

A note from the Chair:

Dear colleagues,

Welcome to our first IPAC bulletin for 2018 – a little delayed due to the press of work and other changes at WHO. In April I attended the six monthly **Strategic Advisory Group of Experts (SAGE) meeting** on our behalf. I wanted to share a few of my own reflections on that meeting – though note that the formal report on SAGE will appear in an upcoming Weekly Epidemiological Review. All the presentations made at SAGE are available at :

http://www.who.int/immunization/sage/meetings/2018/april/presentations_background_docs/en/index1.html (note the separate tab for Presentations).

Among many general issues affecting immunization programmes raised at SAGE, four trends seem particularly important: the need to keep vaccines well integrated within broader moves towards **universal health coverage**; the interaction of **conflict and migration** (massive population movements in some cases) creating new 'hard-to-reach' populations

(although timely preventive cholera vaccination of refugee populations in Bangladesh is to be celebrated); pockets of **rapid population growth** are outstripping immunization capacity (the related 'adolescent bulge' in Africa and South Asia will test adolescent vaccination programmes); and the growing challenge of vaccinating those unreached in **middle-income countries** where much of the world's poor now live.

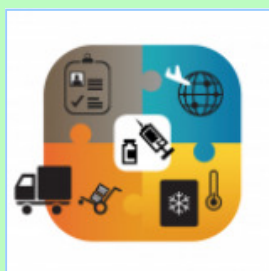
The **future global vaccination strategy**, from 2020 onwards, is now under development, and will need to consider the need for greater granularity in sub-national programme performance data, new delivery technologies in terms of products and strategies to reach across the life-course, policy innovations (especially considering where so-called 'mandatory vaccination' fits), and increasing use of new information and communication technologies. This SAGE also saw introduction of the concept of estimating the '**Full Public Health Value of Vaccines**', aiming to describe a vaccine's value in terms of its economics, disease control

benefit, protection against financial risk, reduction in outbreaks, amelioration of antimicrobial resistance, support to stronger health systems, and other broad outcomes; balancing these benefits against the costs of research, development, and deployment. The tools and concepts of **Total Systems Effectiveness (TSE)**, which we have considered in recent IPAC forums, also form a part of this thinking.

This meeting heard an update of the public health implementation pilots of **malaria** vaccine in Kenya, Ghana and Malawi, with field work slated for late 2018, along with preparatory work on determining just how data from these pilots will inform policy. As you have probably tracked, a revision to the recommendations on one **dengue** vaccine was also discussed and drafted; tightening



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the advice on deployment in relation to endemicity, previous exposure to the virus, and particular age groups. Other vaccines discussed, with presentations and background documents available on the SAGE site, include **polio, diphtheria, meningococcal, yellow fever, cholera and measles**.

Measles discussions included discussion of the progress towards regional elimination (many steps forward, some back), estimates of the total possible cost of eradication, and the need for continued programmatic innovation and new thinking on vaccination campaigns. On this last point, I'd like to thank all IPAC

members who have helped with thinking on micro-array patches (last year) and in advice on guidance for more **selective measles SIAs** (this year). It has also been great to see the final version of the **Second Year of Life** Handbook, which has received a few rounds of IPAC input, now completed and distributed.

Other IPAC work that is happening through online consultation relates to the **Controlled Temperature Chain** (see below) and vaccination of **health care workers against influenza**. If anyone has ideas to contribute on either topic, please contact myself or Anna-Lea.

Lastly, I'd like to offer sincere thanks to **Dr K.O. Antwi-Agyei**, for his years of service to IPAC that came to an end this month. A fond farewell follows in the coming pages. I'm also grateful to Adelaide Shearley and Craig Burgess for agreeing to renew their terms of service on IPAC.

I look forward to seeing members and observers at our face-to-face meeting in July this year. Stay tuned for updates on the agenda as that approaches.

Best Wishes,

Chris Morgan

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From the Working Group frontlines

CTC Working Group update by Anna-Lea Kahn (CTC focal point at WHO and part of the CTC-WG Secretariat)



Photo credit: D. Di Lorenzo / MSF

In January 2018, Shanchol, the oral cholera vaccine (OCV) produced by Indian vaccine manufacturer, Shantha Biotechnics, was approved for WHO prequalification. This represents a long-awaited milestone and key progress both within the framework laid out in the priority roadmap of the IPAC Working Group on the Controlled Temperature Chain (CTC-WG), but also towards the Global Vaccine Action Plan

(GVAP) indicator dedicated to increased products licensed for use in a CTC.

According to this new label variation, Shanchol vaccine can now be removed from the cold chain and tolerate ambient temperatures up to 40°C for a maximum of 14 days before needing to be administered or discarded, provided that the vaccine has not reached its expiry date and the vaccine vial monitor is still valid.

WHO continues to recommend that CTC implementation only occur with appropriate planning, training and guidance however. Renewed efforts are consequently under way to pilot the use of OCV in a CTC, an activity which will be driven by WHO's Global Task Force on Cholera Control, in collaboration with Medecins Sans Frontieres and WHO's IVB/EPI team. As was the case for Meningitis A and Human Papillomavirus

Vaccines, pilot studies of delivery through a CTC allowed for the effective development of implementation guidance. An OCV-CTC pilot is expected to be completed by the end of Q1 2019 and guidelines available by Q2 of the same year.

Work on field guidelines for the delivery of HPV in a CTC are currently being finalized and expected to be published by June 2018.

Additional work is also under way on a document describing the challenges confronted by the WHO-PATH partnership with respect to Hepatitis B use in a CTC.

The next teleconference of the CTC-WG will take place in June.

Anyone interested is welcome to join these calls. Please contact Rachel Bauquerez for further details: bauquerezr@who.int.

Total Systems Effectiveness (TSE): progress of the pilot and upcoming activities - by Siobhan Botwright



Total Systems Effectiveness (TSE) is a holistic approach to prioritising or deciding between products from a systems perspective, taking into consideration coverage and equity, as well as programmatic implications and full systems cost. In 2017, BMGF, CHAI, PATH, UNICEF, WDI, Gavi-the Vaccine Alliance and WHO came together to form the TSE initiative, with the overarching vision to improve cohesion between downstream country uptake and upstream product decision-making of innovative vaccine products.

As part of this TSE initiative, WHO commenced a 6-month pilot in December 2017 to look at the feasibility of applying a TSE approach to country decision-making. The purpose of the pilot is to assess the relevance of TSE for product selection decisions in LMICs and to determine country requirements for applying TSE to country product selection decisions.

Current progress

Over the past 4 months, WHO has conducted extensive outreach to potential pilot countries through regional offices, forums such as GVIRF, and our partners, whilst also adapting the TSE framework for country use; creating a TSE toolkit to introduce country NITAGs and ministries of health to the concept of TSE; and building a TSE model in Excel. A TSE Modelling Working Group has been convened to leverage learnings from UNIVAC, SMART Vaccines and other initiatives focussed on evidence based decision-making in LMICs.

IVIR-AC review and meeting of the TSE Steering Committee

TSE was reviewed by IVIR-AC in March 2018. Although the committee saw value in demonstrating the trade-offs between products to decision-makers, it was highlighted that the methods for TSE need further development to adhere to good multi-criteria decision analysis methodology, and that it is essential that the TSE framework and tools are built according to country priorities and preferences. In response, the pilot objectives and activities have been revised to take a bottom-up approach and WHO has engaged partners from LSHTM and Radboud University to refine the methodology for TSE.

During the TSE Steering Committee meeting on 16th April, there was positive feedback on the revised objectives for the pilot. Other key themes from the discussion include the potential value of TSE in considering portfolios of vaccine products in an EPI programme, taking an integrated view across diseases; the promise of TSE to improve country decision-making for coverage and equity by considering trade-offs at both the national and sub-national level; and the synergies between TSE, WHO's Full Public Health Value Proposition (FPHVP) and Gavi's Vaccine Innovation Prioritisation Strategy (VIPS) in articulating country barriers, preferences, and priorities to product developers at the local, regional and global level.

Upcoming activities in pilot countries

Indonesia and Thailand have been confirmed as pilot countries. WHO has received interest to conduct the TSE pilot in an additional 7 African countries, and is currently holding discussions to select two of these countries for the pilot, in order to ensure the pilot includes countries with varied income status, geographic location, and immunisation system strength.

The Indonesian pilot is being led by the Indonesian Technical Advisory Group on Immunization (ITAGI), and will be supported in full by the WHO Country Office for Indonesia. The Thai pilot is led by the Health Intervention and Technology Assessment Program (HITAP), a semi-autonomous research unit under Thailand's Ministry of Public Health and member of the International Decision Support Initiative (iDSI). TSE workshops have been scheduled to take place in May 2018 in both countries.

Next steps

It is anticipated that the pilot will end in September 2018, with a report summarising the findings from consultations in pilot countries and a proposal for the future development of TSE. There will be an interim report on status and learnings from country pilots for IPAC in July.

MCV-MAP April 2018 Meeting: a brief summary

Microarray patches (MAPs) are a novel delivery technology that have the potential to increase the equitable coverage of vaccines that are highly effective, but challenging to deliver, in low- and middle-income countries (LMICs). Although early in product development, MAPs may improve vaccine thermostability, enable dose sparing, reduce packaging volume, enable safer, easier administration and disposal. These attributes could facilitate novel vaccine delivery scenarios such as administration by minimally trained volunteers through house-to-house immunization strategies and could potentially ease the logistics and cost of vaccine delivery. The WHO is interested in this strategy to deliver measles and rubella (MR) vaccine to help eliminate the remaining 90,000 deaths per year due to measles and a further 110,000 cases of congenital rubella syndrome.

MAPs are currently in preclinical development for a number of existing vaccines, including influenza, tetanus toxoid, inactivated poliovirus vaccine (IPV), as well as for vaccines in development such as inactivated rotavirus and dengue. Although MR-MAP pre-clinical product development is also now underway, there are a number of unknowns with respect to the appropriate product development strategy and the most expeditious regulatory pathway to licensure, since this is considered a novel vaccine combination product. WHO's Strategic Advisory Group of Experts Working Group on Measles and Rubella (SAGE MR WG) has highlighted that MR MAPs have the potential to help achieve MR elimination goals, and recommended that a WG be established to determine the pathway, barriers and timeline to licensure. With this, in April 2018, IVB convened a working group of subject matter ex-

perts, and a consultation of MR-MAP developers, to evaluate the pathway, barriers and perceived risks to MR-MAP product development.

The major recommendations from this consultation included the need to better describe the value proposition for MR-MAPs, by establishing the use case of this novel product and associated demand forecast, as well as evaluating the product development strategy and timeframe for which MR-MAP is likely to be available. Participants of the consultation worked together to craft an integrated product development plan, including both manufacturing, clinical and regulatory steps to licensure and beyond to WHO prequalification.

The MR-MAP demand forecasting work is now underway, and a meeting report including the product development considerations and assumptions is under preparation.

IPAC bids farewell to Ghana's "Vaccine King"



Photo credit: B&MGF/
Impatient Optimists

Among the key perspectives we count on emanating from IPAC is that of country-level needs and realities. Few members have been able to offer that "reality check" as soundly and consistently as Dr. K.O. Antwi-Agyei. Bringing to the committee the wisdom and insights garnered during his tenure managing Ghana's Expanded Programme on Immunisation, K.O. was keenly aware of the challenges and dedication required to ensure vaccines reach the seemingly unreachable and this is why he is credited with Ghana's success in controlling measles and becoming certified as polio-free. It is also the reason he was nicknamed by the Gates Founda-

tion as Ghana's "Vaccine King".

K.O. offered the following parting words on completing his second term on IPAC at the end of April 2018:

As the good book says "there is time for everything". I am grateful to the Almighty God for all his travelling mercies to Geneva for IPAC meetings. I am also grateful to the Director IVB of the WHO for the opportunity to serve on the IPAC and to interact with colleagues with such high levels of experience. I have learned a lot from colleagues and I wish to thank all IPAC colleagues and secretariat so much. It's been a pleasure working with all of you. As I bow out, I wish IPAC good success in all endeavours.

The Doses Per Container Partnership (DPCP) – 2 years later:

An update from JSI - by Craig Burgess

The widespread use of multi-dose vaccine containers in low- and middle-income countries' immunization programs is assumed to offer benefits and efficiencies for health systems, such as reducing the purchase price per vaccine dose and easing cold chain requirements. Yet the broader impacts on the trade-offs among immunization coverage, costs, health worker behavior, and safety are still not well understood. It is also unclear what processes governments typically go through to determine their choices about dose per container (DPC), and what information decision-makers have or use when determining DPC.

As initially described in the April 2016 issue of the *IPAC Bulletin*, JSI has been leading efforts to build the evidence base on this topic through the **Dose Per Container Partnership (DPCP)**. Since its launch in 2015, this partnership has undertaken a series of activities to explore current decision-making on DPC options and better understand the relationship between DPC and immunization systems, including operational costs, timely coverage, safety, product costs/wastage, supply chain, and policy/correct use.

Through the Partnership, decision-making for DPC at the country level has been explored through key informant interviews and implementation and observational research at national, district, and facility level in Ghana, Zambia, Senegal, and Vietnam. The Partnership has analysed and is documenting the broader decision points at a global and national country level, as well as decision-drivers in routine immunization for

the frontline health worker.

A few key findings have emerged to date:

Often the decision to change DPC is due to external forces and organizational preferences, not necessarily based on Ministry of Health preference. Ghana provides a good example of dose per container changes in yellow fever and pentavalent in 2012 where global market availability dictated DPC change, which was then successfully managed by the Ministry of Health (MOH) in Ghana.

The healthcare worker (HCW) preference of DPC is often not considered at national or global levels. Evidence from qualitative research in Zambia, Senegal and Vietnam indicates that HCW would prefer smaller vial sizes of BCG and measles in order to reduce wastage.

In lieu of smaller vial sizes, HCW sometimes create workarounds to reduce wastage, such as offering specific vaccines on specific days, having selected immunization days, or waiting until a specific number of children present before opening a vaccine vial. With smaller multi-dose vial sizes, HCWs would be more willing to open a vial during scheduled sessions or opportunistically on any day to improve timely and higher vaccination coverage. This has been evident through the implementation and observational research in Zambia, Senegal and Vietnam.

Currently there is not a decision support tool that can help a MOH decide what DPC to use, although there are planning tools that could be adapted to respond to this question. The DPCP reviewed 10 immunization planning tools with

user feedback on the DPC applicability.

When pressed with this DPC question, MOH staff often consider only some variables, such as purchase price per dose and cold chain capacity, and may not factor in the need for timely vaccination. The DPC issue is considered mostly during annual forecasting and ordering processes, new vaccine introduction application, and when developing the Comprehensive Multi-Year Plan (cMYP).

As countries' immunization programs are growing and more DPC options are becoming available from manufacturers, there is an opportunity to inform and support key decision makers at the country level when deciding on product choice and close the information gap between country preference, procurement agents such as UNICEF, and manufacturers.

The DPCP is synthesizing research findings to develop guidance to help countries weigh the complexity of the trade-offs of DPC. For example, a 5-dose vial of measles may cost more in purchase price per dose (although considerably less per vial) but would reduce the anxiety of health workers to open a vial when only a few children present -- and lead to higher and more timely coverage rates. Each country context is different, and this DPC decision must be based on evidence that is applied to that context. The Partnership is generating the evidence and will share the results by the end of 2018.

*All documents are available on the project webpage:

<https://goo.gl/Dr9f23>

Announcing WHO's new Vaccine Market Initiative:



The objectives of MI4A are to:

- enhance the understanding of global vaccine demand, supply and pricing dynamics;
- identify affordability and shortage risks;
- convene global health partners to develop policies, strategies and guidance to address the identified risks; and
- strengthen national and regional capacity for improved access to vaccine supply.

To learn more, please visit www.who.int/immunization/MI4A or contact.

Upcoming Meetings & Events:



- ⇒ 08-10 May 2018 — Geneva, Switzerland: **WHO meeting on Shigella vaccine development and policy pathways**
- ⇒ 21-26 May 2018 — Geneva, Switzerland: **World Health Assembly**
- ⇒ 26-27 June 2018 — Geneva, Switzerland: **Annual Meeting of WHO Product Development for Vaccines Advisory Committee (PDVAC)**
- ⇒ 26-28 June 2018 — Kigali, Rwanda: **Global Immunization Meeting (GIM)**
- ⇒ 10-12 July 2018 — Geneva, Switzerland: **Annual Meeting of WHO Immunization Practices Advisory Committee (IPAC)**

A final word from the IPAC Secretariat

Following a number of repeated postponements, the 2018 dates for the annual IPAC meeting have been confirmed and preparations are under way for the committee to convene in Geneva, Switzerland on 10-12 July. We thank you for your patience and understanding over the last few months as we worked on identifying the most appropriate timing and venue for this meeting, and we apologize for any confusion or inconvenience caused by the changes in timing. One positive outcome is that this year's meeting is returning to the WHO campus, the first time since June 2014. However, it will also mean that participation will need to be limited. We therefore request that you respond to meeting invitations with minimal delay and inform us of any changes in your planned participation as promptly as possible.

The meeting agenda is still evolving, however the following key topics will likely be featured:

- *Recent activities and outputs of IPAC Working Groups;*
- *Guidance for an innovation agenda for improved coverage and equity, which includes the evaluation of the outcomes from an initial round of Total System Effectiveness (TSE) Pilots and reviewing progress on the Vaccine Innovation Prioritization Strategy (VIPS);*
- *Optimizing vaccine delivery through selective vaccination for campaigns, improved management and supervision, and the new approach to Effective Vaccine Management (EVM, 2.0).*

Looking forward to seeing you all in July.

The IPAC Secretariat Team