review of specific experiences in India and the Democratic Republic of the Congo, where fractional dosing of vaccines was implemented as a mitigating strategy during IPV and yellow fever shortages.

A. Global situation on vaccine shortages, stock-outs and consequences *(Patrick Lydon, EPI/WHO) – presented for feedback*

The Committee was shown how alarming global supply shortages were 15 of 25 key vaccines are at risk, both “traditional” and new, and the disturbing prevalence of in-country stock-outs. The impact on middle-income countries and countries procuring vaccines outside Gavi, UNICEF or PAHO systems was also indicated.

Discussion

The Committee reviewed WHO’s strategic and implementation responses, including the Vaccine Shortage Project. The Committee also discussed the potential usefulness of information-sharing mechanisms, and suggestions were made on consolidating good practice programmatic examples of managing short supplies or localized stock-outs through resource sharing and adaptation of service delivery. On global vaccine shortages, members of the Committee suggested that global Alliance partners develop practical guidance for countries on what to do when faced with a vaccine shortage or a national stock-out.

B. Home-based records of stock-outs (*Marta Gacic-Dobo, EPI/WHO*) – presented for information.

The Committee reviewed recently published evidence on national shortages of home-based records of immunization status, highlighting with concern the many settings where supply is interrupted even when external funding for home-based records is available. Work is ongoing to ensure that home-based records are recognized for their critical role in providing data for decision-making, ensuring timely vaccination, reducing wastage through eliminating unneeded re-vaccination, and in second year of life service delivery platforms. IPAC will continue to pay attention to the need for advocacy for country sustainability of funding for home-based records, and to the strengthening of designs of home-based records to optimize their use, acceptance among families, and utility in responding to new vaccines and expanded age ranges of vaccination.

C. How to use fractional doses to address shortages: progress for IPV and yellow fever (*Diana Chang Blanc, EPI/WHO*) – presented for information.

IPAC reviewed updates on experiences of fractional dosing with IPV in India and yellow fever vaccine in the Democratic Republic of the Congo. Linkages to the activities of the delivery technologies working group (such as technologies enabling intradermal injection) and of the Polio Research Committee were identified. IPAC members supported continued work on developing operational guidance on fractional dosing, noting the location of this approach within emergency responses, the regulatory concerns, and the need for nuanced communications to avoid loss of confidence.

Discussion

The Committee was interested in particular in the questions of when dose sparing is an appropriate strategy, and whether it should remain a practice reserved for exceptional circumstances such as the current IPV and YF vaccine shortages including the SAGE recommendations related to fractional dose delivery. On fractional dosing, IPAC members recommended that a specific framework for decision-making be developed by WHO and to maintain this as strategy for future exceptional circumstances and in settings where this practice can be implemented safely (sufficiently trained health workers on proper injection techniques).

Session III. Immunization in the second year of life

Routine vaccination in the second year of life (2YL), while already provided in many countries, is expected to increase in the coming years. There are multiple benefits to establishing a healthy child visit in the 2YL, both for immunization and other preventive health interventions, including:

- providing an additional routine contact to deliver primary doses, booster doses, and second doses (e.g. MCV2, MenA, PCV, booster doses of DTP);
- improving overall coverage through catch-up vaccination of doses missed in the first year of life; and

- opportunities to integrate with other health interventions such as vitamin A supplementation, nutrition services, growth monitoring, deworming, etc.

Immunization in the 2YL had been discussed at the October 2015 IPAC meeting. The purpose of the current session was to:

- provide an update of the work undertaken on immunization in the 2YL since the last IPAC meeting;
- gather substantive feedback from IPAC members on the draft WHO 2YL guidance document, *Establishing and strengthening a healthy child visit in the second year of life (2YL) for immunization and other health interventions*, and provide an opportunity to discuss key issues.

A. Update from WHO: 2YL case studies, guidance document and implementation support (*Emily Wootton, WHO*) – *presented for feedback*

WHO, together with John Snow Incorporated (JSI), has been strengthening the 2YL platform. Two country case studies (Zambia and Senegal) were used as key inputs to draft the global guidance document on the 2YL, alongside additional contributions from other partners, including the US Centers for Disease Control and Prevention (CDC) and UNICEF. Technical assistance is being provided by WHO to Zambia and Senegal to strengthen their 2YL platforms, while additional assistance is under discussion with two countries that are planning to introduce the meningitis A vaccine shortly into their routine immunization systems in the 2YL. Work on the 2YL is linked to work on reducing missed opportunities for vaccination, including some of the implementation challenges related to catch-up vaccination. Data from four recent assessments of missed opportunities for vaccination suggest that the proportion of missed opportunities is higher among children aged 12–23 months than among children aged 0–11 months, particularly where no vaccine is scheduled for administration in the second year of life.

B. Progress on the WHO guidance document and 2YL case studies (*Rebecca Fields, JSI*) – *presented for information*

Additional details were provided on the case studies mentioned above concerning introduction of a second dose of measles-containing vaccine (measles-rubella second dose in Senegal and measles second dose in Zambia):

- Both experiences were initially driven by measles objectives rather than the broader goal of vaccination in the 2YL as part of well-child services.
- There is a need to ensure that health workers understand that no opportunity for immunisation be missed, particularly regarding the vaccination of children that present at health facilities after the recommended age of administration for vaccines.
- No problems were detected regarding the supply chain.
- Challenges were identified regarding the screening, recording and reporting of vaccinations, probably linked to the design of data instruments.

The next steps for the guidance document would be to include the incorporation of feedback from IPAC members and designing a user-friendly layout.

C. Update on 2YL and costing tool (*Imran Mirza, UNICEF*) – *presented for information*

UNICEF's work on the 2YL immunization platform includes a global landscape analysis, the development of information, education and communication materials in Ghana (in partnership with CDC) and the ongoing development of a costing tool for the 2YL immunization platform. The costing tool is being developed in Microsoft Excel and its outputs are expected to include the incremental cost per child reached and total annual incremental costs. The tool will differentiate between one-time costs and recurring costs. Following piloting, the tool will be made available for country use from mid-2017. UNICEF is also considering adding effectiveness estimates to the tool, so that the tool could generate "costs per life year gained" and "costs per Disability Adjusted Life-Year (DALY) averted".

D. CDC experience on the second year of life Platform for Immunization (*Laura Conklin, CDC*) – *presented for information*

The United States Centers for Disease Control and Prevention (CDC) is working in Ghana and Malawi to strengthen Second Year of Life (2YL) immunization platforms. In Malawi, the work focuses on improving data quality and service delivery. Health facility and household surveys were planned for early 2017, and interventions would be designed to address the issues identified and rolled out in the second half of 2017.

The project in Ghana is broader in scope and CDC is working there with partners, including UNICEF and WHO on six strategic focus areas: training and supervision, data recording and reporting, social mobilization and demand generation, programme integration, vaccine-preventable disease surveillance and special innovations. A baseline survey was carried out in 2016, which found, for example, a predominant belief that routine immunization services end at nine months of age. The implementation phase of the programme is expected to continue until 2020, with a follow-up survey scheduled for May 2017 and a final study planned for 2020.

Many of the challenges associated with developing a 2YL immunization platform are similar to those of any new immunization platform, namely the importance of behaviour change in health workers and caregivers, the implementation of catch-up vaccination, and vaccine safety.

Discussion

IPAC members acknowledged the significant work that had been undertaken since the October 2015 meeting and welcomed the draft guidance document. They also acknowledged the growing importance of this work, following the October 2016 SAGE recommendation that all countries should introduce a second dose of measles-containing vaccine, regardless of the coverage level of the first dose of measles-containing vaccine.

It was recognized that more work could be undertaken to document outcomes beyond immunization for interventions provided in the second year of life and to ensure that microplanning tools, such as Reaching Every District, are adapted to include the 2YL immunization platform. IPAC members noted the lower coverage of the second dose of

measles-containing vaccines, as compared to the first dose, and emphasized the potential role of a 2YL platform in improving this performance, as well as in providing catch-up vaccination. In addition, it was suggested that the costing tool may benefit from the inclusion of time-motion studies to provide data on the additional health worker time required to deliver the intervention(s) and that the tool should eventually be integrated with other existing tools, such as comprehensive multi-year plans and/or the OneHealth tool.

IPAC members recommended placing the 2YL platform in broader context as: (i) an integral part of country essential health packages for universal health care (supporting links between the Measles and Rubella Initiative and primary health care approaches); and (ii) an approach that increases equitable access, reducing missed opportunities and inequities to improve child survival, along the life-course, including, but extending beyond, the second year of life. This could help increase sustainability with broader political support for resource allocation. Using a life-course approach may also avoid unnecessary restriction of programme focus to children aged less than 24 months, by ensuring that messages refer to vaccination in the second year of life and older.

IPAC members welcomed the draft 2YL guidance document, expressed appreciation for the progress made since the October 2015 meeting and provided extensive feedback both during this meeting and by email. Among the key points of feedback were to allow for multiple visits in the second year (noting nutritional and other preventive care at this age may take place at six month intervals); to use the second dose of measles-containing vaccine as an 'anchor' to focus the guidance but ensure there remains provision for catch-up vaccination; to support inclusion of 2YL provisions within comprehensive multi-year plans; to consider how outcomes from other programmes beyond immunization could be incorporated; and to design the guidance as a module that can be inserted into complementary programmes such as Reaching Every District micro-planning; Missed Opportunities for Vaccination; and those beyond immunization dealing with nutrition, growth monitoring and well child visits.

IPAC noted the importance of having this document serve as a guide to implementation by immunisation and other programmes, noted the linkage to other discussions reviewing definitions of timeliness and completeness of immunisation, and expressed a strong interest in observing the evolution of the final product.

Session IV. Controlled temperature chain working group – update

The purpose of the session was to update IPAC on progress to date concerning work on the Controlled Temperature Chain (CTC), which first came to the attention of the Committee in 2012 concerning efforts made in support of hepatitis B vaccine use outside the cold chain and later for the meningitis A vaccine. The CTC working group, under the authority of IPAC, was established in June 2016 with the mission to convene key stakeholders to define a shared vision and strategy for CTC and to increase advocacy with vaccine manufacturers as well as with implementing countries for CTC. The working group has held three teleconferences and met in person for the first time on 13 February 2017, to allow for more thorough discussions around which vaccines should be prioritized for CTC.

A. Update on CTC status and achievements to date (*Dorte Petit, EPI/WHO*) –
presented for information

Three vaccine products have received full licensure and prequalification for use in a Controlled Temperature Chain (CTC) so far: a meningitis A vaccine (MenAfriVac®, produced by Serum Institute of India) in late 2012, a pneumococcal conjugate vaccine/PCV (Pneumovax 13®, produced by Pfizer, though the labelling has since removed any CTC indications) in early 2015, and a human papillomavirus (HPV) vaccine (Gardasil4®, produced by Merck) in mid-2016.

The CTC program continues to be driven by the recognized benefits of increased flexibility in the cold chain combined with a confirmed discomfort noted by countries with off-label use of certain vaccines, despite data suggesting their thermostability. There has also been a well expressed concern by country-level decision-makers around possible health worker confusion in the face of varied options around vaccine handling and cold chain adherence. The latter can be overcome with carefully crafted guidance, appropriate training, and well documented best practices. Activities shaping WHO's CTC workstream to date therefore include advocacy and technical support promoting the application of the CTC concept to multiple antigens, as well as documentation of, and support to, the successful implementation and promotion of CTC deployments of MenAfriVac. A number of challenges to CTC usage have become apparent. These are lack of awareness and understanding of the concept and associated criteria, lack of evidence in support of the potential benefits of CTC, the need for increased incentives for industry, and insufficient global partner engagement.

Continuing priorities are to confirm country level need and interest to manufacturers, generate evidence on the added value of CTC for vaccination programs, and boost country uptake to translate into sufficient levels of demand.

B. Priority vaccines for CTC licensure and implementation (*Debbie Kristensen, PATH*) – *presented for feedback*

The following initial four priority vaccines had been identified by the CTC working group based on their heat stability, the likelihood of their being licensed for CTC use soon, and their high potential for public health benefit if used in a CTC:

	Priority vaccine	Licensure/pre-qualification status	CTC Activity focus
1.	Human papillomavirus vaccine (HPV)	One product already licensed and prequalified. Additional products in the pipeline.	Implementation guidance and country experiences to generate evidence.
2.	Oral cholera vaccine (OCV)	One product already licensed and nearing prequalification. An additional product in the pipeline.	Implementation guidance and country experiences to generate evidence.
3.	Tetanus Toxoid (TT) vaccine	No products licensed to date.	Identification of focus products/formats and facilitation of licensure and prequalification.
4.	Hepatitis B birth dose vaccine	No products licensed to date, though one product is under review for a label variation that includes CTC. Additional products in the pipeline.	Identification of focus products/formats and facilitation of licensure and prequalification.

C. Outcome of the CTC working group meeting of 13 February 2017 (*Nora Dellepiane, IPAC member and chair of the CTC working group*) – presented for feedback

The Committee was provided with an overview of the presentations made by partners at the working group meeting and a summary of the recommendations that emerged. The presentation highlighted the need for improved communication efforts at all levels (WHO internal, with manufacturers, partners and countries) as well as for increased partner engagement in translating commitments into policies and resources.

The working group examined extensively whether the current definition of CTC remains appropriate. While there have been calls to broaden the criteria currently defining CTC, such as lowering the required threshold temperature (currently set at 40°C), it was ultimately decided to recommend maintaining the current CTC criteria and definition. Likewise, the CTC program has long encouraged that the implementation of this approach be limited to a context of campaigns or special strategies. This implies that CTC focuses on delivery of a single antigen rather than a mix of vaccines, especially where it is not certain that all would qualify for the CTC approach and the added advantage offered by CTC would thereby be lost. This has met with some resistance by partners, with the suggestion that it is too restrictive. However, in the interest of preserving the successful outcomes of CTC implementation while the program is still in its infancy, it was finally proposed that this guiding principle be maintained, while ensuring that opportunities be nevertheless sought out for combined approaches when multiple CTC-licensed vaccines are able to be delivered together.

Discussion

IPAC members expressed their appreciation of the value of the CTC concept as well as the progress that WHO has made on the CTC agenda since 2012. The Committee endorsed the CTC working group's selection of four priority vaccines, noting that each will contribute contrasting lessons on CTC implementation. They acknowledged that use of meningococcal A vaccine in a CTC is now established, and that evidence for other priority vaccines, including measles-containing and rotavirus, is being gathered. In addition, IPAC noted that other vaccines should still benefit from the attention of the working group should the need and opportunity arise. Examples are a rotavirus vaccine currently under consideration for WHO prequalification or measles vaccines that remain an important priority, especially for remote populations that are difficult to reach with existing usages.

The Committee recommended that the currently agreed definition and applications of CTC be maintained for at least two years, possibly aligning any review with GVAP timelines; this includes limiting CTC to campaigns or special uses, applying current temperature recommendations, and ensuring that vaccines make only a single excursion outside the cold chain. IPAC members suggested aligning the CTC roadmap timelines with the Global Vaccine Action Plan (GVAP), which expires in 2020 for the first phase, after which both the priority vaccines and CTC criteria can be re-evaluated.

IPAC also recommended that the working group revisit its communications to ensure that CTC is viewed not simply as a supply chain issue, but as a service delivery or equity related innovation that allows programmes to increase equitable access to coverage. The

Committee suggested additional advocacy and communication materials, including those for: informing regional and national stakeholders about the situations that CTC may help address; describing the economic and programmatic benefits of CTC as compared to standard usage; describing the potential demand in order to inform manufacturers and other global partners; and supporting front line health workers in understanding and communicating the safety and efficacy of CTC. Discussions also emphasized the need for greater engagement of other partners, including USA CDC, the Bill and Melinda Gates Foundation, and Gavi; both from the perspective of their ability to shape the market and their focus on coverage and equity. Support for CTC was re-affirmed by industry representatives from both the Developing Countries Vaccine manufacturers' Network (DCVMN) and the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA).

IPAC noted that the CTC working group will continue work on these and other matters, and asked that a roadmap for action be brought to the Committee through a virtual forum in mid-2017.

Session V. Delivery Technology working group – update

A. Update on working group activities to date and future activities *(Darin Zehrung, PATH and co-chair of the DT working group)- presented for information*

The Delivery Technology (DT) working group was established in December 2015, and is co-chaired by WHO and PATH. Its mission is to maximize the impact of immunization products for public sector use, including stand-alone delivery technologies, novel primary containers, combination vaccine/device products and other alternative delivery technologies. Members include private and public sector vaccine stakeholder groups with a variety of expert subject matter profiles (WHO, PATH, BMGF, DCVMN, IFPMA, Gavi, UNICEF, CDC, MSF, JSI, and EVI). In the 15 months since its inception, the DT working group has undertaken the following activities (keeping IPAC regularly informed through bulletin updates and endorsement requests):

- development of a target product profile (TPP) for measles-rubella microarray patch, and held a stakeholder workshop on microarray patch product development;
- development of the GVAP Platform Delivery Technology (Indicator G4.2) report and recommendations for future activities;
- reviewing and providing feedback to manufacturers/developers on various new technologies including blow-fill-seal (BFS), vial and compact prefilled auto-disable (cPAD) designs (parenteral delivery) and glass cartridges for parenteral delivery;
- reviewing the vaccine technology prioritization framework and Vaccine Technology Impact Assessment (VTIA) tool developed by PATH.

B. Status of microarray patch vaccine technology development, and the TPP for measles-rubella on a microarray patch (MR MAP) *(Birgitte Giersing, IVR/WHO and co-chair of the DT working group) – presented for decision/endorsement*

Since the year 2000, an estimated 20 million lives have been saved by measles-rubella vaccination. However, significant immunization gaps persist, with 134 000 deaths reported in 2015, 75% of which are in the world's six most impoverished countries. The current measles-rubella presentation requires complex logistics to accommodate and end-to-end cold chain, reconstitution and administration by fully trained health care workers.

The features of the microarray patch DT, which could potentially address these issues, includes single-dose administration, simplicity of administration by non-medically trained health care workers, potentially reduced volume footprint, extended thermostability/potential CTC compliance, and reduced sharps waste. Collectively, these attributes enhance measles-rubella vaccine's programmatic suitability and end-user acceptability, which are critical in low-resource contexts. Despite these attributes, microarray patches present significant challenges with respect to investment in product development, due to the perceived high cost of the goods, the uncertain clinical and regulatory pathway and the relatively low returns offered in the low- and middle-income vaccine market.

The measles-rubella/microarray patch delivery concept was presented to SAGE in October 2016. SAGE recommended the most expeditious clinical development and regulatory pathway to licensure of measles-containing vaccines microarray patches be determined, and that barriers to the development, licensure and use of microarray patches for measles-rubella delivery be identified and addressed urgently. With this in mind, WHO's Initiative for Vaccine Research intends to form a working group in 2017 to focus on this subject. The DT working group is also seeking to better define the microarray patch value proposition through the use of the Vaccine Technology Impact Assessment tool (VTIA) and the total systems effectiveness approach, which considers the trade-offs in the total cost of immunizing a child for the current technology versus novel options, where there may be reductions in service and delivery costs that offset higher commodity costs. Additional benefits could also be considered such as impact on systems aspects, including supply chain, wastage, safety, health care worker behaviour, and coverage.

Discussion

The Committee endorsed the MR MAP TPP, provided that the following considerations be taken into account:

- Use case scenarios:
 - consider other products that will be delivered at the same time (schedule) from a supply chain logistics perspective (example: vitamin A capsules).
- Stability:
 - include separate characteristic for the inclusion of a suitable vaccine vial monitor (VVM) for measles-rubella/microarray patch technologies;
 - consider including and specifying separate requirements for CTC and extended controlled temperature conditions;
 - for CTC temperature conditions, ensure that references and language are consistent with WHO recommendations.
- Packaging:

- address the requirements for secondary and tertiary packaging in terms of suitability and impact on the immunization supply chain;
- secondary packaging – consider a format that will allow the vaccinator to see remaining microarray patches within the package (potential optimal target).
- Delivery: time required for application + delivery: time required.
 - consider combining the times stated to compare with current needle and syringe delivery and standardize language between the two characteristics;
 - once additional data are made available from developers, assess the potential for reducing the wear time for microarray patches to further minimize the potential for removal by children.
- Application site: should be considered in terms of efficacy but also in a location on the child that will be less likely to be disturbed and/or removed (example: scapular region).

In additional discussion, the Committee members agreed that microarray patch DT appears to be compelling, particularly as an innovation for improving equity and access for the “last mile”. They suggested the potential that new cadres of vaccinators may be enabled by such technology, and that this be included as part of total systems effectiveness considerations, and that microarray patches could be delivered with other products in development, such as IPV. It was agreed that end-user feedback should be sought as a means of further informing design and disposal.

IPAC suggested that the DT working group should continue to advocate for the use of microarray patches for measles-rubella in EPI in low- and middle-income countries, among donors and bodies responsible for public health policy formation, and publish data from studies. Discussions also noted the need to consider market considerations, including alternative vaccine indications for microarray patches that may have a more favourable value proposition in high-income countries, such as HPV, and the applicability to vaccines in development where there is not yet an established market. The Committee cautioned that measles-rubella microarray patches will be considered a completely new product from a regulatory perspective, as vaccine reformulation is needed for this novel combination product.

C. Progress report on delivery devices and containers (*Darin Zehrung, PATH and co-chair of the DT working group*) – presented for feedback

Disposable syringe jet injectors (DSJIs) will soon be entering programmatic use. One subcutaneous/intramuscular injection (SC/IM) capable device has received WHO prequalification in 2013¹ and an intradermal injection (ID) capable device has been recently been submitted for prequalification review. 5 million cartridges and 5000 ID capable DSJI devices are being purchased for the global polio eradication effort. Delivery of measles containing vaccine (MCV) by DSJI is also anticipated in 2017, following a MMR phase IV clinical study that showed comparable non-inferiority performance and safety as compared to delivery by needle and syringe.

¹ http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/categorypage.aspx?id_cat=37

One type of ID adapter that facilitates the angle and depth of needle upon insertion will be submitted for prequalification in 2017, once the prequalification specification currently under development has been completed and approved. Approximately 4M units of this ID adapter and AD syringe has also been purchased for use in global polio eradication efforts in 2017. Both the DSJI device and the ID adapters have been and currently are being evaluated for fractional dose IPV delivery. Countries are considering which technologies to use for fIPV delivery, to include consideration of needle and syringe use as well.

Blow Fill Seal (BFS) packaging technology is being advanced by a large pharmaceutical company in preparing production of a rotavirus vaccine in a Multi Monodose 5-dose conjoined strip format (single VVM, BFS ampule opened upon removal from conjoined strip and must be delivered), with 10 strips per secondary package (cold chain volume reduction) by BFS. A European based injection device developer and BFS manufacturer are developing a parenteral capable BFS design that would have cPAD functionality. In addition, BMGF is supporting a BFS CMO to evaluate the feasibility and compatibility of various vaccines with the BFS filling process. Other technologies, such as an integrated reconstitution administration device for heat stable rotavirus vaccine packaging and delivery is also under development. This integrated reconstitution technology has dual chambers for both the powdered vaccine and diluent with a frangible seal that can allow for reconstitution/mixing in the device and oral delivery. The DT working group has provided feedback on both BFS and glass cartridge device designs with a view to informing design decision-making during early stages of product development.

Discussion

IPAC members emphasized the need for early and comprehensive solicitation of end-user needs to ensure successful product implementation. In addition to end-user acceptability studies, clinical studies that can provide the evidence basis for vaccine effectiveness are needed to support decision-making prior to vaccine product implementation. A holistic feasibility assessment for novel vaccine product introduction would be needed.

D. Introduction to the VTIA tool (*Birgitte Giersing, IVR/WHO and co-chair of the DT working group*) – presented for information

VTIA is a Microsoft Excel-based model that provides a comparative economic evaluation of the commodity and system costs, as well as the health impact, of current vaccine/technology presentations in contrast with new presentations. It is an example of a TSE modelling tool. It enables scenario analyses for new presentations for technologies under development, and helps identify the key variables/trade-offs of new technology designs and features that influence the estimated costs and health impact. VTIA is intended to enable cost modelling beyond merely considering the weighted average price for a vaccine or commodity, to include all delivery costs, and to determine if a lower programmatic delivery cost might be possible for a new vaccine presentation and/or delivery and packaging technology.

Discussion

IPAC reviewed the development of the VTIA Tool, noting its potential to contribute to a better understanding of programme and system costs, as well as health impact, and the clear linkage to related concepts of Total System Effectiveness. IPAC members commented that the VTIA tool is informative for vaccine technology prioritization, but cautioned that the limitations of currently available delivery infrastructure will be likely to impede the introduction of novel technologies. This needs to be considered as part of the TSE assessment of new delivery technologies. The DT working group was encouraged to assess how VTIA could be incorporated into an existing tool, such as comprehensive multi-year planning or alternative modelling approaches. Collaboration with the Immunization and Vaccine Related Implementation Research Advisory Committee at WHO for to examine their work on modelling population and programme benefits was also suggested. The VTIA model should be tabled and presented to IPAC before the next meeting for further feedback.

IPAC members welcomed the broad scope of the work of the DT working group and noted the links to other work streams, including that of the Product Development Vaccine Advisory Committee. Committee discussions covered the variety of issues raised by new DTs, including tools to support intradermal injection for fractional dosing of vaccines to conserve supply, the need to consider programmatic suitability in some detail from early in the process, the cost benefits or drawbacks in routine deployment, and the importance of assessing system readiness and potential disruption or strengthening. Discussants emphasized the need to make a clear link to the potential of new delivery technologies to increase health worker or community acceptance, and/or to increase access for equitable coverage, especially in the "last mile". IPAC asked for continuing updates, including timescales for the various work streams underway within this group.

Session VI. Immunization advisory committees – update

The WHO Departments of Immunization, Vaccines and Biologicals and Essential Medicines and Health Products are supported by several advisory committees, including the Product Development for Vaccines Advisory Committee and the Immunization and Vaccines Related Implementation Research Advisory Committee, which address immunization and vaccine-related subjects and provide evidence-based guidance for policy and programming purposes.

In an effort to keep IPAC well aligned and better linked with these committees, the respective secretariats or chairs informed the Committee of recent activities by their committees relevant to IPAC's mandate.

The Chair of the Programmatic Suitability for Prequalification (PSPQ) Standing Committee also summarized the PSPQ process and criteria, as well as describing the products that had been reviewed to date, while noting that the Committee had been inactive since 2015. A call for nominations was launched in 2016, through which two new members of the Committee were selected from among IPAC members.

Close

Dr Morgan thanked all in attendance and summarized the proceedings. All IPAC members were thanked for their important contributions and dedication. It was confirmed that the next IPAC meeting will take place during Q1 of 2018. Specific dates will be determined and announced later.