

**WHO's 5th Product Development for Vaccines Advisory committee (PDVAC) meeting  
26–28 June 2018  
Executive Summary**

On 26–28 June, WHO's Product Development for Vaccines Advisory Committee (PDVAC) was convened for its 5th annual meeting. Progress was discussed in vaccine and monoclonal antibody (mAb) development for the 10 previously prioritized pathogen areas and also for 3 new pathogens with candidates in, or approaching, clinical development. Several cross-cutting topics were considered and two new vaccine product development initiatives were presented. Below, is a high-level summary of the major activities and advances in the product development of vaccines and other technologies, and in new initiatives, since the June 2017 PDVAC meeting.

**Vaccines against pathogens prioritised by the Global Vaccine Action Plan:**

**\*Human immunodeficiency virus (HIV):** Both vaccine (ALVAC//bi-gp120/MF59 and Ad26/4 mosaic + gp140/Alum) and broadly neutralizing monoclonal antibody (BnAb) (VRC01) candidates are in proof-of-efficacy trials in adults. Data are anticipated in the 2021 and 2020 timeframe, respectively. Both the vaccine candidates listed above are based on complex heterologous prime-boost regimens. The VRC01 BnAb study will assess proof-of-concept of the passive immunization approach and determine the serum level or neutralization titer of antibody required for protection. These data will inform optimization of the approach, which will likely be a combination of multiple BnAbs administered at a frequency to be determined. The development of these promising vaccine and BnAb approaches is in the context of epidemiologic changes, increased access to treatment and availability of other HIV prevention technologies, such as pre-exposure prophylaxis. In May 2018, WHO convened HIV experts for a consultation to evaluate the routes from proof-of-efficacy to policy decision, to inform on the access to, and use for future HIV vaccines and also mAbs for prevention. The report from that meeting is in preparation.

**\*Tuberculosis (TB):** WHO Preferred Product Characteristics (PPCs) for TB vaccines have been finalized and are publicly available. Since 2017, several vaccine candidates have advanced through the pipeline, including one recombinant Bacille Calmette Guérin (BCG) candidate (VPM1002), which is moving into a phase 2/3 prevention-of-recurrence study in India. Another candidate, known as MTBVAC, a genetically attenuated *Mycobacterium tuberculosis* isolate, is progressing from phase 1 to two phase 2a studies in infants and adults, in South Africa. The candidate H4:IC31 was evaluated for prevention of infection alongside BCG in a Phase 2b study, also in South Africa. The study population was previously BCG-vaccinated adolescents who had no evidence of latent infection. Although the primary objective of the study was not met for H4:IC31, a secondary analysis showed moderate efficacy of BCG revaccination measured by sustained QuantiFERON conversion. The development of H4:IC31 will be discontinued, but are ongoing with respect to the rationale for, and issues regarding, BCG-revaccination. Other candidates such as DAR901 (an inactivated whole cell *M. obuense*), H56:IC31 (an adjuvanted multi-component protein vaccine), and the GSK M72/AS01 subunit protein candidate are also progressing through clinical development. Results from GSK M72/AS01 proof-of-concept evaluation are expected imminently.

**\*Malaria:** Significant progress has been made in the preparation for RTS,S/AS01 Malaria Vaccine Implementation Programme in Ghana, Kenya and Malawi, with earliest introductions through the Expanded Programme on Immunization (EPI) anticipated by early 2019. These pilot programmes will collect key evidence on the safety, programmatic feasibility and vaccine impact of RTS,S for consideration by WHO's Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Committee that advise WHO on vaccine and malaria policy

**\* denotes pathogens prioritized by PDVAC**

recommendations, respectively. In parallel, a study evaluating pre-seasonal malaria vaccination strategy with RTS,S/AS01 is ongoing in Burkina Faso, which has a high seasonal malaria transmission rate. Another clinical study is evaluating a schedule that includes the addition of a fractional dose of RTS,S/AS01 with up to three annual additional doses. This will examine both protection against uncomplicated and severe malaria and protection against infection. The study is in 5–17 month olds in Ghana and Kenya, with interim results expected in 2021. Several other next-generation candidates are in clinical development (phase 2 or beyond) including pre-erythrocytic, blood-stage and transmission-blocking approaches, and some groups are considering passive protection with mAbs.

**\*Influenza:** In light of the ever-present epidemic threat from influenza, development of a universal influenza vaccine continues to be a major research and development (R&D) focus and remains a public health priority. A recent workshop organized by the US National Institute of Allergy and Infectious Diseases defined the required characteristics of a universal influenza vaccine and resulted in the development of strategic plan to guide future investments in influenza research. New technologies (particularly structural biology, rapid isolation of human mAbs, high-throughput sequencing, protein engineering, single-cell analysis, and their derivatives) have provided new development options for influenza vaccines. Several approaches are in development, and those undergoing clinical evaluation include candidates based on the hemagglutinin (HA) stem or head-stem chimera, matrix 2 ectodomain, HA rosettes, individual full-length HA nanoparticles, and virus-like particles (VLPs). In addition to vaccines, BnAbs that have the ability to cross react with the stem region of multiple HAs are being developed; these aim to protect against future drifted and pandemic strains of influenza.

**Vaccines targeted for maternal immunization:** In 2017, WHO estimated that 23% of the 2.6 million deaths that occurred in the neonatal period (0–28 days) were due to infectious diseases, most of which are potentially vaccine preventable. The current EPI vaccines provide little protection to neonates and improved strategies to protect neonates are urgently needed. Through initiatives such as the Maternal Immunization and Antenatal Care Situation Analysis and Advancing Maternal Immunization projects, WHO is working to assess the challenges and opportunities to implement routine maternal immunization services within the EPI or antenatal care systems. This is for delivery of approved maternal immunization vaccines, as well as to prepare the pathway for implementation of vaccines under development, such as respiratory syncytial virus and group B streptococcus.

**\*Respiratory syncytial virus (RSV):** The RSV vaccine pipeline is robust and diverse, with 47 candidates in development, including 19 vaccine and mAbs candidates that are in clinical trials. The most advanced candidate is Novavax's sub-unit F-protein based VLP, currently undergoing a phase 3 clinical study in both the Northern and Southern hemispheres. The result of an informational assessment using threshold criteria for a commercial product was announced in December 2017 and enrolment was completed in May 2018 after recruitment of 4,600 mother–infant pairs. Results of an interim analysis of the primary endpoint readout is anticipated in Q1 2019. A 'vaccine-like', single-injection, long-acting mAb approach is also in late-stage clinical development, with data from a phase 2b study expected in late 2018. An over-arching issue for both approaches relates to defining the most appropriate implementation strategy for these interventions, considering the absence of RSV seasonality in some settings, and the need to provide sustained protection through the first six months of life when disease is most severe.

**\*Group B Streptococcus (GBS):** WHO PPCs and technical R&D roadmap are now publicly available. A key component of the technical roadmap is the establishment of a serological correlate of protection (CoP), because the low incidence of the primary endpoint of invasive disease means that phase 3 clinical efficacy trials are likely to be complex and prohibitively costly. A GBS Assay Standardisation Group has been established to standardise the methodology for both antigen-binding and functional

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assay. This work could support a regulatory pathway based on a surrogate endpoint, which could be validated clinically through post-licensure studies. Currently two candidates are in the clinic, with the most advanced in phase 2 testing. Additionally, a health economic evaluation is underway of the potential value of GBS vaccines for global use in pregnant women.

#### **Enteric pathogens:**

**\*Enterotoxigenic *E.coli* (ETEC):** The leading ETEC vaccine candidate has progressed to a phase 2b efficacy study in adult travellers to Benin, with proof-of-concept data expected in 2019. This candidate has also demonstrated encouraging safety and immunogenicity in an age-descending phase 2 study in Bangladesh, where the youngest cohort was aged 6–11 months. However, the most recent burden of disease (BoD) estimates suggest that ETEC mortality rates are declining, in part due to the overall reduction in diarrhea mortality, which is creating uncertainty regarding the value proposition of ETEC vaccines. Current estimates are lacking for ETEC-specific BoD data from many countries in the African, Eastern Mediterranean and South American regions, which contributes to uncertainty in mortality estimates for this enteric pathogen. In addition, ETEC morbidity remains high, with an estimated 75 million cases of diarrhea annually.

**\*Shigella spp.:** The vaccine pipeline of Shigella vaccines is diverse with both oral and parenteral approaches in clinical development. The most advanced candidates aim to elicit responses to the Shigella O-antigen and have data from phase 2 controlled human infection models (CHIMs), field safety and immunogenicity clinical studies. In May 2018, WHO convened a workshop to evaluate the role of CHIMs in the pathway to licensure and policy recommendation (meeting report in preparation). Three pathways were identified, including one for a travellers' vaccine, which could be accelerated significantly by the availability of CHIM proof-of-concept data. However the pathway for policy recommendation in low- and middle-income countries (LMICs) will likely require demonstration of safety and efficacy in the target population of young children. That, said, the LMIC licensure and recommendation may be supported and potentially accelerated if there are data from an existing licensed vaccine for travellers.

**Non-typhoidal Salmonella (NTS):** Progress towards an NTS vaccine was presented for the first time to PDVAC, stimulated by the 2015 Institute for Health Metrics and Evaluation (IHME) BoD estimates, which ranked it third with respect to all age diarrheal mortality, and also the observation that 43% of its BoD occurs in under 5 year-olds. In addition to heritable risk factors, acquired risk factors for invasive NTS disease in children in Africa include HIV infection, malnutrition and malaria. Emerging antimicrobial resistance (AMR) is of increasing concern, with many antibiotics becoming less effective treatment options. There are three common serovars of invasive NTS, and a tri-valent vaccine will be needed to broadly impact bacteremia. All of the current vaccine candidates are in preclinical development; however, two are expected to enter phase 1 studies in the coming year. The commercial incentive to develop these vaccines is lacking and changes in the rates of underlying conditions that affect invasive NTS risk further increase uncertainties of disease burden; that said, combination with the licensed typhoid vaccine may strengthen the value proposition for development and use of NTS vaccines.

**Second generation rotavirus vaccines:** As of 2017, 92 countries have introduced oral rotavirus vaccine. Although effective in reducing hospitalization and disease severity, the residual burden of rotavirus-associated diarrhea remains high in populations in which the vaccine has been introduced. Next-generation, non-replicating parenteral vaccines are in development, and aim to achieve improved efficacy, safety (although the latter will be difficult to evaluate), lower cost of goods sold, potential for combination, and optimized scheduling compared to the current oral vaccines. The

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most advanced parenteral vaccine candidate is expected to enter a phase 2b/3 efficacy study imminently, with efficacy data expected as early as 2020.

#### **Other PDVAC prioritized pathogens:**

**\*Group A *Streptococcus* (GAS):** There are many types of very common and also rare acute GAS infections, and also common and rare chronic sequelae. This suggests there is a clear public health need for a preventative GAS vaccine, considering that 33 million people live with rheumatic heart disease and there are approximately 300,000 deaths per year. In April 2018, member states of the WHO unanimously adopted a “Global Resolution on Rheumatic Fever and Rheumatic Heart Disease”. The value proposition for a vaccine as an intervention strategy needs to be further articulated, as evidenced by the sparse pipeline of only three early-stage candidates. A CHIM is undergoing optimization and will likely inform, and may incentivize, product development. WHO PPCs and technical R&D roadmap documents will soon be publicly available.

**\**Herpes simplex virus* (HSV):** WHO PPCs for prophylactic and therapeutic HSV vaccines have been drafted and will soon be ready for public consultation. Since the 2017 PDVAC meeting, significant progress has been made towards articulating the full public health vaccine (FPHVV) of HSV vaccines, particularly with respect to improving BoD estimates. A key consideration has been the potential impact of HSV vaccines on the reduction of HIV susceptibility and transmission. Publication of the first global estimates of HSV-associated HIV infections, as well as the revised global genital ulcer disease estimates are expected in late 2018. Whilst the greatest public health need is for a prophylactic vaccine, the therapeutic candidates, which are envisaged for high income country (HIC) use, are the most advanced. The development of two of these has recently been placed on hold or discontinued.

***Neisseria gonorrhoeae* (GC):** There are 78 million new GC infections annually, with the greatest impact on women and neonates in LMICs. AMR significantly compromises the management and control measures for GC infection and, for this reason, GC has been identified as a high priority pathogen by WHO; R&D of new antibiotics and vaccines is urgently needed. A retrospective case-control study of the use in one population of one type of meningococcal B (MenB) outer membrane vesicle vaccine (MenZB) recently provided initial proof-of-concept for a GC vaccine by demonstrating 31% efficacy against GC in adolescents and adults. It is hypothesized that, the vaccine induced cross-reactive antibodies to outer membrane protein and lipopolysaccharide of the MenB and GC strains. However, there remain several questions for GC vaccine development, including understanding the appropriate use and implementation strategy, and the full public health value of GC vaccines, including the identification of critical data needs.

***Chikungunya virus* (CHIKV):** Two candidates are now in phase 2 clinical proof-of-concept field testing for this low mortality but high morbidity epidemic virus, which has an increasing geographic range. A major challenge for vaccine development is the feasibility of phase 3 vaccine efficacy studies, because outbreaks are sporadic, hard to predict and usually cease within 6–8 months or less. The Coalition for Epidemic Preparedness Innovations, with the Indian Government Department of Biotechnology, convened a workshop on CHIKV in Delhi, on February 5–6, 2018, with the objective to create opportunities for cross-sectoral and cross-geographical R&D collaborations, innovation and data sharing. Several recommendations were identified; including the development of international reference reagents, validating virological and serological assays and standardizing neutralizing antibody assay/reference serum. These will be key to identifying a potential CoP, and efforts are already underway to establish a WHO reference reagent. A WHO collaborative study expected to commence early in 2019.

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## **Cross-cutting initiatives:**

***ETEC etiology estimates:*** A meta-analysis of quantitative PCR data from five recently conducted studies to estimate the etiology-specific attributable fraction of moderate-to-severe diarrhea episodes in sub Saharan Africa and South Asia in children under 5 years was presented by the Bill and Melinda Gates Foundation (BMGF). ST is the heat-stable toxin of ETEC. The majority of these data, and the revised estimates are not yet published, but suggest that the attributable fraction and under 5 mortality due to (ST) ETEC is lower than previous BoD estimates, and that other enteric pathogens have a more significant association with growth faltering in the first two years of life. Within the broader diarrheal disease vaccine development community, there remain concerns with respect to the robustness of pathogen-burden estimates, and the lack of transparency as to how burden estimates are derived, particularly since they are used for the basis of funding prioritization.

***International Vaccine Task Force (IVTF):*** The World Bank created the IVTF in the wake of the Ebola crisis to promote clinical research, in general, and vaccine trials, in particular, for all countries, but especially in LMICs, in the inter-epidemic periods. This is so countries will be ready to respond when needed. This well-funded initiative represents an opportunity for global collaboration to identify gaps and priority needs in clinical trial resources and capacity that could significantly benefit the development of all vaccines and interventions against priority pathogens for use in LMICs.

***Antimicrobial resistance (AMR):*** The threat of AMR and its contribution to mortality in developing countries is important to characterize in order to quantify the potential impact of vaccines and their role as a key intervention in its reduction. Disease-targeted analyses to model and estimate the potential vaccine impact on AMR are being developed and could help better articulate the value of vaccines that are of interest to PDVAC.

***Total Systems Effectiveness (TSE) and the Vaccine Innovation Prioritization Strategy (VIPS):*** WHO, Gavi, Unicef, PATH, The US Centre for Disease Control, the BMGF and others are working together to develop new approaches to identify and prioritise vaccines and vaccine-related innovations that meet the preferences and priorities of LMICs. The intent of these initiatives is to communicate a common strategic vision regarding preferred products and attributes to vaccine manufacturers. TSE is an approach to identify the public health value of different vaccine products from a country perspective, which is intended to rationalise global market shaping and investment for R&D of both pipeline and existing products. As such, TSE will help to inform a novel strategic framework known as the VIPS. VIPS may leverage TSE to assess and communicate priority vaccine product innovations, and to provide greater clarity to manufacturers, technology developers and partners to make investment decisions.

***Vaccine delivery by microarray patch (MAP):*** MAPs, also referred to as microneedle patches, are a novel methodology that have the potential to transform the way that vaccines are delivered within immunization programs. If successfully developed, MAPs could overcome several programmatic challenges, including the need for a stringent cold chain up to the point of delivery, missed opportunities to vaccinate due to reluctance to 'waste' vaccine by opening a multi-dose vial and the need for safe reconstitution, handling and sharps disposal. WHO is interested to understand how MAPs can improve ease of use and increase equitable coverage of vaccines in LMIC contexts, and the need for accelerated product development of MAPs for delivery of measles and rubella (MR) vaccines has been highlighted by SAGE. To this end, WHO held a consultation in April 2018 to evaluate the technical, economic and programmatic challenges of MR-MAP product development, to establish assumptions where they are known, and to propose areas of priority focus. The report from this meeting is in progress.

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**WHO Preferred Product Characteristics (PPCs) and WHO Full Public Health Value of Vaccines (FPHVV):** PDVAC has made great progress developing PPCs for each of its priority pathogens. Following the 2017 PDVAC meeting, several stakeholders, including vaccine development funders, wanted to better understand the value proposition of at least some of the vaccines that PDVAC prioritizes and for which it has produced, and is producing, PPCs. PDVAC, in collaboration with WHO's Immunization and Vaccines Related Implementation Research Advisory Committee (IVIR-AC) is developing an approach to best estimate and describe the FPHVV. This approach considers the aspects that would need to be assessed to address both the direct benefits, demonstrated in licensing trials, and also the broader impacts and indirect benefits of the vaccine. For some pathogen targets, it can be difficult to make a strong case for vaccine development based on perhaps prevention of mortality, but a valuable vaccine for LMICs could make a huge impact on factors not usually measured in clinical trials such as morbidity, educational achievement and economic development. This concept was presented to SAGE on Immunization in April 2018. An early and improved articulation of the FPHVV, that includes participation of LMICs public and private partners, would better inform development of PPCs and FPHVVs.

#### **PDVAC Recommendations:**

**\*Human immunodeficiency virus (HIV):** Develop PPCs for both vaccines and mAb approaches, through stakeholder convening and in collaboration with partners, especially those in LMICs. As part of the ongoing consideration for policy evaluation and implementation, evaluate the acceptability and programmatic fit of vaccine and BnAb approaches within existing interventions for both adult and mother-to-child-transmission.

**\*Tuberculosis (TB):** WHO's Initiative for Vaccine Research (IVR) will continue to collaborate with the TB vaccine development community through expert working groups to define priority research avenues and favourable investments for this major public health priority.

**\*Malaria:** IVR advised to collaborate with the Global Malaria Programme to develop WHO strategy and prioritization framework for next-generation malaria vaccines, evaluate the potential role and use case (public health need) for mAb approaches in the context of RTS,S and pipeline vaccines, and develop guidance on the product development pathway for vaccines that decrease transmission, all of which should be including in an update of the Malaria Vaccine Technology Roadmap.

**\*Influenza:** WHO will continue to monitor development under the Universal Influenza Roadmap and identify gaps in product development that need to be addressed.

**\*Respiratory syncytial virus (RSV):** Develop PPCs for mAb approach, including assessment of implementation strategy and requirements for global use, in the context of a potential vaccine for maternal immunization. Collaborate with RSV Vaccine and mAb manufacturers to communicate data, analysis and evidence required to support SAGE policy recommendation.

**\*Group B Streptococcus (GBS):** Whilst planning and preparing for a phase 3 study, support initiatives aimed at evaluating and establishing of CoP that may enable an accelerated route to licensure. In parallel, the subsequent evidence that will need to be acquired through post-licensure studies to support a policy recommendation needs to be articulated.

**\*Enterotoxigenic E.coli (ETEC):** PDVAC acknowledges that one major funder has deprioritized funding for ETEC vaccine development, however ETEC remains a priority pathogen in LMICs and PDVAC will continue to advocate for, and support, the development of a vaccine. A key component

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of this effort should focus on improving the understanding and credibility of BoD estimates (see 'cross cutting issues').

**\**Shigella spp.*:** Shigella remains a priority pathogen for PDVAC, with the primary strategic goal being to develop safe, effective, affordable vaccines to reduce diarrhea, dysentery and morbidity caused by Shigella in children aged under five years, in LMICs. PDVAC recommended further investigation into the reported burden estimates in adolescents and adults, and this would be included in the activities proposed under the enteric burden of disease estimates (see cross-cutting issues).

***Non-typhoidal Salmonella (NTS)*:** Include NTS in the proposed evaluation of BoD estimates (see cross-cutting issues). Continue horizon scanning, and revisit when clinical data become available. Communicate the need to evaluate NTS through WHO AMR task force.

***Second generation rotavirus vaccines*:** Leverage the TSE approach to evaluate the public health impact of potential enteric or other parental combinations that could be enabled by a successful next-generation vaccine, to help inform the prioritization of and value proposition for these candidates.

**\**Group A Streptococcus (GAS)*:** PDVAC commended the progress that has been made over the last year with respect to the vaccine roadmap, and in particular the product development pathway. Further investment in GAS efforts is warranted to maintain momentum. The GAS Roadmap recommendation to form a consortium of global stakeholders to advance GAS vaccine development is fully endorsed by PDVAC. CHIM development will be followed with interest to understand its potential impact in decision making and identification of correlates.

**\**Herpes simplex virus (HSV)*:** Considering the changes in the HSV therapeutic pipeline, and progress in development of HIV vaccine and BnAb candidates, PDVAC appreciates the challenge of developing the FPHVV assessment for HSV vaccines on the basis of its potential impact on HIV transmission. PDVAC recommended evaluating the LMIC need and potential demand for both a therapeutic and prophylactic HSV vaccine that has an impact on genital ulcer disease and sexual reproductive health as the basis for its FPHVV.

***Neisseria gonorrhoeae (GC)*:** Develop a statement of interest for GC vaccines with respect to PHPVV and considerations for PPCs (not yet prioritized by PDVAC).

***Chikungunya*:** Communicate for the need to utilize the WHO reference serum, once available, to enable comparison of neutralization assay data, which is needed to support identification of a CoP.

#### **Cross-cutting issues:**

***Enteric BoD estimates*:** In order to increase transparency, credibility and acceptance of BoD estimates, existing guidelines for good modelling practices for decision making should be adhered to, as stipulated by International Society For Pharmacoeconomics and Outcomes Research and IVIRAC. PDVAC recommended that a joint IVIRAC/PDVAC independent working group be established to evaluate diarrheal burden models, particularly to assess the level of uncertainty of regarding ETEC mortality estimates.

***Anti-microbial resistance (AMR)*:** Vaccine impact on AMR should be considered as a key criterion in PDVAC's prioritization of pathogens. Tools to model the impact of vaccines on AMR, are needed to help define the FPHVV of these vaccines.

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***Heterologous prime-boost regimens:*** In the context of the leading HIV and TB vaccine candidates, there is a need for development of WHO technical standards and norms guidance on heterologous prime-boost regimens to prepare for regulatory and policy evaluation.

***Passive immunization:*** Evaluate the technical, regulatory and commercial barriers to development, licensure and availability of mAb, specifically for use in LMICs.

***Total Systems Effectiveness (TSE) and Vaccine Innovation Prioritization Strategy (VIPS):*** PDVAC recognizes the potential utility of TSE to assess and articulate the public health value of vaccines, beyond the conventional commercial return on investment. The TSE approach could represent an important mechanism to understand end user (country) product preferences, and thereby rationalize R&D priorities and investment. PDVAC is highly supportive of the VIPS initiative and four PDVAC members have been identified to participate in the VIPS technical steering committee. Early and full participation of LMICs public and private partners will facilitate the full public health value and use of both vaccines and mAbs in LMICs.

***Vaccine delivery by microarray patch (MAP):*** MAPs are perceived as potential game-changers to achieve the coverage, equity and ultimately the eradication goals of current MR immunization strategies. PDVAC supports continued efforts and activities to inform the public health value for this innovative delivery technology, particularly in the case of MR-MAP product development.