Executive Summary

1. Context and format of the meeting

Established in 2014, the Product Development for Vaccines Advisory Committee (PDVAC) is an independent standing WHO committee of experts that provides external advice to WHO’s Department on Immunization, Vaccines and Biologicals (IVB), related to development of vaccine and monoclonal antibody products for infectious diseases. The committee’s remit covers disease areas where there is substantial disease burden in low- and middle-income countries (LMICs), where none of these products currently exist, but where there is some ongoing research and development activity which may benefit from WHO guidance. This committee may also have a role where vaccines are already licensed, and development of improved products, including novel presentations or innovative immunization technologies is a priority for WHO.

In recent years, the strategic role of PDVAC has evolved to look beyond the most expeditious route to licensure for priority vaccine and technology candidates. The committee aims to anticipate the near- and long-term barriers and roadblocks to investment in product development, by developing approaches to ensure a clear understanding of country preferences and development of products that meet the needs of LMICs. Consideration of the full public value for vaccines (FPVV) and novel technologies is becoming an increasingly critical element of the PDVAC approach to identifying public health priorities. In addition, PDVAC provides recommendations on the impact of cross-cutting activities that may benefit several candidates, such as novel manufacturing platform technologies or delivery strategies.

The Decade of Vaccines, and its accompanying Global Vaccine Action Plan (GVAP) are coming to an end in 2020, and work is underway across global and regional stakeholders to define strategic goals for the next decade. With this in mind, day one of the PDVAC 2019 meeting was dedicated to discussion of the strategic themes for determining R&D priorities and goals for 2021-30, and covered aspects such as the definition and strategies to quantitate vaccine value, improving country engagement in determining R&D priorities and overcoming the various ‘valleys of death’ along the road to vaccine licensure, policy, financing and uptake. These discussions will be captured in a separate report, but the perspectives were brought in to the pathogen-specific
discussions that followed on days 2 and 3. Due to the increasing number of topics that PDVAC covers, only those pathogen areas for which there were significant new data or strategies were discussed in the meeting. The remaining topics were reviewed at a higher level in the ‘Year in Review’ summary, in most cases to provide updates for information. Finally, PDVAC convened for a closed session to formulate its recommendations, which where appropriate, are captured following each topic in this summary report.

2. A year in review

WHO leads, and PDVAC typically engages development of the following types of guidance, to facilitate development and access to vaccines that are appropriate for use in LMICs:

<table>
<thead>
<tr>
<th>Pathogen-specific documents developed by WHO’s PDVAC</th>
<th>Purpose/description</th>
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<tbody>
<tr>
<td>Preferred product characteristics (PPC)</td>
<td>Describe preferred characteristics for vaccines with emphasis on the LMIC use context</td>
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<tr>
<td>Vaccine R&amp;D roadmap</td>
<td>Provides a high-level vision, near and long term goals, and strategic framework of priority activities</td>
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<tr>
<td>Considerations for product development pathways</td>
<td>Considers the manufacturing, clinical development, regulatory, policy and commercialization pathways and barriers</td>
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<tr>
<td>Full public value of vaccines (FPVV)</td>
<td>Describes the full health, economic and societal value of a vaccine to a broad range of global stakeholders, including from a LMIC perspective, and aims to articulate the full direct (individual) and indirect (population) effects of a vaccine</td>
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These documents complement other formal WHO guidelines on ‘Assessing the programmatic suitability of vaccine candidates for WHO prequalification (PQ) (2014)’ which describes the process and criteria for prospective vaccine PQ in terms of their programmatic suitability for LMICs, and the Generic Preferred Product Profile for Vaccines (gPPP) (2015) that provides recommendations on presentation and packaging of new vaccines for use in LMICs.

The table below summarizes the status of WHO guidance for vaccines against the PDVAC prioritized pathogens:
2.1 Next generation malaria (and RTS,S):

The Malaria Vaccine Advisory Committee (MALVAC) is being reconvened to help WHO formulate updated guidance about public health targets and priority activities in malaria vaccine R&D. MALVAC will convene in July 2019. Briefly, recent progress in parallel to the initiation of the RTS,S/AS01 implementation pilots in Ghana, Malawi and Kenya include the evaluation of RTS,S/AS01 pre-seasonal vaccination, in seasonal transmission settings, and a study to evaluate the role of fractional doses in conditions of natural exposure. With respect to next generation candidates, R21 is a RTS,S bio-similar developed by the Jenner Institute in Oxford and the Serum Institute of India Private Limited (SIIPL). Sanaria has communicated intentions to progress their irradiated sporozoite to a phase III study starting in 2020, but it but success criteria justifying large investments investigations in vulnerable populations have not been clearly defined. Important progress in translational science is being made in development of blood stage malaria vaccine candidates, in man-to-mosquito challenge models, and in the development of monoclonal antibodies targeting malaria antigens. Progress on MALVAC activities will be reported to PDVAC regularly.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Landscape analysis*</th>
<th>PPC</th>
<th>RM</th>
<th>Pathways</th>
<th>VP underway</th>
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<tr>
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<td>✓ (P&amp;T)</td>
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<td>HIV</td>
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<tr>
<td>Influenza</td>
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<td>✓ (improved Vx)</td>
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<tr>
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<td>✓ (STI RM)</td>
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<tr>
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* HIV: human immunodeficiency virus ; RSV: respiratory syncytial virus; GBS: group B Streptococcus ; HSV herpes simplex virus; GAS: group A streptococcus. STI: sexually transmitted infections; P: prophylactic, T: therapeutic; PPC: Preferred product characteristics; RM: Roadmap; VP: value proposition; (✓) indicates in progress; * meeting reports publicly available

http://www.who.int/immunization/research/ppc-tpp/preferred_product_characteristics/en/
2.2 Human Immunodeficiency virus (HIV):

Several large-scale efficacy trials for both vaccines and broadly neutralizing antibodies (BNAbs) are ongoing. The phase III HVTN 702 vaccine trial (NCT02968849) to evaluate the ALVAC/gp120 heterologous prime boost in 5,407 healthy, HIV-negative men and women between 18 and 35 years old, is underway in South Africa with data expected in 2020. In parallel, the phase IIb HVTN 705 (NCT03060629) trial to evaluate the Ad26/gp140 heterologous prime boost in 2,637 healthy, HIV-negative women in South Africa, Malawi, Mozambique, Zambia, and Zimbabwe between the ages of 18 and 35 years is ongoing, with data expected in 2022. The Antibody Mediated Prevention (AMP) VRC01 is being evaluated under HVTN 703 (NCT02568215) & 704 (NCT02716675) with 4,625 participants enrolled across US, Brazil, Peru, Switzerland, Tanzania, Zimbabwe, Botswana, RSA, Kenya, Malawi and Mozambique, with data expected in early 2020.

If these studies are successful, the next step will be to assess combinations of mAbs, and the capacity for commercial manufacturing and worldwide distribution may become a critical constraint. Encouraging regional manufacturing capability for mAbs would be helpful.

The multi-component vaccines present an unprecedented level of complexity, in terms of heterologous product combinations in the same regimen and the number of doses per regimen, that will challenge health delivery systems. One leading vaccine candidate is clade C-based for use in Southern Africa, and not designed for global implementation. The licensure and policy decision pathways for global recommendation have not been clearly articulated and the level of commitment from manufacturers to commercialize these vaccine candidates will need clarification, should these efficacy studies be successful. In 2018, WHO convened global stakeholders to opine on priorities for advancing these emerging HIV interventions, the outcomes of which are articulated as ‘priority actions to prepare the pathway from clinical proof-of-concept to policy decision and use’. The report from this meeting has been submitted for publication. To summarise, to prepare for results of these studies in 2020-2022, the target product profiles and full public value proposition for both categories of products should be defined and the regulatory, policy and implementation pathways should be prepared. Economic and health benefits, cost of goods, delivery complexity, and user perspectives will constitute key considerations for roll-out of effective products. Investments in manufacturing capacity and public-sector delivery systems will be needed to prepare for product introduction and scale up.

Recommendations from PDVAC:

- PDVAC endorsed the need for WHO to develop consensus regarding Preferred Product Characteristics for HIV vaccines and broadly neutralizing antibodies, particularly for LMIC use, and articulation of their investment cases.
• PDVAC proposed **evaluating the relative benefits and trade-offs of the vaccine and BNAbs candidates by using a total systems effectiveness approach** to ascertain information from countries on preferences and acceptability, in the context of existing interventions.

**2.3 Next-generation (universal) influenza:**

There are numerous influenza vaccine candidates under development that are aimed at inducing more broadly protective immunity than existing seasonal vaccines, which could increase vaccine efficacy and avoid the need for annual strain-change of the vaccine. The leading concepts for broadly cross-protective vaccines include vaccines based on hemagglutinin (HA) stem or head-stem chimeras (in phase I), and HA head chimeras (preclinical) which present principally the conserved regions of the HA. Other candidates include the incorporation of conserved M2 ectodomain (phase I/II), and vaccines based on HA but with improved immunity through the addition of neuraminidase (NA) or nucleoprotein (NP), delivery by gene-expression, or alterations in dose and adjuvant formulations.

The efficacy of current vaccines, and potentially of future vaccines, is subject to a number of biological challenges including immunological imprinting from infection early in life, the immunodominance of serotype-specific epitopes and of antibody lineages. One approach being developed to bypass some of the challenges seen with current candidates is mosaic antigen display in which multiple HA from different clades are presented on the same nanoparticle. Studies conducted by NIAID demonstrate that a mosaic expressing H1, H3 and two B strains elicits broad cross-reactive heterologous antibody responses that are protective in mice. This approach may provide a way to overcome antigenic diversity and immunodominance.

Recommendations from PDVAC:

- Given the rapid progress being made in this area, PDVAC suggested that WHO should **review the current PPCs for Next-generation Influenza Vaccines** that were produced in 2017 to ensure that this guidance is still appropriate and relevant. It is also recommended that **PPCs be specific for the major target populations**, particularly young children, pregnant women, and the elderly.

**2.4 Enterotoxigenic E.coli:**

Two candidates are currently in clinical studies, with Scandinavian Biopharma’s oral quadrivalent inactivated vaccine ETVAX® being the most advanced. Field efficacy data from a phase IIb study (NCT03729219) in 743 adult travellers to Benin is expected in Q3 2019. In parallel, a descending age phase I/II study (NCT02531802) in Bangladesh to evaluate ETVAX® safety and
immunogenicity in infants down to 6-11 months of age has shown that fractional doses (1/4th or 1/8th of the adult dose) improved the tolerability of the vaccine and were immunogenic. The addition of the adjuvant dmLT to the vaccine formulation did not show impact on tolerability but improved the frequency, magnitude and breadth of the mucosal antibody response to key vaccine colonization factors antigens (CFA/I, CS5 and CS6) in the vaccine. A phase I descending age study in Zambia will begin in Q3 2019, and assuming clinical endpoints are met, a phase IIb study in the Gambia will follow to estimate the protective efficacy of the vaccine in children 6-18 months over a 1-2 year period.

The other clinical candidate is fimbrial tip adhesin (FTA), a subunit vaccine which recently completed a phase 1 study (NCT03404674) with monovalent antigen (CssBA targeting CS6) and dmLT administered via the parenteral route. It was shown to be safe and immunogenic and funding is being sought to assess efficacy of the CssBA component delivered IM with dmLT against a CS6-expressing ETEC strain (B7A) in a controlled human infection model. There are several candidates in preclinical development for both oral and parenteral administration, and the parenteral ShigETEC vaccine is expected to proceed into First-In-Human phase I testing in Europe in 1Q 2020.

Recommendations from PDVAC:

- The ETEC vaccine pipeline has declined significantly since this pathogen was prioritized by PDVAC in 2016, associated with the decline in IHME estimates of mortality in U5s (see summary of enteric burden of disease modelling). Given the work ongoing to better understand and potentially improve the BoD model methodology, and the fact that phase IIb efficacy data for an oral vaccine candidate in adults is imminent, PDVAC have not deprioritized ETEC at this time. Both the phase IIb data, and the outputs from the BoD working group will be discussed when available.

**2.5 Shigella**

The Shigella vaccine pipeline remains diverse with both oral (live attenuated and formalin inactivated) and parenteral (subunit based) approaches evaluated in clinical studies. The O-Antigen based candidates are the most advanced in their development, with two having demonstrated proof-of-concept as monovalents in controlled human infections models (CHIM), however a quadrivalent combination will be needed to confer coverage over the most commonly circulating S. sonnei and S. flexneri strains. Field efficacy of O-antigen-based Shigella vaccines was established over 20 years ago with a first-generation conjugate vaccine composed of Shigella sonnei O-specific polysaccharide bound to Pseudomonas aeruginosa recombinant exoprotein A (S. sonnei-rEPA). However, O-Ag antibody responses, and the protection observed decreased with subject age, and no efficacy was observed in the target age group of infants and toddlers. It
is hoped that the new candidates will demonstrate improved immunogenicity and efficacy in the target population of young children in LMICs. The proposed licensure strategy involves leveraging the CHIM model to establish an immunological threshold of serum O-Ag IgG antibody that could offer protection. As such, O-Ag ELISA standardization and development of reference reagents are underway, WHO is planning a consultation with regulators on the potential role of CHIM in Shigella licensure, in particular for addressing the acceptability of CHIM to LMIC regulators and the data that will be needed for establishing WHO recommendations.

2.6 Group A Streptococcus (GAS)

GAS was prioritized by PDVAC in 2016 because infection causes upwards of 500,000 deaths per year through a variety of invasive and toxin-mediated diseases, as well as post-streptococcal auto-immune sequelae resulting in rheumatic heart disease. While the medical need is highest in high endemicity LMICs, the potential value of a vaccine, primarily for prevention of GAS pharyngitis, skin infections, cellulitis and invasive disease and associated antibiotic use also resides in HICs. In 2018, the World Health Assembly adopted a resolution calling for greater action on rheumatic heart disease. Both WHO PPCs and vaccine R&D technology roadmaps have been published, expressing the critical aim of demonstrating clinical efficacy against GAS pharyngitis and skin infection as short-term goals. In February 2019, the Australian government pledged 35M AUD to develop a vaccine to combat the disease. In recent months, important progress has been seen in the establishment of a standard GAS CHIM. A global GAS vaccine consortium has been established, with support from Wellcome, with one of the aims being to support implementation of recommendations articulated in the WHO GAS vaccine R&D Technical Roadmap. The consortium will to continue to advocate for GAS vaccine development, lead an investment case evaluation, and consider the appropriate use of biomarkers in vaccine safety monitoring.

2.7 Sexually Transmitted Infections (STI)

Five pathogens are included in WHOs’ roadmap to advance STI vaccines development: herpes simplex virus (HSV), Neisseria gonorrhoeae (gonorrhoea), Chlamydia trachomatis (chlamydia), Treponema pallidum (syphilis), and Trichomonas vaginalis. Only HSV and Chlamydia vaccine candidates are in clinical development, however recent clinical evidence suggests that the licensed Neisseria meningitidis B vaccine may provide some efficacy against Neisseria gonorrhoeae. NIAID has recently awarded grants to six research centers for STI vaccine development and will continue to collaborate with WHO to co-ordinate the STI roadmap activities and partners.
Following PDVAC prioritization in 2017, WHO published PPCs for prophylactic and therapeutic HSV vaccines. In the last 12 months, efforts have focused on generating data to better determine the full public value of HSV vaccines, including estimation of current disease burden for HSV infections. There were an estimated 473 million prevalent HSV-2 infections in 2016, among 15-49 year-olds globally, and in addition an estimated 130-200 million people had genital HSV-1 infection, mostly in high income countries. An estimated 180 million people infected with HSV experienced at least one episode of genital ulcer disease in 2016, the vast majority of which were due to HSV-2 infection. This burden translates into roughly 8 billion symptomatic days, per year. In addition, population attributable fractions (PAFs) of HIV due to HSV-2 infection have been estimated, with PAFs of 12-13% in Europe and Asia, 21% in the Americas and 37% in Africa. Overall, HSV-2 infection is estimated to contribute to over 400,000 HIV infections, which is particularly critical for LMICs in Africa where there is a high burden of both HSV-2 and HIV. Other components of the FPVV under development include estimating the economic burden (costs of HSV care and treatment) and modelling of vaccine impact, on both HSV and HIV prevalence and incidence. **PDVAC observed that there are fewer vaccine candidates in the HSV vaccine pipeline than when HSV was prioritized and will reconvene to discuss how to stimulate interest in vaccine development.**

With the high global incidence of gonorrhoea (87 million new cases in 2016, among 15-49 year-olds), the evidence of antimicrobial resistance against conventional gonorrhoea treatment, and recent MenB vaccine data suggesting that protection against Gonococcal (GC) disease may be biologically feasible, WHO convened a stakeholder consultation to discuss the potential public value of a gonococcal vaccine. Several data gaps were identified that need to be addressed to better understand the global need, and value, for a GC vaccine. In particular, improved data on gonorrhoea-related disease burden in LMICs, such as infertility, as well as the current antimicrobial resistance (AMR) due to gonococcal disease and predicted impact on GC and AMR rates in the absence of an efficacious vaccine are needed. These will be the priority areas of focus moving forward, in parallel to the development of WHO PPC guidance for gonorrhoea vaccines. Furthermore, an appropriately designed clinical study to evaluate the ability of the meningococcal B vaccine to reduce acquisition of gonococcal infection would inform the necessity for development of a stand-alone gonococcal vaccine.

Chlamydia is the most common bacterial infection worldwide, and can result in infertility, ectopic pregnancy and chronic pelvic pain. In 2019, the first Chlamydia vaccine candidate in decades completed phase I clinical studies (NCT02787109). The Statens Serum Institute, Denmark, is planning to commence a phase 2a study with their CTH552:CAF01 candidate later in 2019.

3. **Pathogens previously prioritized by PDVAC:**

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This section covers vaccine that were prioritized by PDVAC at previous meetings, and that had a dedicated session at the 2019 convening due to significant shifts in product development status.

### 3.1 Respiratory syncytial virus (RSV):

Nineteen RSV vaccine candidates are in clinical development, across six different manufacturing platforms, in pregnant women, pediatric and elderly populations. Two next generation, long-acting monoclonal antibodies are also in clinical development for infant immunization, in addition to the licensed Synagis®, which needs to be dosed monthly during the RSV season and is only licensed for use in preterm infants.

The vaccine candidates for maternal immunization are the most advanced. Vaccine candidates containing RSV F stabilized in the prefusion conformation, produced by Pfizer and GSK, are scheduled to begin phase II clinical studies in pregnant women in the coming year. Novavax's recombinant F protein vaccine recently reported results from a phase III efficacy study (NCT02624947) in 4,636 third trimester women in a multi-center trial across both the Northern and Southern hemispheres. The primary objective of the study was to determine the efficacy of maternal immunization against medically significant RSV lower respiratory tract infection (LRTI) through 90, 120, 150 and 180 days of life in infants. The vaccine efficacy against the primary endpoint of medically significant RSV-LRTI at 90 days was 39.4% (97.5%CI: -1 to 64%; 95%CI: 5.3 to 61.2%), and against the secondary endpoint of RSV LRTI with severe hypoxemia or hospitalization was 48.3% (95%CI: -8.2 to 75.3%). Most trial participants were enrolled in either South Africa (52%) or the USA (23%). The study was not powered for country-specific efficacy estimates, however South Africa showed positive efficacy; in a pre-specified exploratory endpoint, using both site and hospitalization data, the efficacy against medically significant RSV LRTI was 57% (95%CI: 33 to 73%). Notably, the attack rate for the primary and secondary endpoints among placebo recipients were 2 to 10-fold greater in South Africa than in the US.

RSV mAb produced by Astra Zeneca and Merck are in clinical development. Each product contains YTE mutations in the Fc portion of the mAb to extend half-life, enabling one intramuscular dose per RSV season. The most advanced mAb candidate is Astra Zeneca’s MEDI-8897 (Nirsevimab), which has just completed a phase IIb pivotal registration study (NCT02878330) in 1,453 late preterm infants across 23 countries in both Northern and Southern hemispheres, including USA and South Africa.

WHO has an RSV technical advisory group (TAG) that reviews evidence from clinical trials and assesses the RSV pipeline that may be supportive for policy evaluation. WHO also supports a meta-analysis by Vanderbilt University and held an expert consultation to define the causal role of RSV infection on long term respiratory sequelae, such as wheezing and asthma. In addition, WHO is supporting an evaluation of global RSV seasonality in collaboration with the University of Edinburgh. Early work suggests that most LMICs have an annual RSV season, which will be
important in considering the implementation strategy for both mAbs and maternal immunization. The Global Influenza Program at WHO is also expanding surveillance of RSV to a total 22 countries, including several GAVI-eligible countries. Lastly, WHO is finalizing guidelines on the Quality, Efficacy and Safety of RSV Vaccines. These guidelines are required for WHO prequalification that occurs post-licensure and SAGE policy recommendation, and support market authorization in LMICs and vaccine purchase by UNICEF. Development of a WHO PQ process for monoclonal antibodies is underway with two cancer therapeutics as an initial pilot and could begin for RSV mAbs once SAGE and WHO indicate that RSV immune prophylaxis with mAbs is a priority indication with public health potential.

Recommendations from PDVAC:

- As regards the Novavax vaccine candidate, PDVAC cautioned that additional clinical trials will likely be needed to generate data in both HICs and LMICs, particularly because of the stringent exclusion criteria for enrollment in this study and since the South African population may not be representative of other African countries. The committee underscored the importance of identifying a correlate of protection, or of risk, from the Novavax study that could be used to bridge to other clinical studies and support demonstration of efficacy. Efforts are already underway in this regard.

- The Medi8897 mAb phase IIb study results are encouraging, however the committee cautioned that the vaccine and mAb efficacy data may not be directly comparable because of the different target population and risk profile (MEDI 8897 study infants were all premature and were not enrolled at birth, whereas ResVax™ study infants were followed from birth and most were born at term). In addition, the case definition and clinical endpoints were not standardized and overall incidence of disease was higher in the mAb study. It would be useful for the RSV TAG to evaluate the variables included in the case definitions for each study and identify where comparability is feasible. Going forward, collecting data with methods that allow cross-study comparisons will be critical for decision-making. It would also be informative to collect data to assess the potential role of breastfeeding in protection following maternal immunization.

- Although the mAb is ‘vaccine-like’ in terms of delivery, the cost per dose is unknown and global access strategy is unclear. PDVAC recommended undertaking cost impact modelling for both maternal immunization and mAbs, considering the use cases for both alone and in the context of each other.

- PDVAC reaffirmed its recommendation for development of preferred product characteristics (PPCs) for RSV immunoprophylaxis with mAb to indicate this as a priority intervention from the perspective of WHO, and to begin socialization of the candidates with SAGE.

- Overall, PDVAC’s position is that, assuming data from clinical trials conducted in a broad set of LMICs supports the efficacy findings in South Africa, and that other products with
greater efficacy are not yet available, there may be a rationale for introduction of such a RSV vaccine in LMICs. This is particularly the case considering that cost per dose for immunoprophylaxis with mAb in LMIC contexts is currently unknown. Regarding the Novavax RSV vaccine candidate, PDVAC raised the potential risk and acceptability of introducing a vaccine with partial efficacy into LMICs, which is not licensed for use in HICs, and the ramifications of maintaining investment in the RSV vaccine and mAb pipeline of products that may be more effective.

- The WHO Strategic Advisory Committee of Experts (SAGE) on Immunization should be briefed on the Novavax vaccine candidate and MEDI-8897 mAb study data and the proposed pathway(s) forward for RSV immune interventions, to offer any potential guidance on data that should be collected to support a policy recommendation.
- PDVAC calls for establishment of an RSV prophylaxis ADIP (Accelerated Development and Introduction Plan) to identify the data needs for a policy and financing recommendation and to advocate for RSV vaccine and mAb introduction.

3.2 Tuberculosis:

In 2017, an estimated 10 million people developed TB, and 1.6 million people died of the disease. TB is the first cause of death of people living with HIV/AIDS. Approximately 1.7 billion people—23% of the world’s population—have latent TB infection (LTBI) and carry the risk of developing TB during their lifetime. The emergence of *Mtb* strains resistant to TB drugs causes a major and increasing burden of hard-to-treat infections. The existing TB vaccine Bacillus Calmette-Guérin (BCG) is recommended for use in neonates for prevention of severe forms of childhood TB but has not been demonstrated to significantly protect against TB when used in adults.

The current pipeline of TB vaccine candidates in development is diverse, with various classes of products including adjuvanted proteins, antigen-expressing recombinant viral vectors, live-attenuated whole cell vaccines derived from BCG, *Mycobacterium tuberculosis* or other mycobacteria, or inactivated mycobacteria or mycobacterial extracts. WHO recently developed guidance on preferred product characteristics (PPC) of new TB vaccines, to inform stakeholders of the product attributes that would have the greatest public health impact. Specifically, the PPC highlights the priority need to prevent pulmonary TB in adolescents and adults, as the approach most likely to rapidly impact transmission and curb the epidemic. For products being considered for BCG replacement, demonstration of superior efficacy, and favorable safety in the HIV infected, will be key drivers of value and policy decisions.

In 2018, GSK’s M72/AS01E candidate TB vaccine was demonstrated to provide 54% (90% CI: 14-to 75%; P = 0.04) protection against pulmonary tuberculosis, over approximately two years of follow-up, in a Phase IIb study (NCT01755598) conducted in Kenya, South Africa and Zambia, in individuals with evidence of latent TB infection. These results, in showing protection in those with
a past infection with tuberculosis (i.e., interferon-γ release assay positive), are unprecedented in the history of TB vaccine research and constitute a major scientific breakthrough and potential public health opportunity. Licensure for primary indication based on prevention of active TB in adolescents and adults would raise the prospect for post-licensure expansion of the indication, including use in vulnerable populations, such as people living with HIV/AIDS. Efforts are now underway to urgently prepare a pathway to licensure for this candidate, should it prove efficacious in further trials, and to secure funding commitment from global health stakeholders for the studies that remain to be undertaken.

Also in 2018, important results emerged from a study in South Africa that evaluated the effect of BCG revaccination in adults vaccinated with BCG at birth and with no evidence of LTBI. The co-primary endpoints of this trial were not achieved, but secondary analyses suggested that BCG revaccination reduced the proportion of sustained conversion of in vitro markers of LTBI by 45%. This result contrasts with past studies that have shown no impact of BCG revaccination on TB, and BCG revaccination is currently not recommended by WHO. The risk of disseminated BCG disease in people infected with HIV would constitute an important hurdle to BCG revaccination strategies in HIV and TB co-endemic areas. This research signal nevertheless constitutes an important opportunity to characterize immunological mechanisms of protection against Mtb infection, and such investigations are planned.

Recommendations from PDVAC:

- Given the unparalleled public health burden of TB, and the reality that this candidate is the first to indicate efficacy in decades of vaccine R&D, PDVAC unanimously expressed the view that the M72/AS01 Phase IIb efficacy signal warrants progression to late stage development including phase III evaluation, without delay. PDVAC further iterated the urgency for WHO to convene stakeholders to proactively determine the late stage development approach, and licensure, policy and access strategy for this vaccine, in the event that favorable results are confirmed.

- Successful licensure and implementation will depend on the ability of major public health stakeholders to partner with the manufacturer, and to establish and operationalize financing mechanisms that will support steps to commercialization and procurement of the vaccine. The risk of undue delays is significant and WHO should direct its efforts to understand the vaccine use cases, potential health and socioeconomic vaccine impact and expected demand. Specifically, consultation with BRICS countries, that represent the majority of the potential market is recommended.

- The status of TB vaccine development, and in particular the M72/AS01 candidate should be presented to SAGE in the coming year to determine data and evidence that will support policy consideration.
3.3 Group B Streptococcus (GBS):

Group B Streptococcus (GBS) is a leading cause of maternal, foetal, neonatal and young infant invasive bacterial disease. Recent global disease burden estimates suggest that GBS causes 319,000 cases of early life invasive bacterial disease and 90,000 infant deaths annually. A conservative assessment suggests that yearly, 57,000 stillbirths are caused by GBS and 33,000 women have GBS pregnancy-associated sepsis. There is also a significant, unquantified burden of GBS-related prematurity and neurodevelopmental sequelae. The African continent accounts for an estimated 54% of cases of GBS invasive disease and 65% of all foetal/infant GBS deaths.

The GBS vaccine pipeline includes 2 candidate vaccines being evaluated in humans, and preclinical candidates. While double blind randomized controlled trials are traditionally considered the ‘gold standard’ approach to demonstrate vaccine efficacy, sample size requirements for such a trial to assess GBS vaccine efficacy against the most relevant clinical endpoints, under conditions of appropriate ethical standards of care, constitute a significant obstacle on the pathway to vaccine licensure via this route. The acceptability of an alternative pathway based on an antibody-based correlate of protection for initial licensure, to be followed by post-licensure studies to confirm clinical efficacy, is being considered, and WHO is engaged in defining reference reagents and standardized assay procedures to support this strategy.

In collaboration with the LSHTM, WHO is developing global economic investment case for GBS vaccines. This incorporates three workstreams: i) assessment of GBS burden of disease which encompass long-term physical, neurological, cognitive, educational, psychological, and economic outcomes including QALY/DALY weights, by setting up cohort re-enrolment or electronic data linkage studies in 7 countries, ii) economic evaluation of maternal GBS vaccination which involves a range of different methods including cost-effectiveness analysis, return on investment, budget impact, extended cost-effectiveness analysis and global surplus, and iii) operationalization of GBS vaccine implementation through the maternal immunization platform, which will evaluate the factors that may influence adoption and programmatic effectiveness, such as the capacity of existing service delivery models, the impact of vaccination schedule, the potential delivery through EPI or anti-natal clinics, barriers to uptake and acceptance by pregnant women and health care workers. The objective is to provide data and analyses that will facilitate decision making by multiple stakeholders along the product development continuum (including donors, manufacturers and countries), thereby accelerating product development and mitigating against delays typically encountered in late stage development or post licensure.

Recommendations by PDVAC:

- PDVAC welcomed the progress in investigating an alternative, correlate based licensure strategy with post-licensure effectiveness studies. There was a recommendation to identify and collect data that could inform post licensure study design during early
phase clinical studies, to reduce the time and financial burden of vaccine effectiveness studies.

- PDVAC also endorsed the approach for developing global economic investment case, and its alignment with including the broader non-health related public value aspects. However, there is likely a need to raise awareness of GBS disease and vaccination as a potential control strategy in LMIC context.
- GBS infection is effectively treated by penicillin and therefore antibiotic resistance is not a leading concern; however, the wider impact of intrapartum antibiotic use on the health of women and children could be an important contributor to the value attribution of a vaccine.

4. Pathogens not previously discussed by PDVAC

4.1 Salmonella Paratyphoid A:

IHME estimates of paratyphoid burden of disease for 2017 (due predominantly to paratyphoid A) are 3.4M cases, 19,100 deaths, 1.4M DALYs and an age-standardized incidence of 47/100,000 with a case fatality rate of 0.56%. Paratyphoid A is most common in parts of South Asia with incidence highest amongst children, and its overall relative burden compared to typhoid has been increasing. There are observations of increases temporally associated with vaccination against typhoid, but it is not clear if these may be attributed to typhoid vaccination. AMR is a major threat including the potential for extreme drug resistance and azithromycin resistance.

*Salmonella* Paratyphoid A (SPA) generally has a lower incidence than *Salmonella* Typhi (ST) and varies by geography and age distribution with SPA peaking approximately 2 years later than ST. Collectively these factors render it unlikely for an SPA vaccine to be used as a stand-alone vaccine, but a bivalent typhoid-paratyphoid vaccine could be attractive for comprehensive control of enteric fever. A conjugate vaccine for typhoid was licensed and received a WHO policy recommendation in 2017, and SPA candidates are now in clinical development, based on both conjugate and live attenuated platforms.

Demonstration of vaccine efficacy against SPA is considered difficult and probably not feasible, with study sample sizes in the region of 100,000 – 250,000 subjects. The University of Oxford has developed SPA and STCHIMs which could support vaccine licensure on the basis of phase II efficacy plus field immunogenicity for the SPA component, and immunobridging with demonstration of non-inferiority (on immunogenicity) for the ST component to licensed typhoid vaccines. Such an approach is proposed as a potential accelerated pathway to licensure and PQ that would likely necessitate post-licensure effectiveness studies.

Recommendations from PDVAC:
• Since this will not be a universal vaccine, robust burden of disease data will be needed, on both SPA and ST incidence and coincidence, to determine the optimal use case and implementation strategy for such a bivalent vaccine.

• The proposed licensure strategy is based on an accelerated approval pathway that assumes CHIM model results will likely predict a clinical benefit. Careful consideration should be given to data requirements for SAGE policy recommendation, including the perceived cost of goods for the monovalent and bivalent vaccines.

5. Other pathogens discussed at the 2019 meeting:
This section provides an update on the status of vaccines that have been previously discussed at PDVAC and were revisited as part of PDVAC’s horizon scanning role.

5.1 Invasive nontyphoidal *Salmonella* (INTS)

With the recent licensure, WHO recommendation and prequalification of the Typbar typhoid conjugate vaccine (TCV) in 2017 on the basis of CHIM, there is increasing global interest in the accelerated development of broadly protective vaccines against *Salmonella* disease, including invasive non-typhoidal *Salmonella* (INTS) disease. INTS disease is the most common presentation of bacteremia in sub-Saharan Africa with peak age in infancy and early childhood and high mortality. It commonly presents as fever alone and can be associated with HIV, malaria and malnutrition, though often occurs with no comorbidity. IHME estimates of global burden of disease from INTS in 2017 are 535K cases, 59,100 deaths (77,500 including INTS deaths in HIV+ subjects) with a case-fatality rate of 14.5% (41.8% in HIV+ subjects), 4263 DALYs and an age-standardized-incidence of 7.5/100,000. Multi-drug resistance is common and resistance to ceftriaxone and fluoroquinolones is emerging. A bivalent vaccine, including both *S. Typhimurium* and *S. Enteritidis* would be required to protect against these predominant circulating serovars, and ideally would be combined with another schedule-compatible enteric vaccine, such as Typbar TCV, to ease delivery.

In May 2019, Wellcome and BMGF convened a scientific consultation to discuss how to advance *Salmonella* vaccines, focusing on the status and research needs for both paratyphoid A and INTS product development. In the case of INTS, there are currently 2 candidates that are poised to enter phase I clinical testing. However, there are several complexities that may hamper product development. These include co-dependence of INTS disease on co-morbidities such as malaria and HIV, uncertainty with respect to the optimal vaccination strategy in a crowded EPI infant schedule, and the fact that there is no CHIM model available to test proof of concept of INTS vaccine candidates. Field efficacy studies would be needed to provide the first indication of efficacy. Efforts are currently focused on ascertaining safety and immunogenicity in the target population, infants in LMICs.
Recommendations from PDVAC:

- iNTS has not been prioritized by PDVAC at this time. The committee concurred with the conclusions of the WT/BMGF consultation that additional data on the burden of iNTS disease, including its comorbidities, is needed to articulate the use case, vaccination strategy and potential value of this vaccine.
- There are several research gaps that have been identified. This pathogen may benefit from a technical R&D roadmap that articulates and structures the pathway to assessing the full public value, in parallel to the candidates moving into the clinic, to avoid the risk of this vaccine succumbing to the ‘second valley of death’, i.e. no funder to support development through to licensure and policy recommendation.

5.2 Non-replicating rotavirus vaccines (NRRV):

Despite the licensure and WHO prequalification of four live attenuated oral rotavirus vaccines, and the well-established impact of these vaccines on reducing rotavirus related mortality, rotavirus remains a leading cause of severe diarrhea among children under five 5 years, globally, with more than >250 million cases of diarrhea annually and 129,000 diarrheal deaths in 2016. There are several oral rotavirus vaccines in the pipeline with distinguishing product presentations, including two that are awaiting WHO PQ. Next generation parenteral NRRVs are also advancing, and PATH’s trivalent V2-VP8* candidate is expected to begin phase II/III efficacy testing, with Rotarix as a comparator, in Q3 2019.

The rationale for development of NRRVs includes potential superior efficacy and safety, and lower cost of goods sold as compared to oral vaccines, as well as opportunity for combination with other parenteral vaccines to facilitate delivery. Given the broad acceptability and the rich pipeline of oral rotavirus vaccines, product developers are seeking to understand the value (and therefore the specific product attributes) that the NRRV vaccines will need to offer to various stakeholders, including end-users, to be taken up in immunization programmes. Efforts to evaluate this within the full public health value proposition of these vaccines is underway and will also seek to identify the evidence that will be needed inform a policy recommendation or introduction decision for these novel vaccines.

Recommendations from PDVAC:

- Oral rotavirus vaccines are effective and have had a substantial public health impact. However, the NRRV pipeline candidates may perform even better and there is precedence for improved efficacy, and impact, of next generation parenteral vaccines with typhoid. There are trade-offs between the characteristics of the oral and
parenteral vaccine that need to be evaluated while the phase II/III study is going, to inform the use case and potential demand for NRRV if the candidate is licensed.

- One such trade-off is the potential for combination, and PDVAC recommended evaluating the vaccine impact of NRRV in combination with pentavalent vaccine vs a stand-alone vaccine, at various efficacy thresholds including 70%.

5.3 Norovirus
The recent data from Phase IIb study to evaluate the efficacy and immunogenicity of the intramuscular norovirus GI.1/GII.4 bivalent virus-like particle vaccine in healthy adults aged 18 - 49 years was presented to PDVAC during closed session.

6. Cross-cutting initiatives
6.1 Enteric burden of disease modelling:
For LMICs, vaccine prioritization is primarily driven by the number of deaths caused by different pathogens. For enteric diseases, two main modelling groups provide mortality estimates by pathogen: the Institute for Health Metrics and Evaluation (IHME) at the University of Washington, Seattle and the Maternal Child Epidemiology Estimation (MCEE) group, led by Johns Hopkins Bloomberg School of Public Health. Whilst previous global diarrhoea mortality estimates for under five-year-olds from these two groups were closely aligned, more recent estimates for 2016 have diverged, particularly with respect to numbers of deaths attributable to different enteric pathogens. This has impacted prioritization and investment decisions for vaccines in the development pipeline. For this reason, PDVAC recommended the formation of an independent working group of subject matter experts to explore the differences between the IHME and MCEE estimates, and to assess the respective strengths and limitations of the estimation approaches adopted, including a review of the data on which the estimates are based. The WG group was established and convened, with both modelling groups, in late 2018, and collectively formulated recommendations related to assessing differences in model structure, methodology for processing the data and data quality. Various workstreams are now underway to evaluate these elements. The report from the 2018 meeting is pending publication and outcomes from the workstreams are expected in 2020.

Recommendations from PDVAC:

- PDVAC acknowledged the criticality of this effort, given that burden estimates underpin vaccine investment decisions and policy recommendations. PDVAC endorsed the approach and current workstreams to improve the understanding and potentially the variability of enteric disease mortality estimates in U5s.
PDVAC cautioned that the majority of burden from these pathogens is due to morbidity and the socioeconomic consequences of long term sequelae, and encouraged expansion of burden assessment to include these aspects as soon as possible.

6.2 Novel vaccine manufacturing and delivery platform development:

CEPI (Coalition for epidemic preparedness innovations) provided an update on their efforts to support and facilitate the development of vaccines for MERS-CoV (middle east respiratory syndrome coronavirus), Lassa virus, Nipah virus, Chikungunya, Rift Valley Fever and ‘disease X’ (the unknown outbreak pathogen). Of particular interest to PDVAC is the potential synergy across manufacturing and potentially also vaccine delivery technology platforms between the vaccines for epidemic and endemic pathogens. CEPI’s portfolio focuses on platforms that are able to express multiple antigens and can be rapidly deployed against known and newly emerging pathogens. As such, it has a number of preclinical and clinical candidates that are leveraging viral vectors and nucleic acids for antigen delivery, and it is also investigating the molecular clamp technology platform. It is seeking to support candidates from preclinical through to phase II clinical studies, and investigational stockpile generation, in addition to numerous cross-cutting activities such as assessing the assay and preclinical model development needs and ensuring sufficient clinical trial site capacity for field testing.

There is increasing recognition and acceptance that novel delivery technologies and approaches are needed to reach global coverage goals for well-established vaccines, which have stagnated for several years at 85%. Twenty million infants are un- or under vaccinated each year, resulting in 1.5 million deaths in children under 5 from diseases, for which vaccines are available. Innovations are needed to overcome programmatic barriers, such as the requirement for a stringent end-to-end cold chain, and vaccine reconstitution for delivery with needle and syringe.

The Vaccine Innovation Prioritization Strategy (VIPS) was established as an alliance in 2017 between Gavi, WHO, BMGF, PATH and Unicef. Its vision is to drive vaccine product innovation to better meet country needs and support the alliance goals on immunisation coverage and equity, through prioritizing innovations in vaccine product attributes. It aims to provide greater clarity to manufacturers and partners to make investment decisions, and to incentivize product development of innovations. The approach includes two analytical prioritization phases, the first of which focused on assessing a long list of 24 innovations according to their characteristics and potential public health value, as well their potential breadth of use (antigen applicability). This phase has just been completed, and five early stage innovations have been recommended to proceed to the second prioritization phase which will assess the potential impact and feasibility of these innovations with a range of priority antigens. The prioritized innovations include microarray patches (MAPs), solid-dose implants, compact prefilled auto-disable devices (CPADs)
(both separately and in combinations with heat stable/ qualified liquid formulations), heat stable/controlled temperature chain (CTC) qualified liquid formulations and dual-chamber delivery devices (separately and in combination with heat stable/ CTC qualified dry formulations).

In addition, four downstream innovations were recommended for lighter analysis. These include the combined vaccine vial monitor (VVM) and threshold indicator (TI), autodisable sharps-injury protection (SIP) syringes, freeze damage resistant liquid formulations and barcodes / radio frequency identification (RFID). Included in the further analysis of these nine priority innovations will be their socialization with DCVMN and IFPMA vaccine manufacturers, civil society organizations, NGOs, PDPs and other stakeholders thought the WHO/PATH delivery technologies working group. The next phase of VIPS analysis should be completed in early 2020 and aims to further prioritise the current list of nine to 3 or 4 innovations for further support by the alliance. The results of the analysis and recommendations for nine phase I prioritized innovations will be reported in early 2020.

There has been considerable focus on the product development of MAPs since these offer potentially transformational benefits to the current delivery challenges of vaccines, with particular utility for diseases such as measles and rubella (MR). WHO, in collaboration with Unicef, recently finalized a target product profile for MR-MAP and this will shortly be publicly available. In 2018, PATH established a MAP Center of Excellence with the remit to accelerate the development and manufacture of the MAP platform for critical vaccines, essential medicines, and diagnostics, and ensure maximal impact by meeting global public health needs.

PDVAC recommendations:

- PDVAC strongly endorses the work ongoing under the VIPS initiative, and PDVAC members actively participate in its technical oversight. PDVAC also encourages continuation of activities to facilitate and accelerate the product development of MR-MAP as a priority vaccine innovation that has been identified by WHO’s SAGE committee. The work ongoing with MR-MAP and the MAP platform in general are considered to be sound precedence for support that will be needed for innovations that are prioritized from the VIPS initiative. PDVAC cautioned that it will be critical to work with immunization programs at the country level to define the full incremental socio-economic value that these innovations could affect, to assist with their prioritization and determining their optimal product characteristics. PDVAC also underscored the importance of considering vaccine delivery considerations in its antigen-specific guidance to facilitate early integration of novel delivery technologies into pipeline vaccine candidates.