

**WHO's 4th Product Development for Vaccines Advisory committee (PDVAC) meeting
21-23 June 2017**

**Executive Summary
(full meeting report to follow)**

On 21-23rd June 2017, WHO's Product Development for Vaccines Advisory Committee (PDVAC) was convened for its 4th annual meeting. Product development progress in 10 pathogen areas that had been previously prioritized was discussed, and 4 new pathogens with candidates in, or approaching clinical development were reviewed. In addition, 6 key cross-cutting topics that have implications across several priority pathogens were considered.

There have been significant advances in the product development of vaccines and other technologies since the June 2016 PDVAC meeting, including:

- **Global Vaccine Action Plan (Objective 6) / Decade of Vaccines (Goal 5):**
 - **Human Immunodeficiency Virus (HIV):** Two HIV vaccine candidates are currently in late stage clinical trials in HIV-uninfected populations, as heterologous prime-boost approaches. Data from these studies are anticipated in 2020-21, and may be proposed as the basis for licensure application in some countries, if efficacy is demonstrated. Numerous broadly neutralising antibody approaches for HIV are also in development, with a prototype monoclonal antibody in Phase IIb studies, and pivotal proof-of-concept data are anticipated in the same timeframe as the vaccine candidates.
 - **Tuberculosis (TB):** There are seven tuberculosis vaccine candidates in phase II clinical studies, and one in phase III. Two candidates target reduction of disease in adolescents and adults, previously identified and endorsed by PDVAC as the priority public health goal for TB vaccine development, and will deliver clinical proof-of-concept data over the next 12 months. BCG replacement candidates are also advancing, with the leading candidate in Phase IIb studies.
 - **Malaria:** Development status of second generation malaria vaccines will be covered by a separate consultation (MALVAC) in 2017-18.
 - **Influenza:** WHO Preferred Product Characteristics for Next-Generation Influenza Vaccines have been published. Several candidate vaccines designed to elicit antibodies to conserved epitopes on the hemagglutinin head or stem are advancing to early stage clinical development with the goal of achieving broad and durable immunity.
- **Major currently non-vaccine preventable diseases:**
 - **Respiratory Syncytial Virus (RSV):** The RSV vaccine and monoclonal antibody (mAb) pipeline remains well-populated and diverse, with 15 vaccine candidates in clinical studies, and two mAbs in late stage clinical development. Two recombinant protein, post-fusion F-based vaccine candidates did not demonstrate efficacy in clinical proof-of-concept studies in the elderly. The majority of candidates in clinical evaluation incorporate alternative antigens or constructs and are targeting maternal or pediatric immunization strategies. Anti-F antigen mAbs are in phase IIb and III clinical development. WHO Preferred Product Characteristics (PPCs) and the Technical Roadmap for development of RSV vaccines have been finalized and will soon be publically available.

- **Enteric and diarrheal diseases:** Recently published global burden of disease estimates for enterotoxigenic *E. coli* (ETEC) and *Shigella* differ markedly from previous estimates with respect to mortality and are incomplete with respect to morbidity. Further work will be needed to evaluate the global public health need for, and potential impact of, vaccines against each of these pathogens. The leading ETEC vaccine candidate has advanced to a Phase IIb proof-of concept field study in adult travellers; the leading *Shigella* candidates have been evaluated in Phase I and are undergoing evaluation in a controlled human infection model (CHIM). The proof-of-concept Phase IIb study with the leading Norovirus candidate in adults continues.
- **Group A streptococcus (GAS):** Updated global disease burden estimates for GAS are eminent. There are currently 4 candidates in preclinical, or early clinical development. Following a global consultation convened by WHO and the International Vaccine Institute (IVI) in 2016, WHO technical vaccine roadmap and preferred product characteristics documents are in preparation.
- **Sexually Transmitted Infections:**
 - **Herpes Simplex Virus:** Several therapeutic vaccine candidates against Herpes Simplex Virus (HSV) are in late stage clinical development, and have demonstrated clinical proof-of-concept in Phase II studies. In line with the previously published Roadmap for Sexually Transmitted Infections, development of PPCs for therapeutic and prophylactic HSV vaccines is underway, in tandem with a value proposition to articulate the public health need for these vaccines in low- and middle-income country contexts.
 - **Gonorrhoea :** Gonorrhoea is associated with a significant infertility burden, is a strong co-factor for HIV infection, and is the leading cause of preventable neonatal blindness. While previously relatively easy to treat, first line therapy is now failing as a result of increasing antimicrobial resistance. No vaccine candidates are currently in clinical development, but recently published data demonstrates that outer membrane vesicle (OMV)-based Group B meningococcal vaccine provides some cross-protection. This supports the feasibility of reverse vaccinology approaches to Gonorrhoea vaccine development in the near term.
- **Maternal immunization:** The development of vaccines specifically for use during pregnancy are advancing, for example against both Respiratory Syncytial Virus (RSV) and Group B Streptococcus (GBS). In addition, there has been substantial progress in the development of several vaccines that could offer protection against diseases that are important to maternal and child health, through maternal immunization strategies, for example those against Zika, influenza and Cytomegalovirus (CMV). Whilst these vaccines may be evaluated in men and non-pregnant women, priority should be given to identifying mechanisms for evaluation of these vaccines for use in pregnant women.
 - **Group B Streptococcus (GBS):** WHO Preferred Product Characteristics (PPCs) and the Technical Roadmap for development of GBS vaccines have been finalised and will soon be publically available. There are currently two GBS vaccine candidates undergoing clinical evaluation, with several in preclinical development. Global assay standardization efforts, particularly in support of establishing a correlate of protection, are continuing in parallel with consultations regarding an acceptable regulatory route to licensure.
 - **Cytomegalovirus (CMV):** Congenital cytomegalovirus infections are common throughout the world, and severely affect the central nervous system resulting in a range of sequelae; however, the burden of CMV in low and middle income countries

(LMICs), and its contribution to developmental disorders in these contexts is not well defined. Several live and recombinant vaccine approaches are in clinical development, and may have utility in LMICs, in which CMV seropositivity in women of child-bearing age is considered to be significantly higher than in high income countries.

- **Platform delivery technology:**
 - **Passive immunization:** Monoclonal antibody products to prevent infection and disease are in development against an increasing number of pathogens, for example HIV, RSV, Staphylococcus aureus and rabies. Candidates for HIV and RSV are currently in Phase IIb and Phase III development, respectively.
 - **Nucleic acid-based delivery technologies:** A new generation of DNA and RNA-based vaccine candidates are in pre-clinical and early clinical development, the former delivered by a variety of devices (e.g., electroporation or needle-free injection devices) and the latter through enhancements in stability and/or expression levels in conjunction with lipid nanoparticle emulsions and/or incorporation of self-amplifying replicon sequences.
- **WHO R&D Blueprint:** The R&D Blueprint is a global strategy and preparedness plan that allows the rapid activation of R&D activities, such as vaccine development, during epidemics. In support of this, target product profiles (TPPs) have been developed for prioritized pathogens.
 - **Zika Virus:** The TPP for a vaccine to protect against congenital Zika syndrome for use during an emergency has been updated twice through public consultation. There are now 47 Zika virus vaccine candidates in development, 7 of which are in clinical studies. The most advanced candidates (3 of 7 in clinical studies) are based on nucleic acid platforms.
 - **Other of priority diseases:** Vaccine TPPs have been developed for three other diseases: Nipah, Lassa fever, and Middle East Respiratory Syndrome (MERS).
- **Antimicrobial resistance (AMR):** WHO published its first ever list of antibiotic-resistant "priority pathogens" that pose the greatest threat to human health. The role of vaccines in the overall strategy to combat AMR has been underestimated and should always be considered in the estimation of the medical need and value proposition of vaccines available or in development.
- **Cholera (2nd Generation):** In the context of the challenges experienced with uptake of previously licensed oral cholera vaccines, several second generation cholera vaccine candidates are in the pipeline, with three in late stage clinical studies. A TPP for second generation cholera vaccines is in development, to articulate the incremental improvements that will be needed to offer significant benefit over existing and available vaccines.
- **Rabies:** Although Rabies immunoglobulin is licensed for both pre-exposure (PreP) and post-exposure (PEP) prophylaxis, it is costly and its administration schedule is challenging with respect to compliance. The development of a human prophylactic vaccine is considered key to an effective rabies control strategy. Three candidates are in clinical studies, and a WHO PPC may be developed, resources permitting.

Specific recommendations that emerged from the meeting include to:

Pathogen-specific:

- **HIV:** Facilitate scenario planning and development of communication strategies in preparation for HIV vaccine and monoclonal antibody study outcomes. Evaluate the development pathway

beyond ongoing proof-of-concept studies. Identify gaps in guidelines to support licensure, availability and use in LMICs for both adult and infant populations.

- **TB:** Continue to facilitate and seek to accelerate development of vaccines for prevention of tuberculosis in adults and adolescents, including development of a PPC for this indication.
- **RSV:** Review the data from the late stage, clinical trials in the elderly of recombinant protein based post-fusion F-RSV vaccine candidates, and consider implications for product development of other F-antigen based approaches, specifically with respect to the recently finalized RSV vaccine PPC and technical roadmap. Develop WHO Preferred Product Characteristics for RSV monoclonal antibodies.
- **GBS:** Pursue implementation of the priorities identified in the R&D technological roadmap for Group B Streptococcus vaccines, including efforts to identify a correlate of protection. Evaluate the vaccine value proposition considering health, economic and societal dimensions.
- **CMV:** Undertake a vaccine landscape analysis of CMV vaccines, including the global public need and potential product development pathways and target populations for use in LMICs. Consider as part of maternal immunization/platform strengthening agenda.
- **ETEC/Shigella:** Evaluate the mortality and morbidity estimates for ETEC and Shigella, and the methodology used to derive them. Both ETEC and Shigella remain priority pathogens; PPCs and clarity on development pathways for use in LMICs are needed for both.

Cross-cutting and platform delivery technology

- **Maternal immunization:** Consider the clinical and regulatory pathway for the safe and ethical evaluation of vaccine candidates in pregnant women, in order to expedite the licensure and availability of vaccines that would have public health impact through maternal immunization strategies.
- **Passive immunization:** Evaluate the technical, regulatory and commercial barriers to development, licensure and availability of monoclonal antibodies (mAb), specifically for use in low- and middle-income countries (LMICs).
- **Nucleic acid-based delivery technologies:** Evaluate the product development considerations for nucleic acid vaccine platforms, including in the context of maternal immunization strategies.
- **AMR:** Develop a quantitative framework through which the public health impact of vaccines to combat AMR can be evaluated, to inform the incremental value that these vaccines could offer over and above reduction of disease. Such an analysis will inform vaccine R&D investment and prioritization.
- **Value propositions:** For pathogens areas where there are candidates that are targeted for launch in high income countries, for example GAS, develop value propositions early on in product development to evaluate and articulate the need in LMIC contexts, and thereby strengthen their *global* investment case.