WHO Product Development for Vaccines Advisory Committee
12-14 December 2023
Executive summary & recommendations

On 12–13 December 2023, the WHO Product Development for Vaccines Advisory Committee (PDVAC) held its annual hybrid face-to-face/virtual meeting. Participants included subject matter experts across a range of pathogens, vaccinologists, regulators, vaccine developers from both the public and private sectors, as well as policy makers from the national, regional and global levels. The closed meeting was convened on 14 December, with the PDVAC members, to discuss novel guidance documents presented for endorsement, to respond to questions posed by presenters and to develop recommendations for WHO and the wider vaccine development community.

The major objectives of the meeting were to:

- Review the process and progress towards partnering with regions to identify priority pathogens for new vaccines for development and investment, and to:
    - endorse a proposed short-list of global endemic pathogen priorities for which new vaccines are needed;
    - endorse the proposed approach for monitoring and evaluation of the vaccines in development against the priority endemic pathogens, as part of Immunization Agenda 2030.
- Review the progress of pipeline vaccine and monoclonal antibody candidates against specific endemic pathogens, including those on the proposed global priority list, and provide strategic advice on the critical activities that are already ongoing and/or needed to advance new vaccine and monoclonals for priority endemic pathogens;
- To review the draft WHO Preferred Product Characteristics for therapeutic HPV vaccines, for endorsement following public consultation;
- Review of the draft Preferred Product Characteristics and technical roadmap for invasive non-typhoidal *Salmonella* (iNTS) vaccines for input;
- Discuss how WHO/IVB can effectively drive and/or partner with immunization stakeholders to support the development of multiple vaccines and vaccine-like monoclonals for low-and-middle-income countries (LMICs).

Below is a brief synopsis of the pertinent discussion to address the questions in the sessions presented to PDVAC for endorsement and/or recommendation, and a list of the recommendations for each session. The role of PDVAC is to advise the director of the Immunization, Vaccines & Biologicals Department (IVB), who will determine which of these recommendations IVB will undertake to implement. A full meeting report for publication in the journal Vaccine will follow.

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Identification of (endemic) pathogen priorities for IA2030 SP7 (for endorsement)

The seventh strategic priority (SP7) of IA2030 is on Research and Innovation. In support of one of SP7's objectives, **PDVAC was asked to identify a global list of priority (endemic) pathogens for new vaccine R&D** in order to inform regional collaboration, global engagement, and IA2030 monitoring and evaluation (M&E). To this end, an extensive exercise has been undertaken with stakeholders in each of the six WHO regions, to identify a priority set of pathogens to guide new vaccine development. The scope of the exercise included endemic pathogens for which no vaccine is currently available or existing vaccines do not fully meet public health needs, that have been prioritized by existing PPCs, prioritization exercises or identified by regional advisors. Prioritization of epidemic pathogens is being conducted by the WHO R&D Blueprint (https://www.who.int/news/item/21-11-2022-who-to-identify-pathogens-that-could-cause-future-outbreaks-and-pandemics).

The prioritization approach, based on the **"multi-criteria decision analysis" (MCDA),** was developed over several months in broad consultation with experts across country, regional and global levels. A regionally distributed survey has been used to generate a ranking of eight assessment criteria that are then mapped to regional data for 26 pathogens within scope, to identify a minimally biased assessment of priority pathogens for each participant. Data from individuals in each region were collated to produce regional pathogen priority lists. Interim findings have been presented to regional immunization technical advisory groups and WHO's strategic advisory group of experts (SAGE).

In order to generate the *global* (endemic) pathogen priority list, the top 10 pathogens for each region were compiled into a global list of 17 priority pathogens. These 17 pathogens represent priorities for all 6 WHO regions; some are common to several regions such as Tuberculosis and HIV and are within PDVAC scope; others are specific to one or two regions such as Cytomegalovirus, and are unlikely to feature in PDVAC scope as they are not public health priorities in low-income contexts.

To assess progress (M&E) during the course of the IA2030 decade, vaccine **"use cases"** have been identified for each of the 17 global priority pathogens. A vaccine 'use case' is defined as 'the intended target population (e.g. infants, older people) and outcome (e.g. prevention of infection, prevention of disease) to be achieved by use of the vaccine or monoclonal antibody'. Once identified, use cases were assigned to one of three 'action categories' according to the status of product development: research, advance R&D, prepare for policy. The action category broadly describes the activities and actions needed for a particular pathogen and use case to meet either indicator as defined below.

In order to monitor and evaluate progress for the priority pathogens, two indicators were proposed from M&E of the use cases identified for each pathogen:

- SP 7.2.a defined as % of use cases that have vaccines or monoclonal antibodies (mAbs) in Phase 3 trials
- SP 7.2.b defined as % of use cases with licensed vaccines or mAbs that have supportive or permissive policy recommendations

where:

- Licensed: by a WHO-listed authority (WLA) of maturity level 3 or above or transitional WLA
- Policy recommendations: by WHO SAGE if within SAGE scope, by a national immunization technical advisory group if not in SAGE scope

In preparation for the December meeting (including pre-meetings), and during the closed session, **PDVAC was asked to:**

- Endorse the proposed global list of 17 priority pathogens;
- Endorse the proposed use cases for each priority pathogen;
- Endorse the proposed categorization of each use case for M&E under IA2030.

Recommendations from the closed session:

- *PDVAC endorsed the 17 proposed endemic pathogens as global priorities for vaccine development.* *See Appendix A.*

- *PDVAC endorsed 34 use cases for the 17 priority pathogens, and their assigned action categories, for M&E as part of IA2030. See Appendix B.*

Combination vaccines (for recommendation)

The childhood immunization schedule is becoming ever more crowded and complicated to implement with respect to the number of separate vaccine administrations currently required. This creates significant challenges for the development and introduction of new vaccines intended for use in young children – as well as to populations where are there not well-established vaccine delivery programmes such as adolescents. In addition to the cost and logistical barriers to new vaccine introduction, national immunization programmes are concerned about potential reluctance of caregivers to countenance additional injections, resulting in missed vaccinations and a drop in immunization coverage.

Combination vaccines, i.e. combinations of vaccines against different pathogens that are co-formulated and delivered in the same dose, may help to mitigate these issues. Indeed, DTP- and measles-based combinations have previously shown great success. As well as reducing the "vaccination burden" on infants, combination vaccines could enhance programme efficiency resulting in improved equitable coverage and increased cost-effectiveness of some antigens that might not otherwise be introduced for financial reasons. It is acknowledged that combinations bring development, manufacturing, supply chain, and regulatory complexity; however, it is likely that the programmatic benefits outweigh these considerations in most cases. 'Combination packs' may be an interim step in the co-formulation process, i.e., co-packaging vaccines that are administered together and that have common components such as diluent, or that can be ad-mixed at the point of delivery.

National Immunization Programmes (NIPs) have signalled that they would favour more combination vaccines to ease vaccination hurdles and **are asking technical agencies to evaluate and identify opportunities for novel combinations**. Vaccine developers and manufacturers are seeking guidance from global bodies regarding combination priorities to meet public health needs. There is currently no process or policy making body to provide this guidance, nor to advocate use of specific combinations (over the standalone components), once developed. In its absence, vaccine developers are making their own choices, taking on considerable risk, and few new combinations appear to be currently in development.

Questions for PDVAC:

- What role should WHO and PDVAC play in development of a strategic framework to identify and signal the need for combination vaccines?
- What does PDVAC think is needed to provide guidance to vaccine developers and other stakeholders on priority combination vaccines?

Discussion and recommendations from PDVAC:

The development of combination vaccines is complex, with many aspects to consider, including: 1) pathogen epidemiology (in terms of similarity in geography and population subgroups affected),2) technical feasibility of combination 3) intellectual property/ownership (components that may be desirable to combine may be owned by different companies) 4) programmatic compatibility (schedule and dose regimen) 5) cost (combination products may be more expensive than individual components, though increased costs may be offset by delivery efficiencies). Country demand and community acceptability are also important considerations. Some platforms, such as mRNA and viral vectors, may be more amenable to combinations than others because, conceivably, they can present multiple antigens withn a single construct. The public health and economic value of combination vaccine, compared to individual components will need to be assessed to inform and create demand from country level stakeholders and de-risk investment by manufacturers.

PDVAC recommends:

- *Establishment of a sub-group to develop a (vaccine agnostic) strategic framework to identify and structure the considerations for determining preferred, feasible vaccine combinations, acknowledging that the success of developing hypothetical combinations will be determined by technical feasibility. Consider collaborating with strategic partners in this effort, for example Gavi, who have mutual interest in promoting development of combinations through their*

Vaccine Investment Strategy and in prioritizing enabling technologies/approaches through the Vaccine Innovation Prioritization Strategy;

- *Once developed, apply the framework to vaccines in the current pipeline, initially seeking to use existing licensed vaccines that ideally have an immunological surrogate or an established correlate of protection as the 'base', to ensure the highest probability of technical and regulatory success;*
- *Consult extensively with immunization stakeholders and programmes at the national and regional levels, including civil society organizations, on potential public health benefits, priority of and demand for the provisionally preferred combinations identified;*
- *Consult with vaccine manufacturers and developers to assess the probability of technical and regulatory success for new vaccine combinations emerging from application of the strategic framework;*
- *Where appropriate, signal potential combinations that could be of interest through WHO PPCs, as is the case for the iNTS (and TCV) PPC that is currently under development;*
- *Engage PDVAC and SAGE in the evaluation the framework, and the proposed combinations that emerge from the analysis. Consider whether it would be desirable and feasible for SAGE to express a preference for use of combination formulations over the standalone components.*

Group B streptococcus (for recommendation)

Group B streptococcus (GBS) is a common cause of invasive disease in neonates, increases the risk of stillbirth and can also affect maternal health. **Maternal immunization is considered to be the optimal approach for protecting neonates**, and vaccine development for GBS is well advanced with two candidates poised to begin a pivotal licensure study.

Because of the relatively low incidence of invasive GBS in neonates (0.1-2.2/1000 livebirths), and the logistical challenge of vaccinating and following up pregnant women for safety and efficacy, modelling suggests that traditional phase III field efficacy trials would be too large to be considered feasible – requiring approximately 100,000 participants. An **alternative regulatory strategy would be to license a vaccine based on immunogenicity data relating to an immunological threshold most likely to predict protection** against invasive neonatal and young infant disease, namely antigen-specific IgG, with effectiveness and additional safety data collected post-licensure. Either a binding or a functional assay could be appropriate, depending on the candidate and its anticipated mechanism of action.

An international public–private consortium is carrying out a range of studies to validate such an immunological correlate, including the development of international reference reagents and standardization of assays. In addition, consultations with regulatory authorities are planned to discuss the potential role of immunological correlates in vaccine licensure and to identify areas of consensus and data gaps. Once there is alignment and clear consensus on the expected pathway to regulatory approval of GBS vaccines, including in LMICs, WHO intends to develop Evidence Considerations for Vaccine Policy (ECVP) to anticipate the evidence needs that may be needed to support a global policy recommendation.

Question for PDVAC:

- Does PDVAC agree with the proposed approach to create regulatory consensus on the feasibility of the correlate pathway for GBS vaccines intended for use in LMICs?

Discussion and recommendations from PDVAC:

- *PDVAC agrees that regulatory approval of a GBS vaccine by a traditional phase III efficacy study is prohibitively costly and logistically challenging to accomplish and is therefore not commercially viable. An alternative licensure pathway, such as that based on an immunological correlate, is the most likely approach to ensure continued investment and the commitment to commercialisation by vaccine developers/manufacturers;*
- *To this end, PDVAC recommends the urgent convening of regulators from high burden countries including the African Vaccine Research Forum (AVAREF) and WHO Prequalification, with support and facilitation from both the US FDA and the EMA, to*

facilitate convergence and discuss the potential feasibility of a correlate-based pathway for regulatory approval. A key outcome of this convening will be alignment on the evidence to support IgG as a putative correlate, including how such a threshold might be determined and data gaps that need to be addressed as part of this licensure strategy;

- *If consensus on a correlate-based regulatory pathway is reached and there is clarity on the expected phase III study design, PDVAC recommends proceeding with development of ECVP to identify the additional data and evidence that are anticipated to be needed to support a global policy recommendation;*
- *Post meeting note: two regulatory convenings have been scheduled on the 6th February and the 19th and March to discuss the feasibility and acceptability of a correlate-based pathway for GBS vaccines.*

Chikungunya (for recommendation)

Chikungunya is an emerging mosquito-borne viral infection causing an increasing number of outbreaks in LMICs. Although rarely fatal, infections can be associated with arthralgia for extended periods and render some patients unable to work for many months. Those at particular risk of severe disease outcomes in terms of death include neonates and older people.

A chikungunya vaccine has been developed and approved by the FDA for adults at increased risk of disease. Because of the challenges associated with assessing the efficacy of a vaccine designed to combat an epidemic-prone pathogen, licensing was based on immune correlates derived from an animal model (the 'animal rule' pathway), plus a Phase 3 trial in human recipients using immune correlates as the endpoint. The current vaccine is not licensed for individuals at the highest risk of severe disease (neonates and older individuals). Other vaccine candidates are in development and are anticipated to be approved by regulatory agencies. WHO has not yet discussed the policy for Chikungunya vaccine use, and Gavi has not short-listed it as part of its 2024 Vaccine Investment Strategy (VIS); it remains on Gavi's learning agenda.

Challenges in the policy and financing pathway for Chikungunya vaccines include the unpredictable epidemiology, which creates uncertainty regarding the most appropriate use case(s) and the associated vaccine delivery strategy, the fact that the current vaccine is not licensed for use in the highest risk populations and variability in candidate vaccines that differ in terms of numbers of doses per regimen, safety profile, etc. The full public health and economic value of chikungunya vaccination is also uncertain, given that mortality is low but infection can cause significant and prolonged morbidity, with major economic impact.

Potential use cases include stockpiling for reactive use during an outbreak or introduction into routine immunization schedules in high risk geographical areas, i.e., prone to outbreaks. The acceptability of the correlate-based animal rule as a basis for regulatory approval in countries that are at high risk and frequently of low- and middle income – and to immunobridge from healthy adults to high-risk populations is unknown and must also be considered.

Questions for PDVAC:

- Should WHO engage with National Regulatory Authorities (NRAs) in countries targeted for endemic use to gather their perspectives on regulatory approval based on immune correlates?
- Is there a need for a SAGE Working Group to deliberate on use-case scenarios for policy development?

Discussion and recommendations from PDVAC:

PDVAC acknowledges the multiple challenges to accelerating broader regulatory approval for Chikungunya vaccines and in developing a pathway to regional and global policy recommendations.

- *With respect to broader engagement of NRAs on the regulatory approval pathway for existing and emerging Chikungunya vaccines, PDVAC recommends enhanced, co-ordinated and facilitated engagement of NRAs, particularly from countries in which Chikungunya vaccines are anticipated to be approved, to:*
    - *Raise awareness about the availability of new Chikungunya vaccines, and the (limitations in the) data available and that can be generated to support regulatory approval;*

- *Socialise the concept of non-traditional licensure pathways and their necessity for Chikungunya vaccines, for which clinical field efficacy studies are not feasible;*
- *Explore the acceptability of the correlate-based animal rule as a basis for licensure in a broader set of countries, and also as a mechanism to immunobridge to additional high risk populations that may not have been included in the pivotal licensure study;*
- *Discuss the need for and the potential design elements of a phase IV post-marketing study in the context of the anticipated regulatory package, to enable clear communication on funding needs and timelines for broad use.*

Other entities, such as CEPI, are already engaged in such regulatory convenings, and these could be co-facilitated with WHO - particularly when LMICs are involved.

With respect to the need for a SAGE working group to deliberate on the optimal use cases for Chikungunya vaccine policy development:

PDVAC supports the formation of a SAGE working group, at the appropriate time determined by the SAGE secretariat, to signal WHO's support of and interest in Chikungunya vaccines, but concurs that this may be premature in the absence of additional modelling data on the impact of Chikungunya vaccines in different use case scenarios. For this reason, PDVAC recommends undertaking activities that would inform a future SAGE working group, specifically:

- *Further modelling, including economic and budget impact – to assess and compare the vaccines under different use case scenarios, and with different product profiles (specifically dose regimen and duration of protection);*
- *Assessment of the acceptability and feasibility of new Chikungunya vaccines to facilitate engagement at the community level, to inform vaccine advocacy efforts and demand forecasts;*
- *Continued engagement at the regional level, through regional initiatives such as the Chikungunya Vaccine Initiative in PAHO, and through the regional immunization technical advisory groups to identify evidence gaps, co-ordinate activities and monitor demand.*

Shigella (for recommendation)

Shigella is an intestinal bacterial pathogen causing shigellosis, with young children particularly at risk in endemic settings. As well as causing diarrhea and dysentery, repeated infections lead to damage to the intestinal tract that is associated with stunting and impaired physical and cognitive development. In addition, Shigella species are increasingly resistant to antimicrobials. Shigella thus results in both significant disease and economic burden and is an emerging public health threat because of increasing antimicrobial resistance (AMR).

Several *Shigella* vaccines are in clinical development, and the first pivotal multi-country phase III study to demonstrate efficacy and to validate putative correlates of protection is expected to begin in 2025. Serum IgG responses to the O-antigen have been proposed as a putative correlate of protection on the basis of seroepidemiologic studies and previous Shigella vaccine studies, which, if validated in the phase III trial, could accelerate the regulatory approval of next generation Shigella vaccine candidates.

Mortality due to *Shigella* is comparatively low, and the extent of country awareness and demand for a *Shigella* vaccine is uncertain. Prevention of morbidity outcomes such as impact on infant growth and development, economic/productivity gains and impact on the use of antimicrobials (as a proxy for potential impact on AMR), could strengthen the case for Shigella vaccine introduction, but limited data are currently available.

Shigella vaccines are currently included on the VIS shortlist, and Gavi has confirmed that these 'non-traditional' value parameters will be important to consider in the Gavi investment case. As such, a regulatory consultation is planned for March 2024 to raise awareness of Shigella's potential public health impact among country and regional level stakeholders and to discuss phase III study design, including the feasibility of measuring vaccine impact on growth stunting and AMR.

Developing a combination vaccine could make a *Shigella* vaccine more attractive to country decision-makers, but there is currently no formal guidance on possible components (see section on combination vaccines).

Questions for PDVAC:

- If correlate of protection (CoP) status can be established in the paediatric global health target population (LMIC infants) from a Phase 3 efficacy study of a first Shigella vaccine, could PDVAC opine on the broad concept of an accelerated pathway to licensure for subsequent Shigella vaccines based on immunobridging and safety?
- Does PDVAC consider the scope of the regulatory meeting and its objectives/intended outcomes to be sufficiently comprehensive?
- Can PDVAC opine on the importance of a Shigella vaccine demand assessment at this stage of development, particularly with the potential for a future combination vaccine?
- Would PDVAC support a separate, related WHO Workshop to engage regulators and policy makers on combination vaccine strategies, perhaps in the context of "Shigella + X" vaccines?

PDVAC discussion and recommendations:

- *PDVAC agrees with the proposed correlate-based immunobridging strategy to accelerate next-generation Shigella candidates, but the evidence for establishing O-Ag-specific serum IgG as a mechanistic correlate (and the associated threshold of antibody) would need to be discussed with regulatory agencies once data are available from the planned phase III trial.*
- *The use of CoPs as the basis for an accelerated licensure pathway for subsequent Shigella vaccines or indication expansion to other Shigella serotypes will also likely form the basis for inferring efficacy for serotypes where demonstration of clinical field efficacy is not feasible. As such, PDVAC endorses the scope of the intended global consultation and its objectives and considers it to be comprehensive.*
- *Regarding the Shigella demand assessment, PDVAC supports the need to engage with country and regional stakeholders and decision makers to increase awareness of Shigella burden and potential public health and economic vaccine impact, to discuss and validate the potential use cases for such a vaccine, undertaking these discussions in the context of Shigella as a stand-alone vaccine compared to a potential vaccine combination such as Shigella-TCV. to These will contribute to further understanding regarding the necessary properties and data profile of an acceptable Shigella vaccine. This information would be used to inform more robust demand forecasting for Shigella vaccines and potential combinations.*
- *If interest is confirmed by acceptability data, PDVAC supports the concept of a dedicated workshop to discuss the regulatory and policy pathways for 'Shigella + X' combination vaccines.*

Tuberculosis (for recommendation)

Several TB vaccines are in late-stage clinical development, with several in or approaching phase III and / or regulatory approval. Robustness of clinical trial design vary among candidates, as do clinical endpoints evaluated, while the data and evidence to support licensure and policy recommendation are also expected to be different for individual candidates. There is a need to assess the timeline to anticipated licensure of individual candidates, how/whether the data packages for each will support broad implementation, and what trade-offs are likely to between the candidates. This kind of prospective analysis and scenario planning intends to ultimately accelerate vaccine approval, by identifying and addressing evidence gaps and aligning key decision-makers.

Various use cases have been identified for TB vaccines, including prevention of infection (PoI) and prevention of disease (PoD) in infants, PoI and PoD in adolescents and adults, and prevention of recurrence (PoR) in treated TB patients. Modelling suggests that prevention of disease (PoD) in adolescents and adults is likely to have greatest impact on the global TB disease burden. WHO has developed several global guidance documents to inform vaccine developers of the preferred attributes and evidence requirements for licensure and policy and is now developing an analysis of the various late-stage candidates and their potential clinical and policy outcomes.

While PoD has been articulated as the preferential clinical endpoint by WHO and other stakeholders, some candidates may nonetheless be licensed for a PoI or a PoR indication. Given the potentially significant public health impact of a new TB vaccine, but also the detriment that introduction of a poorly efficacious vaccine could have, it is essential that global and national decision-making is based on robust data from well-designed studies. A particular challenge is that efficacy data are likely to be generated in only a subset of the population that could potentially benefit from a TB vaccine, for practical reasons; at the time of licensure, no or limited

efficacy data are likely to be available for younger adolescents (to facilitate TB vaccine delivery along with HPV vaccine), people living with HIV, and people who not been previously exposed to TB – and clinical data often may be limited to one country. Despite this, geopolitical forces may influence individual candidates' introduction in other high-burden countries, before a global policy recommendation is in place.

Questions for PDVAC:

- Does PDVAC consider the proposed/preliminary clinical and policy scenario framework to be useful to guide priorities for new TB vaccine development (for adults and adolescents) and readiness, and to identify gaps?
    - If yes, what other components should be considered?
    - How should such a framework be validated and used?
    - Would there be value in publishing such a framework as a peer reviewed document?

PDVAC discussion and recommendations:

PDVAC recommends the continued development of the preliminary clinical and policy scenario framework that was presented and discussed during the open meeting, and in addition that this document:

- *Is reviewed and validated by an independent technical advisory group (TAG) of experts, to be set up by WHO IVB to evaluate the candidates in clinical development;*
- *Is contextualised to convey the sense of urgency that is needed to identify potential acceleration scenarios, prepare stakeholders to understand the trade-offs of potential vaccines, and the implications (pros and cons) of early introduction;*
- *Underscores the public health need for a vaccine that **prevents active disease in both previously exposed and unexposed individuals,** as opposed to prevention of infection and / or recurrence;*
- *Is used to identify gaps in evidence that will be needed to obtain regulatory approval and policy recommendations, beyond the jurisdictions of the countries in which the initial phase III licensure studies were conducted;*
- *Is used to socialise the TB vaccine pipeline with WHO SAGE and TB vaccine community as appropriate.*

The publication of the analysis in a peer reviewed journal should be in the context of the already developed Evidence Considerations for Vaccine Policy for TB vaccine intended for adults and adolescents.

In addition, PDVAC recommends:

- *Early and robust engagement with civil society as part of WHO's TB vaccine engagement and facilitation strategy, including Civil Society Organizations (CSO) participation in the expert TAG that is to be established.*
- *Development and publication of a 'policy position statement' on behalf of PDVAC, IVB and potentially the TB vaccine TAG and / or accelerator to definitively state the preference for development and regulatory approval of a vaccine with a prevention of disease indication.*
- *Evaluation of the acceptability and feasibility of TB vaccine introduction for older adolescents (15 years and older) and adults, including evaluating and leveraging the experience of COVID vaccine implementation in this target age group, given that efficacy in younger adolescents would likely not be available at the time of licensure.*
- *Evaluation of potential age de-escalation strategies to bridge from initial phase III efficacy in older adolescents and adults to younger adolescents through safety and immunological evaluation, as service delivery in this age group may be more feasible (for example with HPV vaccines).*
- *Continued, proactive engagement of SAGE on the status of the TB vaccine pipeline, candidates in phase 3 clinical studies and issues related to potential global policy.*

Malaria (for input)

The malaria field is rejoicing following the development, regulatory approval, and WHO prequalification of two effective malaria vaccines, RTS,S/AS01E and most recently R21–Matrix M. Supported by Gavi, RTS,S implementation in several African countries is

already underway, soon to be complemented by R21-Matrix M on the menu. Both are moderately efficacious pre erythrocytic vaccines to reduce clinical malaria in infants/children; efficacy has not yet been demonstrated in older children/adults.

The field is now focusing on next generation vaccines, including antigens from other areas of the life-cycle and combinations with the existing approved pre-erythrocytic stage vaccines, for example blood-stage antigens to prevent clinical disease rather than infection, and a transmission-blocking vaccine, targeting the gametocyte stage of the malaria parasite life-cycle. Multistage vaccines aiming to address infection, disease and transmission are the ultimate goal to increase malaria vaccine effectiveness. As yet, no correlate of protection has been identified, but antibody function (as opposed to threshold level) appears to be important.

As well as vaccines, **monoclonal antibodies may also be able to prevent infection,** and are in development. Possible use cases include: as an alternative to antimalarial drugs in seasonal malaria chemoprevention, prevention of malaria in pregnant women, and protection of children recovering from severe malarial anaemia after discharge from hospital.

WHO PPCs have been developed for vaccines intended to prevent blood stage infection, reduce morbidity and mortality and to reduce transmission at the community level. WHO Dept of Immunization, Vaccines and Biologicals and the Global Malaria Programme are now planning a meeting of experts in 2024 to advise on state of the science, and steps needed to advance towards validated measures of correlates, and to establish a technical advisory group (TAG) to address key technical and strategic questions related to clinical development pathways for the next generation malaria vaccines.

PDVAC discussion and recommendations:

PDVAC fully supports the intention to establish a TAG to assess and offer guidance related to the clinical and regulatory questions related to next-generation product development. In addition to the challenges and questions identified in the open session (see slides), PDVAC recommends:

- *Ensuring that the TAG discusses, and that future clinical development strategies account for the broad heterogeneity of the malaria burden and epidemiology in different transmission settings, considering scenarios of seasonal and year round transmission; as well low, moderate and high transmission*
- *Evaluation of alternative trial designs and surrogates for new and next-generation vaccines, including the potential role of the controlled human infection model, consideration of the pathway to assessing efficacy in the context of existing licensed vaccines as well as other control measures e.g., bed nets and chemoprevention, and ensuring early engagement with regulatory agencies through stakeholder consultations;*
- *Consider a technical consultation on the role of systems biology to identify new antigens targets for vaccine development, and correlate of protection/correlates of risk;*
- *Consideration of the end-to-end product development to uptake strategy for the next-generation vaccines – and monoclonals - from the outset, to inform the clinical and regulatory strategy, particularly with respect to identifying clear use cases and delivery strategies for the next generation vaccines through consultation with country and regional experts;*
- *Evaluation of vaccine impact through disease and economic modelling to help identify the optimal and priority use cases for vaccine development;*
- *Consideration of the value of evaluating the efficacy of the existing pre-erythrocytic vaccines in other target populations such as older children, adults, and pregnant women.*
- *Including a discussion of P.vivax epidemiology and vaccine development efforts in the next PDVAC presentation on malaria vaccines.*

Salmonella-containing vaccines (for recommendation)

Multiple serovars of *Salmonella* cause disease in humans, including *Salmonella* Typhi (responsible for typhoid and, alongside S. Paratyphi A, enteric fever) and non-typhoidal *Salmonella* (NTS). *Salmonella* Typhimurium and *Salmonella* Enteritidis are two of the most common NTS serovars that can cause serious invasive NTS (iNTS) disease in young children.

Typhoid conjugate vaccines (TCVs) have been developed for *Salmonella* Typhi and introduced in some countries. Given the challenges of introducing new vaccines into the EPI schedule, there is interest in developing bivalent, trivalent or quadrivalent vaccines that cover multiple *Salmonella* serovars. A particular focus has been bivalent vaccines covering *Salmonella* Typhi and Paratyphi A for enteric

fever and trivalent vaccines for *Salmonella* Typhi, *Salmonella* Typhimurium and *Salmonella* Enteritidis to protect against both typhoid and iNTS disease. Two NTS-TCV candidates are already in clinical development, with the intention to age de-escalate to assess safety and immunogenicity in infants under 6 months.

The *Salmonella* vaccines and their potential combination was previously discussed by PDVAC in February 2022 (see here). At that time, PDVAC's recommendation was that it was premature to signal a preference for any combination but to assess the full vaccine of value assessments (FVVAs) to evaluate each of the potential combination scenarios (NTS bivalent, trivalent permutations, and quadrivalent) to assess multiple trade-offs and the incentives for manufacturers.

Although the broader protection offered by a trivalent vaccine has made it an attractive proposition, the age-related disease burden of typhoid and iNTS disease are different: typhoid burden is mostly in mid-childhood while iNTS infections appear to peak in the first two years of life. There is a lack of epidemiological data on iNTS incidence, but recently presented evidence from Malawi and DRC suggests that **protective immunogenicity needs to be in place before 6 months of age to prevent the most significant disease burden.**

WHO Preferred Product Characteristics (PPC) and a technical R&D Roadmap for bivalent NTS and trivalent NTS-TCV Salmonella vaccines are now under development, and close to finalization. In the week before the PDVAC meeting, new data emerged to suggest waning of the single dose TCV vaccine after 4-5 years and this appeared most pronounced in the youngest children, suggesting that TCV may require a further dose in later childhood, e.g. before school in order to cover the age of peak incidence of typhoid and calling into question its compatibility with potential NTS vaccine schedules. This raises questions about the desirability of combining the typhoid and NTS components of the vaccine, although boosters could be deployed to address waning immunity.The discussion in the closed session focused on this and the guidance to be given in the PPC and Technical R&D Roadmap.

Questions for PDVAC:

- Should 6-36 months remain the target population in the PPC for vaccination against iNTS disease? And should 6 months be the target age for receipt of the first dose?
- What is the advice of PDVAC as to whether the trivalent vaccine should remain the preferred strategy for NTS vaccination against invasive disease?
- Should the current WHO PPC (versus a future PPC) also consider options for combination of Salmonella vaccines with other pathogens?
- Has PDVAC identified any gaps or missing elements that should be in the R&D roadmap for a trivalent S. Typhi/S. Typhimurium/S. Enteritidis combination *Salmonella* vaccine?

PDVAC discussion and recommendations:

The differing epidemiology of iNTS and typhoid means that their optimal immunization schedules are not entirely complementary. The optimal stand-alone TCV schedule is to be determined and could include a booster or a shift of a single dose to an older age depending on the epidemiological context. Equally, PDVAC acknowledged that it will be very challenging to introduce another stand-alone vaccine (iNTS) in children under 6 months, because the immunization schedule is already crowded; where feasible, the use of a combination vaccine would be preferred. However data is not yet available on the safety and immunogenicity – or efficacy - of any iNTS vaccine candidates.

Based on the data available, including the waning of single dose TCV, there are multiple potential schedules that could be contemplated for iNTS and TCV vaccination, for example:

- *The iNTS bivalent could be given at 3 months, followed by the trivalent iNTS-TCV vaccine at 9 months to achieve full immunity against iNTS before 12 months of age, with a monovalent TCV booster at preschool age.*
- *Alternatively, the trivalent iNTS-TCV vaccine could be given at 3 months and 9 months to provide protection to both iNTS and TCV, with a TCV booster at pre-school age.*

- *As such, PDVAC's recommendation with respect to the scheduling guidance within in the PPC is to specify that iNTS doses should be initiated in the first 6 months of life, and that protection (i.e., effective vaccination) is desirable in the first 6 months of life.*

The current epidemiology suggests potential use cases for trivalent iNTS-TCV vaccines, as well as stand-alone vaccines. Age de-escalation studies are ongoing and safety and immunogenicity data could be available in the coming months that will inform the optimal schedule and potential opportunities for iNTS-TCV vaccination and provide the basis for down-selection of an iNTS candidate to move into phase III efficacy testing.

- *At the current time, PDVAC recommends the continued clinical development of both iNTS bivalent as a stand-alone vaccine and the iNTS-TCV trivalent vaccine, to enable flexibility in the immunization schedule, depending on epidemiology and programmatic considerations.*

Several Salmonella vaccine combinations appear to be technically feasible. Selection of the specific combination to use within a country's immunization programme will ultimately be a compromise between programmatic feasibility (i.e., delivery), cost to immunize and full public health and economic impact of the vaccine. Therefore:

- *PDVAC recommends that the current iNTS PPC should continue to be developed to describe the preferred product characteristics for both the bivalent iNTS and the trivalent iNTS-TCV vaccines, without preference for either until additional immunogenicity data and vaccine impact modelling data on scenarios of use are available.*

In addition to the iNTS PPC, a technical R&D Roadmap for the iNTS-TCV combination has been drafted and has completed public consultation.

- *The Roadmap should be revised to align with PDVAC's recommendations for the PPC as above, to include both bivalent and trivalent NTS vaccines*

Lastly, PDVAC support the notion that a SAGE Working Group on TCV is re-established to review the evidence and possibly update the policy recommendations taking the waning of TCV immunity (in particular in those who have been vaccinated at a younger age) into account.

Sexually transmitted infections (STIs) (for recommendation)

- ***Neisseria gonorrhoeae***

The rapid evolution of drug resistance in *Neisseria gonorrhoeae*, as well as observational studies (retrospective cohorts and case control studies) demonstrating 30 to 40% vaccine effectiveness of Meningitis B vaccine against gonococcal (GC) infection, have renewed interest in vaccine development to prevent gonococcal infections. Based on the current evidence of cross-protection, cost-effectiveness and likely impact on gonorrhoea epidemiology, the UK recently recommended that 'a targeted programme should be initiated using the 4CMenB vaccine for the prevention of gonorrhoea in those who are at greatest risk of infection'. Several prospective IIb, III, and IV studies to assess the efficacy and effectiveness of Men B vaccine *N. gonorrhoeae* are underway in both general and high risk populations. The result of these studies could encourage countries that have not introduced MenB for meningococcal infections to reconsider, given the possible additional public health benefits of GC prevention. Stand-alone GC vaccines are also in development, and one has entered a Phase I/II study.

Left untreated, GC infection can cause pelvic inflammatory disease (PID), subsequent infertility and pregnancy complications. In addition, GC infections are becoming increasingly untreatable by existing first-line antibiotic treatments. The public health, economic, and health system burdens attributable to GC infection are expected to increase.

Questions for PDVAC:

- ***Neisseria gonorrhoeae***
  - What are the critical data needs and next steps in preparing for the results from the RCTs of the 4CMenB vaccine for prevention of gonococcal infection?
  - How can we learn from the 4CMenB trials to advance the development of gonococcal specific vaccines?

PDVAC discussion and recommendations:

PDVAC acknowledges that a significant data gap for GC vaccines is related to acceptability and demand, particularly with respect to the potential perceived stigma of receiving a GC vaccine. This gap exists whether immunization is considered under a label extension for the Men B vaccine, or via a stand-alone GC vaccine. Acceptability and demand will likely differ vastly depending on cultural context, and studies are needed to assess the drivers of demand from an end-user perspective, and their impact on potential uptake.

Related to demand, there is also a lack of data on the magnitude of health consequences and health system costs of untreated GC infection, especially for women and in LMIC settings. Modelling of the prevention of GC infection on ectopic pregnancies, PID, infertility, pregnancy complications and other long term sequelae is needed to better quantify the potential health and economic value of a GC vaccine, ***particularly in the context of increasing resistance to existing anti-microbials****. Careful consideration will need to be given to the use cases for such a vaccine, and the delivery modalities to reach end-users, which is closely linked to acceptability and demand.*

With respect to the Men B label extension for GC, and implementation strategies, a better understanding of the epidemiological overlap between MenB and GC incidence and risk is needed (this work is underway and expected to be published soon), and assessment of emerging AMR may further inform the determination of priority countries and use cases for the expanded implementation of this vaccine. Acceptability and demand work will be needed in countries that have high GC incidence and AMR, but currently do not recommend MenB vaccine and/or have Men B disease.

All of the proposed recommendations above will inform the full public health value proposition and investment case for GC vaccine developers and manufacturers, and potential future combination with vaccines for other STIs such as chlamydia.

- ***Chlamydia trachomatis***

Chlamydia trachomatis is the most common bacterial STI worldwide, particularly in adolescents, and is an important cause of infertility, ectopic pregnancy and chronic pelvic pain. Several *Chlamydia* vaccine candidates are now in preclinical development, and one has completed a phase I study with encouraging safety and immunogenicity data. A PPC and/or Vaccine Value Profile (VPP) could be useful for informing the field, identifying data gaps and stimulating and guiding *Chlamydia* vaccine

- Does PDVAC agree that it is reasonable for WHO to explore the development of a PPC for *Chlamydia* vaccines?
- Would a vaccine value profile be useful in the considerations for advancing a *Chlamydia* vaccine?

PDVAC discussion and recommendations:

PDVAC fully supports the development of a Vaccine Value Profile for Chlamydia vaccines to collate the existing publicly available information on the epidemiology, vaccine development status and vaccine impact modelling to identify priority research gaps and as a basis for future WHO PPC development.

Therapeutic HPV vaccination (for endorsement)

Prophylactic human papillomavirus (HPV) vaccines are highly effective in preventing targeted HPV strains and are a critical part of the drive to eliminate cervical cancer as a public health threat. Although more countries are introducing HPV vaccine for adolescent girls, global coverage remains low and many millions of women are already infected with HPV. Programmes to screen and treat for cervical precancers to prevent progression to invasive cancer have been difficult to implement, particularly in LMICs. A therapeutic HPY vaccine could accelerate disease control by preventing or treating precancers in women with existing HPV infections.

Given the natural history of oncogenic HPV infection, which progresses to cervical precancer before invasive cervical cancer, two therapeutic vaccination strategies have been proposed: vaccination to clear infection and vaccination to promote regression of precancerous lesions.

Various vaccine use scenarios for these two types of vaccine could be envisaged. In countries with limited or no cervical screening infrastructure, a therapeutic vaccine clearing infection could be used alone or alongside a prophylactic vaccine, targeting either all women in specified age groups or women with diagnosed infections. A precancer lesion-targeting vaccine could be integrated into screening programmes, particularly where there is a significant risk that women do not receive current curative treatment.

Notably, the timing of therapeutic vaccine development is critical. As coverage of prophylactic HPV vaccine use increases, and vaccinated cohorts of adolescents age into adulthood, the need for a therapeutic vaccine diminishes.

WHO PPCs for therapeutic HPV vaccines, covering the use cases for vaccines that primarily clear oncogenic HPV infection and vaccines that primarily cause the regression of cervical precancers, have been developed and public consultation has been completed. The document was brought to PDVAC for review, discussion and endorsement.

Question for PDVAC:

- Does PDVAC endorse the tHPV PPC?

- *PDVAC endorsed the draft tHPV vaccine PPCs with some minor modifications related to how prophylactic vaccines may be used alongside therapeutic vaccines and inclusion more specific targets for preferred efficacy. The final PPC is expected to be published in Q2 2024.*

MR-MAPs (for recommendation)

Microarray patches (MAPs) offer the prospect of needle-free vaccine delivery, and have several compelling programmatic advantages: they have been shown to be preferable to care-givers and have the potential to facilitate vaccination of those living in hard-to-reach locations. There is an urgent public health need for MAPs to deliver measles and rubella vaccine (MR-MAPs), and their development is prioritised through the Vaccine Innovation Prioritization Strategy (VIPS), led by Gavi with WHO and UNICEF and support from BMGF and PATH who collectively advocate and strategize for their accelerated development. VIPS have identified other priority vaccines for MAP development, published on the Gavi website here.

Encouraging phase I data have been generated for the leading MR-MAP technologies, and phase IIb safety and immunogenicity data was recently presented for the Micron candidate (reviewed by PDVAC in June 2023). However, broad introduction of MR-MAPs will be dependent on the investment in a pilot-scale manufacturing facility to scale-up production and provide clinical trial material for the phase III pivotal licensure study. Key to understanding the potential demand and market opportunity, WHO PDR has conducted several in country workshops to discuss how MR-MAPs could be used to address barriers in MR delivery, to identify critical product attributes and to consider potential use cases and evidence for policy. MR-MAPs will cost more than the existing MR delivery by needle and syringe, but could bring significant gains in equitable MR delivery and progress towards elimination goals, particularly in the hardest to reach populations, especially if policy enables them to be administered by community health workers. Gavi is considering if and how to include MR-MAPs in their 6.0 strategy.

Beyond these workshops, discussions are ongoing and planned on the anticipated data needs of regulators and policymakers to ensure that evidence gaps do not delay implementation after demonstration of efficacy. WHO PDR is planning a global consultation on the clinical, regulatory and policy considerations for vaccine MR-MAP in Q2 of 2024, and presented the objectives and directional agenda to PDVAC for discussion.

Question for PDVAC:

- Is the proposed approach to identify considerations for a phase 3 trial and evidence to inform policy appropriate?

PDVAC discussion and recommendations:

PDVAC endorsed the proposed approach to develop global guidance on the phase 3 study design and to initiate discussions on evidence considerations for policy.

- *The secretariat was urged to identify what evidence is needed for priority use cases initially, such as hard-to-reach populations and zero-dose children, and to consider potential routine implementation as part of life-cycle management, once any potential supply constraints have likely been addressed;*
- *As part of the planned consultation, identify the appropriate time to undertake vaccine interference studies with vaccines that MR-MAP may be co-administered with;*

- *With respect to implementation strategies, consider/investigate opportunities for potential synergy with OPV delivery, since OPV is delivered by community healthcare workers and the Global Polio Eradication Initiative is obligated to deliver other vaccines, where possible.*

In addition:

- *Communicate, through peer-reviewed publication, other priority vaccines for MAP development, to support development of the vaccine-MAP value proposition and investment case for developers/manufacturers.*
- *Include an update on vaccine-MAPs, including outcomes of the MR-MAP consultation at the next PDVAC meeting, to support and echo the advocacy efforts of VIPS.*

Appendix A: Global list of 17 priority endemic pathogens for new vaccine R&D

Cytomegalovirus
Dengue virus
Extra-intestinal pathogenic *E coli* (ExPEC)
Group A Streptococcus (GAS, *Streptococcus pyogenes*)
Group B Streptococcus (GBS, *Streptococcus agalactiae*)
Hepatitis C virus
HIV-1
Influenza virus
Klebsiella pneumoniae
Leishmania spp
Non-typhoidal *Salmonella* (NTS)
Norovirus
Plasmodium falciparum
Respiratory syncytial virus (RSV)
Shigella spp
Staphylococcus aureus
Tuberculosis (TB, *Mycobacterium tuberculosis*)

Appendix B: Unmet vaccine and mAb use cases and their categorization for pathogens on the Global List

Numbering of use cases is for convenience only. Only unmet use cases are listed. Action Category is based on review of candidates potentially relevant to the use case. Potential for SAGE scope not indicated for use cases in the Research category. Click on pathogen names to jump to sources and discussion for each use case.

Pathogen	Target population	Condition to prevent (or indication)	Use case description	Basis for use case	Potential SAGE scope	Action category
Cytomegalovirus (CMV)	Women and girls prior to pregnancy	Congenital CMV	Prevention and/or modification of sequelae associated with congenital CMV, by vaccinating women and girls **prior to pregnancy**	VVP	Unlikely	Advance R&D
Dengue virus	Dengue naïve and seropositive individuals	Dengue fever	Vaccine for dengue naïve and seropositive individuals, to prevent dengue febrile illness induced by any dengue serotype	TRS, SAGE	Yes	Prepare for policy
Extra-intestinal pathogenic *E coli* (ExPEC)	**UC1:** High-risk populations	Invasive *E coli* disease	Prevention of invasive *E coli* disease, including urinary tract infections or bacteraemia, in high-risk populations	Other literature	Unlikely	Prepare for policy
	UC2: Neonates and infants through maternal immunization	Invasive *E coli* disease	Maternal immunization during pregnancy to prevent invasive *E coli* disease, such as neonatal sepsis and meningitis, in neonates and young infants	Other literature	--	Research
Group A streptococcus (GAS, *Streptococcus pyogenes*)	Young children	GAS pharyngitis and/or superficial skin infection (impetigo)	Prevention of GAS disease: pharyngitis, impetigo, and invasive disease in children. Potential for prevention of GAS immune-mediated sequelae: acute rheumatic fever and rheumatic heart disease (RHD)	PPC	Yes, due to WHA resolution on RHD	Research
Group B streptococcus (GBS, *Streptococcus agalactiae*)	**UC1:** Neonates and infants through maternal immunization	GBS-related stillbirth and invasive GBS disease in neonates and young infants	Maternal immunization during pregnancy to prevent GBS-related stillbirth and invasive GBS disease in neonates and young infants	VVP	Yes	Advance R&D
	UC2: Older adults	GBS infections	Prevention of Group B streptococcal infections in older adults	Other literature	--	Research

Pathogen	Target population	Condition to prevent (or indication)	Use case description	Basis for use case	Potential SAGE scope	Action category
Hepatitis C virus	**UC1:** Persons at risk for HCV infection	Chronic HCV infection	Prevention of chronic hepatitis C infection for persons at risk	Other literature	--	Research
	UC2: Persons with chronic HCV infection	Treatment of chronic HCV infection	Therapeutic vaccines to improve treatment outcomes for chronic HCV infections	Other literature	--	Research

Pathogen	Target population	Condition to prevent (or indication)	Use case description	Basis for use case	Potential SAGE scope	Action category
HIV-1	**UC1:** Persons at risk of HIV infection	HIV infection	**Prevention** of HIV in high-risk populations	Other literature	Yes	Advance R&D
	UC2: HIV-positive individuals	Treatment and/or cure of HIV infection	**Treatment and/or cure** of HIV infection in HIV-1 positive individuals (includes vaccines, mAbs, and combined approaches)	Other literature	Yes	Advance R&D
	UC3: Persons at risk of HIV infection	HIV infection	**Preventive mAbs** for HIV-1 infection in confirmed HIV-negative individuals at substantial risk of HIV infection and their sexual partners and/or prevention of HIV-1 infection in neonates and infants with HIV exposure	PPC	Yes	Advance R&D
Influenza	**UC1**: Persons aged 6 weeks and older belonging to a group at high risk for severe influenza illness	Influenza A infection	Universal-type influenza A vaccines for prevention of severe influenza illness caused by human influenza A virus infection in persons aged 6 weeks and older belonging to a group at high risk for severe influenza illness (children aged 6 weeks through 59 months, elderly adults, persons with chronic medical conditions, and pregnant women). Duration of efficacy should be a minimum of 5 years	PPC (being revised)	Yes	Advance R&D
	UC2: Children aged 6 weeks through 59 months	Seasonal influenza	Improved seasonal influenza vaccines, with a duration of protection of at least one year	PPC (being revised)	Yes	Advance R&D
Klebsiella pneumoniae	**UC1:** Neonates and infants through maternal immunization	Neonatal sepsis caused by *K pneumoniae*	Vaccine administered during pregnancy to prevent neonatal sepsis caused by the major disease-causing serotypes of *K pneumoniae*	Other literature	--	Research
	UC2: Individuals at high risk for infection with *K pneumoniae*	*K pneumoniae*-attributable disease	Preventing *K pneumoniae*-attributable disease, including pneumonia, blood stream infections, and/or urinary tract infections in high-risk populations such as older adults, the immunocompromised, and those with anticipated prolonged hospital stay or planned surgeries	Other literature	--	Research

Pathogen	Target population	Condition to prevent (or indication)	Use case description	Basis for use case	Potential SAGE scope	Action category
Leishmania	All age groups in endemic regions starting from 6 months of age	Visceral leishmaniasis (VL), cutaneous leishmaniasis (CL), and post-kala azar dermal leishmaniasis (PKDL)	Prevention of VL and/or CL in all age groups in endemic regions starting from 6 months of age, and/or prevention or treatment of PKDL	VVP	--	Advance R&D
Non-typhoidal *Salmonella* (NTS)	**UC1:** Children aged 6 – 36 months	Invasive disease caused by non-typhoidal *Salmonella*	Paediatric vaccines for prevention of invasive disease caused by non-typhoidal *Salmonella* in infants and children aged 6 – 36 months	VVP	Unknown	Advance R&D
	UC2: Individuals at high risk for NTS invasive disease	Invasive disease caused by non-typhoidal *Salmonella*	Prevention of invasive disease caused by non-typhoidal *Salmonella* in other individuals at high risk, including immunocompromised individuals, children over 36 months, the elderly, immunocompromised individuals, and persons living or traveling in settings with poor sanitation and hygiene	VVP	Unlikely	Advance R&D
Norovirus	**UC1**: Children, beginning at 6 weeks of age	Norovirus acute gastroenteritis	Prevention of norovirus acute gastroenteritis for children in all countries from 6 weeks of age	VVP	Unknown	Advance R&D
	UC2: Adolescents, adults, and/or older persons	Norovirus acute gastroenteritis	Prevention of norovirus acute gastroenteritis for adolescents, adults, and/or older persons in all countries (including travellers)	VVP	Unlikely	Advance R&D
P falciparum	**UC1:** Populations or age groups who experience high incidence of infection	Blood-stage infection due to *P falciparum*	Prevention of blood-stage infection due to *P falciparum* malaria at the individual level, for populations or age groups who experience high incidence of infection	PPC	Yes	Advance R&D
	UC2: Children and adults, including women of childbearing age	Malaria transmission at the community level	Prevention of malaria transmission at the community level for children and adults, including women of childbearing age, who represent the infectious reservoir and will need to be targeted to maximize the vaccine's impact on transmission	PPC	Yes	Advance R&D

Pathogen	Target population	Condition to prevent (or indication)	Use case description	Basis for use case	Potential SAGE scope	Action category
	UC3: Populations or age groups who experience high incidence of infection	Blood-stage infection due to *P falciparum*	mAbs for prevention of blood-stage infection due to *P falciparum* at the individual level, and/or reduction of clinical malaria, including severe malaria and death due to *P falciparum*	PPC	Yes	**Advance R&D**
RSV	**UC1:** Neonates and infants through maternal immunization	RSV lower respiratory tract illness (LRTI)	Active immunization of women during pregnancy, for prevention of severe RSV disease in offspring during the neonatal period and early infancy	PPC	Yes	**Prepare for policy**
	UC2: Infants and young children above the age of 6 months	RSV LRTI	Active immunization of infants, for prevention of RSV disease in infants and young children	PPC	Yes	**Advance R&D**
	UC3: Infants and high-risk toddlers	RSV LRTI	**mAbs** for prevention of severe RSV disease for all infants in the first 6 months of life and for high risk young children entering their second RSV season (e.g with chronic heart or chronic lung disease)	PPC	Yes	**Prepare for policy**
Shigella	**UC1:** Infants from 6 months and children up to 36 months of age	Moderate to severe diarrhoea due to *Shigella*	Prevention of moderate to severe diarrhoea due to *Shigella* in infants from 6 months and children up to 36 months of age	PPC	Unknown	**Advance R&D**
	UC2: High-risk populations	*Shigella*-attributable dysentery and diarrhoea	Prevention of *Shigella*-attributable dysentery and diarrhoea for high-risk populations such as travellers and the military, communities with high incidence, elderly and institutionalized individuals, and/or pregnant women	VVP	Unlikely	**Advance R&D**

Pathogen	Target population	Condition to prevent (or indication)	Use case description	Basis for use case	Potential SAGE scope	Action category
S aureus	**UC1:** High-risk populations	*S aureus* infection	Prevention of severe infection in populations at risk, such as children, those over 60 years of age, and/or those in all age groups who are immunocompromised, experiencing recurrent skin and soft tissue infections, suffering from relevant comorbidities, exposed to epidemic strains, diabetics or undergoing elective surgery or other invasive procedures with high risk of *S aureus* infection	Other literature	Unlikely	Advance R&D
	UC2: Persons at risk for or undergoing treatment for *S aureus* infection	mAbs for prevention or treatment of *S aureus* infection	**mAbs** for prevention or treatment of disease caused by *S aureus*, such as severe pneumonia and/or superinfection in conjunction with viral pneumonia	Other literature	Unlikely	**Prepare for policy**
Tuberculosis	**UC1:** Adults and adolescents	Prevention of active pulmonary TB disease	Prevention of active pulmonary TB disease in adults and adolescents (with or without evidence of latent infection), including in those with HIV infection	PPC	Yes	**Prepare for policy**
	UC2: Infants and young children	Prevention of TB disease	Prevention of TB disease in infants and young children, including in infants with HIV infection	PPC	Yes	**Prepare for policy**
	UC3: Persons being treated for TB	Prevent TB recurrence and/or increase the proportion of cure at the end of drug treatment	Adjunctive treatment of TB or to prevent relapse following cure in patients being treated for active TB, both drug sensitive and drug resistant strains.	PPC	Yes	Advance R&D
	Additional use cases to be tracked, but not counted in SP7.2 M&E					
	UC4: Adults and adolescents	TB infection	Prevention of TB infection in adults and adolescents, including in those with HIV infection	Other literature	--	--
	UC5: Adults and adolescents	TB recurrence	Prevention of recurrence (defined as either reinfection or relapse, whether pulmonary or extrapulmonary) in patients who are cured from active TB	Other literature	--	--

Pathogen	Target population	Condition to prevent (or indication)	Use case description	Basis for use case	Potential SAGE scope	Action category
	UC6: Neonates, infants, and young children	TB infection	Prevention of TB infection in neonates, infants, and young children, including those with HIV infection	Other literature	--	--