WHO/IVB’s Product Development for Vaccines Advisory Committee (PDVAC)

Report from Hybrid F2F/Virtual meeting

5-6 December 2022

Intercontinental Hotel, Geneva, Switzerland

Meeting chairs: Dr David Kaslow and Professor Ruth Karron

Please see hyperlinks for the agenda, list of PDVAC members in attendance and meeting participants, presentations from day 1 and day 2.

The Remit of PDVAC and Context for the 2022 in-person meeting:

The Product Development for Vaccines Advisory Committee (PDVAC) provides external advice to WHO related to priority infectious disease pathogens, associated vaccine and monoclonal antibody product development approaches, and related manufacturing and delivery technologies. Its remit includes the prioritization of target pathogens for vaccine and/or monoclonal antibody development and technology platforms, in addition to oversight of the development of preferred product characteristics (PPCs), technical/R&D roadmaps, full vaccine value assessments and consultations on product development pathways. It specifically focuses on advancing vaccines for licensure and use in low- and middle-income countries (LMICs).

Immunization Agenda 2030: A Global Strategy to Leave No One Behind (IA2030) is the global vision and strategy for immunization, aimed toward maximizing the impact of vaccines. Within IA2030 is the need to monitor progress of vaccine development towards a shortlist of global R&D targets. As such, a prioritization framework and process are needed to align on priorities, targets, and a mechanism for monitoring and evaluation. This call for mutually defined R&D targets is in keeping with the IA2030 core principles of “people-centred, country-owned, partnership-based, and data-guided.” PDVAC has been charged with proposing the short list of pathogen targets for new vaccines (where vaccines do not yet currently exist), for endorsement by the WHO Strategic Advisory Group of Experts on Immunization (SAGE).

Key objectives of this PDVAC meeting were to:

i) review the progress towards partnering with regions to identify priority pathogens for new vaccines as indicators for IA2030 strategic priority 7 (SP7) on Research and Innovation,

ii) assess the progress of pipeline and emerging vaccine and monoclonal antibody candidates against specific pathogens, and reaffirm/identify critical activities needed to advance new products.

This was the first in-person meeting for PDVAC since 2019. PDVAC has convened virtually for topic-specific meetings since the beginning of the COVID-19 pandemic, and topics covered in recent meetings were not revisited in the December 2022 convening. Information on previous meetings can be found here.
Executive summary

The WHO Vaccine Product and Delivery Research Unit (PDR) develops several types of technical guidance to inform pathogen prioritization, to support investment in vaccine or monoclonal antibody development, and to guide developers with respect to preferred attributes, optimal development pathways and data needs. PDR and PDVAC are also supporting objective 7.2 of IA2030, to identify regional and global priority pathogens for new vaccine development. **PDVAC was broadly supportive of the types of technical guidance developed by PDR, and pathogen prioritization approach and methodology** (sections 1 & 2).

The outcomes of the pathogen prioritization survey will be deliberated and finalized through a series of consultations with stakeholders at the regional level. **Consideration of regional manufacturing initiatives will be critical in finalizing the priority pathogen list** (sections 3, 4 & 5). This pathogen prioritization work is an important consideration as the **Gavi Vaccine Investment Strategy (VIS)** (section 6) gets underway, and is due to be completed in 2024.

WHO has developed a new type of guidance, **Evidence Considerations for Vaccine Policy (ECVP, section 8)**, that provides a novel approach to facilitate early engagement and alignment across the stakeholders involved in vaccine development and those responsible for vaccine regulatory, policy, programmatic use and introduction decisions. The ECVP aims to address a chronic gap between data needs for product development for regulatory purposes and the evidence needs for policy and implementation. This guidance may be developed in collaboration with the Gavi policy team to ensure consideration of Gavi VIS criteria. **PDVAC recommended the development of an ECVP for group B Streptococcus** (section 9), given that the regulatory approval pathway is likely to be based on a correlate of protection rather than a conventional efficacy study. The ECVP framework may also be relevant to inform the development strategy for the **bivalent typhoid–paratyphoid vaccine** (section 10), which could be on the basis of demonstration of protective efficacy of the paratyphoid component in a **controlled human infection model (CHIM) in adults**, and equivalent immune responses to the TCV component in field immunogenicity trials in children in endemic settings, with commitment from developers to confirm vaccine effectiveness through post-approval studies.

**Shigella vaccines** (section 11) are also advancing in development, with the **leading candidates approaching phase III trials**, which PDVAC concurred are necessary for licensure in children and use in LMICs. It also highlighted the opportunity for parallel regulatory approval for use in adults from high-income countries on the basis of CHIM studies. **Collection of stunting and antibiotic use data in paediatric vaccine trials is essential to inform future policy decisions.** Norovirus (section 12) and enterotoxigenic *E. coli* (ETEC) (section 13) vaccine candidates are approaching late-stage development for both travellers and paediatric indications. A phase III study of the P2-VP8 candidate, a leading next-generation rotavirus vaccines candidate, was recently halted as it was shown to be non-superior to Rotarix (section 14).

More than 20 respiratory syncytial virus (RSV) vaccines are in clinical development (section 15), with one (RSV preF) approaching licensure for maternal immunization in Q3 2023. A second-generation monoclonal antibody (nirsevimab) can provide protection for the duration of an RSV season and received EMA approval in late 2022; FDA authorization is anticipated in 2023. A SAGE working group is being formed in early 2023 to review evidence for both mAbs and vaccines with the view to present to **SAGE for a policy consideration in early 2024.**
More than a million sexually transmitted infections (STIs) are acquired every day. Gonococcal infections are particularly problematic, owing to the repeated rapid development of resistance when new antibiotics are introduced. Evidence suggests that the four-component meningococcal B vaccine (4CMenB) outer membrane vesicle-based vaccine for protection against meningitis offers cross-protection against *Neisseria gonorrhoeae* (section 16). Prospective phase II and III 4CMenB studies to assess efficacy in prevention of gonococcal infection are now underway. A gonococcal indication for a MenB vaccine could increase the likelihood that MenB vaccine is introduced in LMICs that have not yet introduced the vaccine. *N. gonorrhoeae* vaccines are also in development and may soon enter clinical trials.

Development of therapeutic human papillomavirus (HPV) vaccines is a key part of WHO’s global strategy to eliminate cervical cancer (section 17). Therapeutic HPV vaccines could feasibly perform two roles for those not reached by prophylactic vaccination: (1) clearing infection or low-grade lesions; (2) treating high-grade cervical precancers. **WHO is undertaking vaccine impact modelling of these scenarios to inform development of preferred product profiles (PPCs) for therapeutic HPV vaccines.**

Since 2019, more than 1.2 million children in Ghana, Kenya and Malawi have received at least one dose of RTS,S/AS01 through their childhood immunization programmes as part of the WHO-coordinated Malaria Vaccine Implementation Programme (MVIP). Preparations are also being made for the review of R21/Matrix-M candidate vaccine (section 18). **Multiple other malaria vaccines are in development, spanning several platforms and targeting a diversity of antigens and life-cycle stages.** The pipeline includes pre-erythrocytic, blood-stage and transmission-blocking vaccines, products suitable for pregnant women and *Plasmodium vivax* vaccines. Several WHO advisory committees are in place to oversee the key technical components along the vaccine value chain. With the planned completion of the Malaria Vaccine Advisory Committee (MALVAC), **PDVAC recommended the formation of a technical advisory group (TAG) to advise on new and next-generation malaria vaccines and monoclonal antibodies in development, reporting to PDVAC.**

Multiple influenza vaccines are in the pipeline, including universal vaccines (section 19). Innovations include multiple nucleic acid-based vaccines, including quadivalent vaccines, constructs targeting conserved antigens, and combination vaccines also incorporating COVID-19 and RSV antigens. **A WHO PPC for Next-Generation Influenza Vaccines, first published in 2017, is being updated,** and work has started on development of a Full Value of Vaccines Assessment (FVVA), which will align with and inform the updated PPC. **PDVAC recommended that a TAG, reporting to PDVAC, is set up to revisit and revise the existing PPC in line with the FVVA findings.**

The Vaccine Innovation Prioritization Strategy (VIPS) continues its work to advance development of microarray patches (MAPs), heat-stable vaccines and barcodes on primary and secondary packaging (section 20). For LMICs, measles–rubella (MR) MAPs are the lead candidate, however influenza- and Covid-19-MAPs are likely to be approved in the next 3 – 5 years in high-income countries. **A preliminary list of 12 priority vaccine targets for MAPs has been developed and published for public consultation.** Several publications related to MR-MAP use-cases, demand and need for investment have been published in the last 12 months. However, **PDVAC noted the need to understand likely speed of uptake, anticipated market penetration, and willingness-to-pay** in the context of existing vaccines (at the country level).

Monoclonal antibodies have been developed for prevention of several infections, including COVID-19, *C. difficile*, anthrax, rabies and RSV, and multiple products are in the pipeline for other pathogens (section 21). **PDVAC recommended the development of guidance on the minimum acceptable product attributes**...
for mAbs targeting infectious diseases in LMICs to meet programmatic suitability, since these interventions will be used like vaccines within routine immunization programmes.

In 2019, an estimated 1.27 million deaths were attributable to bacterial antimicrobial resistance (AMR) and 4.95 million deaths were associated with bacterial AMR. The potential of vaccination to reduce antibiotic use, a key AMR driver, is included within FVVAs (section 22). **PDVAC agreed that the most feasible AMR endpoint to include in the context of an efficacy trial is reduction in antibiotic use as a secondary or exploratory measure**, and recommended engaging with regulators to socialize the need to collect data on antibiotic use and other potential indicators during phase II–III clinical development. PDVAC also noted that initial findings from the regional pathogen prioritization exercise (section 3) suggest that *Klebsiella pneumoniae* is an important pathogen for vaccine development and recommended the development of a vaccine value profile to identify research gaps.

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**Main report**

1. **Overview of the PDVAC and IVB’s vaccine product delivery research (PDR) unit scope and activities (for information)**

*Birgitte Giersing (WHO), Mateusz Hasso-Agopsowicz (WHO), Erin Sparrow (WHO)*

The WHO Vaccine Product and Delivery Research Unit (PDR) develops several types of technical guidance to inform pathogen prioritization, to support investment in vaccine or monoclonal antibody development, and to guide developers with respect to preferred attributes, optimal development pathways and data needs. The target audience of these guidance documents includes academics, vaccine product developers in the public and private sector, funders, and policymakers across global, regional and national levels. The following types of technical document have been developed or are in progress:

- **Preferred Product Characteristics (PPCs)** describe the desirable product attributes for use in low- and middle- income countries (LMICs)
- Vaccine Value Profiles (VVPs) are extensive landscape analyses that provide a high-level, holistic assessment of value for vaccine and/or monoclonal antibodies, identifying what is currently known and unknown to inform research roadmaps and Full Value of Vaccines Assessments (see below). VVPs for 19 pathogens are due to be published in a two-volume special issue of the journal *Vaccine* in 2023 and links will then be posted on the PDR website.
- **Full Value of Vaccines Assessments (FVVAs)** address gaps needed to quantitate vaccine value, based on use-case assumptions and attributes described in the PPCs, thereby bringing vaccine impact modelers, economists and disease experts together. Importantly, as well as individual benefits, FVVAs assess population-based benefits and consider health and socio-economic impact of aspects such as long-term sequelae and antimicrobial resistance (AMR), which is often neglected in value assessments and particularly important in low-income settings.
- A new type of guidance, **Evidence Considerations for Vaccine Policy (ECVP)**, has been developed for tuberculosis vaccines for disease prevention in adults and adolescents (see below). ECVPs aim to provide early information on the data and evidence that is likely to be required to support WHO
policy recommendations and implementation. The first vaccine for which this category of guidance has been developed is tuberculosis vaccines for adults and adolescents.

Members of PDVAC participate in development of these guidance documents, and the committee provides input before the final documents are published by WHO.

PDVAC had the following recommendations on PDR’s repertoire of guidance documents:

- Clarify the purposes of these various PDR guidance documents, and how they relate to each other, and communicate in a publication and on the PDVAC website, with links to relevant examples.
- With respect to the FVVAs, articulate how PDVAC and IVB’s Immunization and Vaccines-Related Implementation Research Advisory Committee (IVIR-AC) work together on specific aspects of value assessment.
- Consider an evaluation to determine whether the guidance documents developed by PDR/PDVAC are considered useful and are used by vaccine developers and other stakeholders.
- Develop a matrix of current documents by disease/vaccine area, with expiry dates, and a note about those that are being developed, for publication on the PDR website.
- Survey PDVAC members and meeting participants regarding the content, format and value of the annual PDVAC meeting to coincide with publication of the meeting report.

2. IA2030 and the SP7 working group on Research & Innovations: remit and objectives (for information)

*Kwaku Poku Asante (Kintampo Health Research Centre, Ghana & SP7 WG co-lead)*

IA2030 includes a strategic priority (SP) specific to research and innovation (SP7). Long-term objectives include strengthening local capacity to identify priorities for innovation and to leverage innovation in support of IA2030 goals; to develop and improve vaccines and associated technologies; and to evaluate and scale-up innovations.

An SP7 Working Group has been established with members from each WHO region and links to key global vaccine development stakeholders, including PDVAC. The Working Group convenes quarterly, with a coordination and alignment sub-team meeting monthly. Key focus areas for 2022–2023 have been on strengthening of local and regional capacities for immunization research and innovation, developing a mechanism to align stakeholders around key pathogens for new vaccine development, and establishing longer-term objectives based on country-led R&D priorities. Collaboration with Regional Immunization Technical Advisory Groups (RITAGs) may be a practical approach for facilitating engagement across country, regional and global stakeholders.

Specific SP7 indicators include the proportion of countries with an immunization research agenda, which is currently relatively low, and progress towards global R&D targets. For the latter, the SP7 Working Group is collaborating with PDVAC in a pathogen prioritization exercise for new vaccine development (see below). No indicator has yet been defined for evaluation and scale up of innovations.
3. **Capacity strengthening in Africa, including the establishing the mRNA vaccine manufacturing hub**

*Nicaise Ndembi (Africa CDC), Martin Friede (WHO)*

The African Union has a goal for 60% of the continent’s vaccine needs to be manufactured in Africa by 2040, up from around 1% today. The Partnerships for African Vaccine Manufacturing (PAVM), within the Africa Centres for Disease Control and Prevention (Africa CDC), was established to drive progress towards this goal.

The rapid roll-out of next-generation sequencing (NGS) during the COVID-19 pandemic has demonstrated the capacity of African countries to absorb new technologies. With global support, the number of member states with NGS capacity has increased from seven to 39, and four specialized centres, nine regional sequencing hubs and national laboratories are now operational under the Africa CDC/WHO African Region continental Pathogen Genomics Network.

WHO has made significant progress in the establishment of an mRNA manufacturing “hub” in South Africa, supporting additional manufacturing sites (“spokes”) elsewhere in Africa and in other regions. The initiative was launched in April 2021 and is being run by a public–private consortium based in Cape Town. The hub links to 15 spokes in all WHO regions, and initial training has begun. The mRNA vaccine technology platform is highly adaptable and compatible with rapid product development. The initial focus is on COVID-19 vaccine production, scale up of which is underway.

Going forward, multiple challenges need to be addressed to fully capacitate the WHO mRNA vaccine hub and spoke model, including countries’ capacity to absorb new technology, the capability of national regulatory authorities, and coordination across sites on manufacturing priorities. Capacity-building will be supported through a new biomanufacturing workforce training institute being set up in the Republic of Korea. Networks will be established to support the development and manufacturing of additional vaccines beyond COVID-19, which will be one of the topics for discussion at a network meeting in Cape Town in April 2023. The model also faces a longer-term sustainability issue: although strategically important, it is unlikely to be the most economic approach to vaccine manufacturing. In addition, global support is intended to be catalytic, and it is important that countries and regions also invest in vaccine manufacturing capacity-building.

4. **Partnership with regions to prioritize pathogens for vaccine development (for recommendation)**

*Birgitte Giersing (WHO), Mateusz Hasso-Agopsowicz (WHO), Erin Sparrow (WHO), Angela Hwang (Bridges to Development)*

The IA2030 SP7 pathogen prioritization exercise (see section 2) is designed to identify global and regional priorities for new vaccine development (i.e., for pathogens for which vaccines do not yet exist). A shortlist will be presented to SAGE for endorsement in 2023.

A landscaping analysis was used to identify 24 potential pathogen targets. These are being assessed against eight criteria, including disease burden, social and economic impacts, disruption due to outbreaks, contribution to inequity, antimicrobial resistance challenges, and existence of alternative control
measures, using a five-point scale. Scores for pathogens are generated by region and globally, to reflect differing epidemiology and context.

To generate a pathogen ranking, a preferences survey based on multi-criteria decision analysis (MCDA) is being used, through which respondents prioritize based on multiple pairwise comparisons between anonymised pathogens across a range of criteria. For each respondent, the survey generates a weighting of the criteria and this maps to a ranking of the pathogens.

Starting in November 2022, online surveys tailored to each region were widely shared with regional and country stakeholders. A preliminary analysis of feedback indicates that TB, HIV and malaria are highly prioritized across most regions and some pathogens are ranked low in all regions. Between these extremes, rankings vary by region. Data collection is ongoing, in order to increase the number of responses from each region. An update on progress will be provided to SAGE in March 2023 and regional consultations will be held in 2023 to discuss the findings and rankings, and to consolidate the final priority pathogens per region.

• Does PDVAC have any recommendations for the pathogen prioritization approach?
  
  o PDVAC was broadly supportive of the approach and agreed that the MCDA methodology is appropriate to identify pathogen priorities for vaccine development at the regional level. However, PDVAC suggested that:
    - Additional inputs, ideally from NITAG and RITAG members, are required to ensure that the outputs will be representative and robust.
    - Where feasible, use of national-level data should be considered to ensure greater accuracy and buy-in.
    - The planned consultations at the regional level include materials that are reviewed by disease experts.
    - Interim assessments should be considered to ensure that input is broadly representative and from key stakeholders.
    - The secretariat set expectations for presentation to SAGE; the regional pathogen priority lists will not be finalized by the March SAGE meeting, as further consultation at the regional level will be needed.
  
  o As the preferences survey is complex, PDVAC recommended that the secretariat ensure participants are aware at the outset of its duration and the cognitive effort that will be required to complete the exercise.
  
  o PDVAC will review the regional priority pathogen lists and recommend those that should be considered “global pathogen priorities”, based on the common findings across regions.

• Does PDVAC have any recommendations for effective ways to engage/consult with regions on pathogen prioritization and the broader research and immunization agenda?
  
  o PDVAC made the following recommendations:
    - Engage with partner agencies (e.g. UNICEF, PATH), the mRNA manufacturing hub network, and particularly professional societies within countries, to solicit additional responses.
    - Circulate the survey through the International Society for Infectious Diseases, as members are frequently current or past NITAG members.
Seek increased executive sponsorship for the exercise, including endorsement of the approach and potential convening of regional partners to solicit additional responses.

- Describe how this methodology of prioritization may apply to other questions that likely resonate more with country and regional stakeholders (e.g. prioritizing existing vaccines for implementation and identifying implementation research gaps).

- Ensure that survey respondents are representative in terms of characteristics such as organizations they work for (e.g. government, manufacturers, academia); if not, some kind of weighting of responses may be needed to ensure representativeness.

- Identify possible confounders such as professional and educational background.

5. **Panel discussion: Bridging the gap between global, regional and country priority setting**

Moredreck Chibi (WHO Regional Office for Africa), Raman Rao (Hilleman Laboratories and PDVAC member), Debbie King (Wellcome), Helen Rees (Wits University, South Africa and RITAG chair, African Region), Ghassan Dbaibo (American University of Beirut, Lebanon and member of Lebanon NITAG).

A panel discussion explored some of the key issues related to pathogen prioritization and acceleration of vaccine development and implementation in LMICs. Key themes included:

**The value of pathogen prioritization to ensure alignment across stakeholders:** It was generally agreed that prioritization is important to orient the work of a range of stakeholders. It provides a basis for engaging with developers to explore and promote opportunities for new product development and to identify potential barriers. It can help funders prioritize their activities and align actions with fellow funders. It can also focus early attention on the identification of pathways to licensure.

While prioritization has also been applied to platform technologies, with a heavy focus on mRNA vaccine manufacturing capacity, it was stressed that this platform may not be a suitable platform for all pathogens, and that each platform has its own unique technical challenges. Nonetheless, there is an intent to assess how/if the regional priority pathogen list can be applied to the mRNA platform, particularly in the context of the regional mRNA manufacturing initiative, and the potential opportunities for mRNA vaccine developers.

Prioritization can also help to address uncertainties and evidence gaps and encourage investment in new product development. Pathogen prioritization relies on accurate data, particularly to provide estimates of disease burden and hence the value of prevention through vaccination. There are concerns that insufficient data are available in some LMIC settings, which could affect prioritization. Efforts may be needed to make country data more widely available while additional epidemiological studies could help to close data gaps. A priority pathogen list could therefore complement WHO /global level guidance relating to specific types of vaccine/indications that outline preferred characteristics, data requirements, and potential value, which provide developers with greater clarity and can instill confidence in decision-making. It was emphasized that the R&D / prioritization process should be a dynamic initiative, with increased ownership by regional and country level stakeholders over time.
The importance of engaging at all levels: Many different stakeholders have an interest in new vaccine development, across the public and private sectors, at national, regional and global levels, and in different country settings. In terms of pathogen prioritization, different stakeholders may have differing perspectives on priorities according to their local context and specialist interests.

More generally, many groups need to be engaged to accelerate development and implementation of new vaccines. Vaccine developers play a critical role in chaperoning new products through to programmatic use. Early engagement with vaccine developers is vital to communicate global public health priorities, to identify opportunities and potential barriers, and to establish partnerships that can drive forward the development, licensing and implementation of vaccines that meet key public health needs. Engagement with investors may also help to encourage financing for products for neglected markets.

Taking a holistic approach to capacity-building: It was widely agreed that further capacity-building is essential in LMICs, and should consider the full spectrum of activities required to develop, license and implement new vaccines, not just manufacturing. This includes laboratory science capacity and clinical science infrastructure required to host regulatory-standard clinical trials, human research capacity across all areas of vaccinology, including laboratory science, clinical research, biomedical science, social science and implementation science, and regulatory capacity (and regulatory science capacity).

Although more trials are being carried out in LMICs, in many cases the main role of trial sites is data collection. It was argued that scientific leadership needs to be strengthened so that researchers in LMICs can play a more prominent role in international partnerships.

As well as this integrated approach, it was argued that capacity-building needs to take a long-term perspective, continuing the move away from project-by-project funding towards more sustainable solutions, including support for flexible multi-purpose networks. There are opportunities to build on existing excellence and to build capacity in new areas, bearing in mind the need for long-term sustainability.

Limited financial resourcing remains a major barrier to capacity-building. As well as building academic research capacity, there is also a need to strengthen regulatory capacity, taking advantage of WHO’s maturity-level framework for national regulatory authorities. Capacity also needs to be strengthened in other areas, particularly NITAGs, which are being asked to play an increasingly important role in national policymaking, are typically poorly resourced, and have experienced heavy workloads due to COVID-19 and other outbreaks.

Applying lessons learned: It was argued that success stories may provide important lessons that can be applied more generally. Examples cited included the successful building at speed of genomics capabilities in Africa during the COVID-19 pandemic and the rapid implementation of pre-exposure prophylaxis (PrEP) for HIV prevention in Africa. The latter was felt to illustrate a range of critical factors, including the value of conducting studies in Africa, which generated confidence among policymakers in trial data and built expertise in implementation. In addition, potential challenges were identified early on and addressed.
in implementation, while effective planning as soon as positive data were obtained enabled demonstration projects to begin immediately after licensing decisions.

6. Update on the Gavi Investment Strategy

Marta Tufet Bayona (Gavi, the Vaccine Alliance)

Gavi is initiating a new Vaccine Investment Strategy (VIS) in 2023. Updated every five years, the VIS informs decision-making on inclusion of vaccines in the Gavi portfolio, based on the likelihood that new vaccines will be available within the next Gavi funding cycle.

VIS development is based on a landscape analysis of both pipeline and existing vaccines, and application of an evaluation framework to generate a shortlist for which investment cases are developed. The evaluation framework is retained from previous VIS cycles but is updated to reflect changing circumstances. Final decisions on investment cases for vaccines will be made by the Gavi Board in mid-2024 for inclusion into the portfolio in Gavi 6.0 (2026–2030) subject to successful funding replenishment.

Primary scoring criteria relate to factors such as potential public health impact, value for money, equity, economic impact, and global health security (including AMR relevance). Multiple secondary criteria, such as feasibility of implementation, are also considered, as well as financial considerations (e.g., vaccine cost). For pipeline vaccines, the likelihood of licensure by 2030 is a key criterion.

Demand forecasting and impact modelling are carried out, alongside more qualitative assessments in areas such as epidemic potential, AMR relevance and implementation feasibility. Possible investment decisions include a traditional vaccine programme to support routine immunization, development of a stockpile to support outbreak response or creation of a learning agenda to close evidence gaps on delivery. An independent VIS Steering Committee has been established, chaired by Professor Helen Rees (Witwatersrand University, South Africa).

Some planned introductions from the 2018 VIS were paused because of the COVID-19 pandemic. How and when to restart these programmes will be discussed at Gavi’s Programmes and Policy Committee in May 2023.

7. The role of correlates of protection in accelerating vaccine licensure (for recommendation)

Debbie King (Wellcome Trust)

In 2021, Wellcome published an analysis of the factors driving vaccine developer decision-making and barriers to implementation. This analysis identified 16 priority challenges, including lack of correlates of protection for certain pathogens.

Correlates of protection are likely to be of particular importance for candidates following alternative regulatory pathways (for example when field efficacy trials are not feasible), for extending use of vaccines to new populations (immunobridging), and for licensing based on comparisons with previously approved vaccines.

In September 2022, Wellcome organized an international multi-stakeholder workshop to explore data requirements for use of correlates of protection at different stages of vaccine development, including...
licensure and policymaking. The workshop examined the issues around correlates for a range of important pathogens, from developer, regulator and policymaker perspectives.

Workshop activities included development of a prototype “data purpose matrix” which, for each pathogen, would outline the evidence required to support use of correlates in early vaccine development, licensure and policymaking. A draft data purpose matrix was developed for group B streptococci (GBS).

Important priorities identified at the workshop included the need for an evidentiary framework to assess the quality of evidence required to support different uses of correlates data in licensing; coordination of efforts to define and validate correlates of protection; standardization of assays, reagents and procedures; and improving understanding of mucosal immune responses and the role of T cells as correlates of protection.

Recommendations:

- Does PDVAC have any comments on the data purpose matrix (e.g. on potential use cases and when/how it could be developed for a given pathogen)?
  - PDVAC made the following comments:
    - The data purpose matrix is an important strategic alignment tool that could help to identify the data that will be needed to define an immunological marker as a correlate of protection, and to potentially accelerate licensure. However, it is not yet clear how regulators would be engaged in its development or how the guidance would be used as part of formal scientific advice.
    - The matrix will need to identify, appropriately cross-reference and build upon existing guidelines on correlates of protection, such as WHO’s Correlates of vaccine-induced protection: methods and implications, and the correlates frameworks developed by other groups, for example the Gates Medical Research Institute.
    - This tool may be useful for streamlining and clarifying the process for accelerated licensure based on a correlate of protection. It also needs to consider the evidence expectations for WHO policy recommendations, since a pathway to policy is a pre-requisite for WHO prequalification, and the likely need for post-licensure evaluation to confirm efficacy/effectiveness. Alignment of data needs for both licensure and policy are needed to ensure timely and equitable access of new vaccines, and to map pathways for generating effectiveness data for policy consideration to avoid an introduction gap, particularly in LMICs.
    - The Evidence Considerations for Vaccine Policy (ECVP) framework (see below) may be a useful complement to the data purpose matrix to communicate anticipated data and evidence needs for policy decision-making.
    - The data purpose matrix could be a useful appendix or cross-reference to other WHO guidance documents, such as PPCs and ECVPs.

- Can the committee comment on the utility of the evidence quality framework for assessing biomarker evidence?
  - PDVAC felt that this tool is a potentially useful framework but requires additional feedback from stakeholders (see below).
Would publishing these two concepts now be useful or confusing in the context of other PDVAC strategic and tactical tools (i.e. VVPs, PPCs, Roadmaps, FVVAs, ECVPs)?

- PDVAC made the following comments:
  - Wellcome should publish its initial work on the data purpose matrix and evidence quality framework, and solicit feedback from stakeholders on the value of these tools and how they might be used.
  - PDVAC should consider how the data purpose matrix complements existing guidance and PDVAC tools/processes.

8. Evidence Considerations for Vaccine Policy (for recommendation)

Birgitte Giersing (WHO)

WHO’s ECVP framework provides a novel approach to facilitate early engagement and alignment across the stakeholders involved in vaccine development and those responsible for vaccine regulatory, policy, programmatic use and introduction decisions. Developing ECVP guidance prior to phase III study design, and proactively generating policy-relevant evidence as part of, or in parallel to, clinical development, rather than reactively post-licensure, creates an opportunity to accelerate vaccine policy formulation, adoption and impact, particularly in LMICs.

Is the ECVP framework useful for vaccines with an ‘atypical’ licensure and policy pathway, identifying important policy considerations for developers and other stakeholders?

- PDVAC agreed that the ECVP framework is very useful for highlighting gaps in the data anticipated to be needed for vaccine policymaking and implementation decisions. For now, ECVPs should be prioritized for vaccines that will be reviewed through less standard regulatory pathways (e.g. GBS vaccines, see below).

Does PDVAC agree that, where it exists, an ECVP supersedes a PPC and there is no need to update the PPC?

- PDVAC agreed that Table 1 of the ECVP effectively updates the PPC. PDVAC recommended updating the PPC to include Table 1 of the ECVP, generating a ‘PPC 2.0’, and cross-referencing the ECVP document for broader context.

- PDVAC suggested that PDR clearly articulate how the PPC and ECVP relate, including the stage of development for both and the anticipated timelines for revision.

9. Group B Streptococcus (for recommendation)

Annelies Wilder-Smith (WHO), David Goldblatt (UCL), Richard Isbrucker (WHO)

Globally, there are an estimated 390,000 cases of invasive group B streptococcal (GBS) infection in infants each year, with 91,000 (44,000–187,000) child deaths and 46,000 (20,000–111,000) GBS-related stillbirths.

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1 Building the concept for WHO Evidence Considerations for Vaccine Policy (ECVP): Tuberculosis vaccines intended for adults and adolescents as a test case: https://www.sciencedirect.com/science/article/pii/S0264410X21013955
annually, mostly in sub-Saharan Africa. Two types of GBS vaccine are in the pipeline – polysaccharide conjugate vaccines and protein-based candidates.

The FVVA for maternal immunization against GBS was published in November 2021. It concluded that maternal immunization was likely to be cost-effective and feasible to implement, although some important evidence gaps remain. Given that a phase III efficacy trial may not be practicable due to the required sample size, there is likely to be a need to identify an alternative pathway to licensure. A key priority is therefore to validate reliable correlates of protection. A WHO GBS vaccine Technical Advisory Group (TAG) has been established and an in-person consultation is planned to take place in the global South in 2023. The focus will be on dialogue with regulatory authorities on the potential for conditional approval based on immunogenicity data followed by phase IV effectiveness studies.

Positive phase I/II data have been reported following maternal immunization with the Pfizer hexavalent polysaccharide conjugate vaccine, which covers 97% of disease-causing strains. In 2022, the Pfizer vaccine was granted EMA PRIME and FDA Breakthrough Therapy status to accelerate review. Full results of an ongoing phase II safety and immunogenicity study in pregnant women are expected in early 2024. The Bill and Melinda Gates Foundation (BMGF) has provided funding to accelerate late-stage development and WHO prequalification, including support for development of an affordable multidose vial.

Phase I data have been published for the most advanced protein-based vaccine, developed by Minervax. A second-generation vaccine with additional antigens has been developed and a phase II study is underway in two African countries. The Minervax vaccine has also received EMA PRIME designation.

For polysaccharide-based and protein-based candidates, there is potential for an accelerated licensure pathway based on functional and/or polysaccharide- or protein-binding antibody responses as a correlate of protection. In 2018, FDA’s Vaccines and Related Biological Products Advisory Committee (VRBPAC) signalled a willingness to consider correlates of protection data in licensing of polysaccharide-based candidates. A 2021 workshop convened by BMGF outlined the steps required for validation of GBS polysaccharide correlates. Several ongoing case-control studies are collecting data in high- and low-income countries to facilitate further correlates analyses. A consortium of academic, regulatory and

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industry laboratories has also been established to develop, validate and promote the use of standardized assays and reference reagents to facilitate correlates data meta-analyses.

Three possible regulatory pathways could be envisaged towards marketing authorization of a GBS vaccine: traditional licensing following a phase III efficacy trial; accelerated approval based on immunological endpoints assessed within an efficacy trial; or approval based on immunological endpoints followed by a phase IV effectiveness study. Given that traditional licensing will be the least likely pathway due to the impracticality of large sample size, discussing the acceptability of immunological endpoints to regulators in LMICs is pivotal. The implications for WHO prequalification processes and norms and standards development also need to be considered, should a conditional approval pathway be followed.

- **Would development of an ECVP for GBS vaccines be helpful?**
  - PDVAC recommended that an ECVP be developed for GBS vaccines. However, there is a need for broader alignment on the proposed regulatory pathway(s), through consultation with national regulatory authorities (NRAs) in the countries where the vaccines are likely to be used. This is a prerequisite for ECVP development, since the proposed regulatory strategies would be socialized with policymakers as part of the ECVP development process.
  - Many sections of the ECVP would be common for both types of candidate vaccine in development (polysaccharide and protein-based); PDVAC recommended that a single ECVP document be produced, stratified by platform where necessary.

10. **Salmonella Paratyphi A and TCV–Paratyphi A bivalent vaccines (for recommendation)**

   *Adwoa Bentsi-Enchill (WHO), Cal MacLennan (BMGF), Andrew Pollard (University of Oxford)*

*Salmonella* Paratyphi is a cause of enteric fever (alongside *Salmonella* Typhi), accounting for around one in four cases. Most clinical cases involve serogroup A. *Salmonella* vaccine development focuses on monovalent vaccines, bivalent vaccines covering *Salmonella* Typhi and Paratyphi A, and multivalent vaccines also protecting against non-typhoidal *Salmonella* (NTS).

Two monovalent vaccines for *Salmonella* Paratyphi A are in phase II trials: CVD 1902 (University of Maryland and Bharat Biotechnology), an oral live-attenuated candidate being evaluated in a human infection study in Oxford, and O:2-TT (Lanzhou Institute of Biological Products), consisting of O-antigen conjugated to tetanus toxoid, for which limited information is available. A *Salmonella* Paratyphi A human infection study has found that symptoms may be milder than those associated with *Salmonella* Typhi infection7. Unlike *Salmonella* Typhi, *Salmonella* Paratyphi A infection is associated with protection against re-infection.

Data from TypBar-TCV trials in Asia showed good vaccine efficacy (79%) over two years. Five-year efficacy data from Asia should be available in 2023 and will indicate whether a booster dose is required. There are

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some indications that the incidence of *Salmonella* Paratyphi A enteric fever increases when typhoid conjugate vaccine (TCV) is introduced, potentially due to colonization of the ecological niche previously occupied by *Salmonella* Typhi. However, an increased incidence of *Salmonella* Paratyphi A disease has also been seen at some sites where TCV is not being used.

At least four bivalent enteric fever candidates based on licensed TCVs are in preclinical or phase I development. These could be particularly suitable for South Asia where typhoid and paratyphoid A fever are both common. A phase I study of a bivalent glycoconjugate enteric fever vaccine (Vi-TT and O:2-DT; Serum Institute of India) has recently been completed, with data analysis due to take place in early 2023. A phase II human infection study is scheduled for 2023 and a phase III immunogenicity trial could be conducted in South Asia, beginning in 2023. A second bivalent glycoconjugate enteric fever vaccine, consisting of the WHO-prequalified TCV, TYPHIBEV, in combination with O:2-CRM197 (Biological E/GSK Vaccines Institute for Global Health), is also being evaluated in a phase I study.

Phase III vaccine efficacy studies will be difficult to conduct for *Salmonella* Paratyphi A due to the relatively low incidence of paratyphoid A fever. It may be possible to obtain efficacy data from a human infection study, which could be used to support licensing of a travellers vaccine. For use in endemic countries, challenge data would need to be supplemented by field immunogenicity data. A bivalent vaccine may be considered an “extended-valency” TCV, potentially allowing licensure on the basis of non-inferiority to a licensed TCV in field immunogenicity studies. However, this approach needs to be verified with regulatory agencies.

- Are there adequate data on strategies for a bivalent typhoid–paratyphoid vaccine to define a way forward for accelerating vaccine development? If not, what are the gaps and what data are required? Is the ECVP framework an appropriate tool for the bivalent vaccine?
  - PDVAC supported a proposed regulatory pathway for the bivalent conjugate vaccine based on:
    - Demonstration of immunologic non-inferiority of the typhoid component in comparison to licensed TCVs.
    - For the paratyphoid component, demonstration of protective efficacy in a CHIM study with adults, equivalent immune responses in field immunogenicity trials in children in endemic settings, and commitment from developers to confirm vaccine effectiveness through post-approval studies.
  - PDVAC recommended determining if the FVVA for bivalent combination vaccines is favourable before making a decision to develop an ECVP.
  - PDVAC suggested that prioritization of a TCV–Paratyphi A bivalent vaccine should also be informed by the regional pathogen prioritization exercise (see above), and discussion of the potential benefits of a combination vaccine with regional stakeholders.
  - PDVAC concluded that, if warranted by vaccine value and demand, an ECVP would be a useful tool for alignment on policy considerations, once there is consensus on the proposed pathway to regulatory approval in adult and paediatric populations.
• What evidence will be required to support CHIM data for the regulatory and policy pathways for a bivalent typhoid–paratyphoid vaccine?

  o Previous paratyphoid challenge studies have demonstrated a range of immune responses, but a clear correlate of protection has not been defined. PDVAC agreed that a CHIM study could provide evidence on whether anti-LPS antibodies (or other immune markers) are protective in naive adults, and could support expansion of the valency of the existing TCV vaccine to include Paratyphi A.

11. Shigella (for recommendation)

Bill Hausdorff (PATH), Cal MacLennan (BMGF), Birgitte Giersing (WHO), Patricia Martin (LimmaTech)

Shigella is the leading bacterial cause of death from diarrhoeal disease globally, with deaths peaking in the second year of life. Public health challenges – and value drivers for a Shigella vaccine – include high levels of antimicrobial resistance, an association with stunting and detrimental impact on cognitive development.

Protection is associated with levels of IgG against O-antigen. Multiple vaccines are in the pipeline, including subunit-based candidates and live-attenuated candidates. A WHO PPC for Shigella vaccines was published in 2021. For O-antigen-based candidates, a quadrivalent vaccine is preferred that includes the most prevalent serotypes. The leading Shigella candidate, the quadrivalent O-antigen-based vaccine developed by LimmaTech Biologics, has been tested in the target population of young children and infants in LIMCs, and is expected to enter phase III clinical studies in 2025.

Multiple Shigella human infection vaccine studies and phase I/II trials have been undertaken or are in progress. The Enterics For Global Health (EFGH) consortium has been established to facilitate phase III studies, by generating epidemiological data at potential study sites and ensuring the readiness of potential trial sites.

A PATH consultation with national stakeholders and service providers in LMICs in Africa and Asia has provided insight into the perceived feasibility and acceptability of Shigella vaccines. National stakeholders considered Shigella a lower priority than did providers, in part because of uncertainties regarding disease burden and concerns about additional injections. Perspectives changed when more information was provided about antimicrobial resistance and links to stunting.

Modelling suggests a vaccine that prevents less severe as well as moderate to severe Shigella diarrhoea, and especially stunting, could deliver significant long-term economic benefits. Although these vary by region, benefits are anticipated in all regions, and even at relatively low vaccine efficacies.

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Parallel regulatory strategies could be envisaged for dual markets – children in LMICs and adult travellers in high-income countries. Data from human infection studies might be sufficient for approval for travellers but a field efficacy trial will be required before licensing for use in children. Conditional marketing authorization is not a viable option as *Shigella* is not considered a public health emergency. Dialogue with policymakers could include discussion of the impact of *Shigella* vaccines on stunting and AMR, and long-term benefits of infection prevention.

- What are the necessary types of clinical and microbiological outcomes (i.e. what needs to be measured) in a phase III efficacy study for a stand-alone *Shigella* vaccine for under-5-year-olds in LMICs?
  - PDVAC agreed that a phase III efficacy study is necessary for licensure in children and use in LMICs. It also highlighted the opportunity for parallel regulatory approval for use in adults from high-income countries on the basis of CHIM studies.
  - PDVAC suggested that collection of stunting data in paediatric vaccine trials is essential – even as a secondary endpoint – as it is likely to be important for policy recommendations. Stunting can be observed within 3 months as a minimum, with more pronounced effects seen at 6 months and 1 year.
  - PDVAC noted that collection of antibiotic use data, or vaccine impact on cases or deaths due to a resistant pathogen within a phase III efficacy study, will be the most feasible indicators of potential impact of a vaccine on AMR; additional data such as on changes to the proportion of resistant isolates will need to be collected post-licensure.
  - Efficacy of the candidates against various circulating serotypes (within the vaccine and beyond) will be important for policy considerations.

- Other than what is presented, is there other critical information that is needed to convey the potential impact of a *Shigella* vaccine and prepare for a potential policy recommendation?
  - PDVAC concluded that, while collection of data on stunting during the phase III trial is important, more work is needed to strengthen the causal link between *Shigella* infection and stunting, and to determine the impact of stunting on social and economic well-being. In particular, it is essential to establish consensus on the proposed case definition of moderate-to-severe growth stunting (height-for-age z-score less than −2). The data purpose matrix and evidence quality framework developed by Wellcome (see above) may be useful tools in this regard.
  - PDVAC recommended that sites with varying levels of *Shigella* incidence and antibiotic resistance be included in the phase III study.

12. Norovirus (for information)

*Astrid Borkowski (HilleVax)*

Highly contagious norovirus is a particular threat to young children and older people. The most advanced candidate is HIL-214, HilleVax’s virus-like particle vaccine comprising VLPs for GI.1 and GII.4 genotypes,
respectively. Phase I and IIb studies have been completed, with safety data generated on 4,500 participants and immunogenicity data on 2,200 subjects. Two CHIM studies have also been conducted.

A field efficacy study has been carried out in a cohort of US Navy recruits, using the final adult single-dose formulation. Few cases accrued in year 1 but good efficacy was seen after year 2 (80% against vaccine strains, although not reaching statistical significance due to the small number of cases)\(^\text{10}\). Protection of 62% was seen against any norovirus strain \((p<0.05)\) and, unexpectedly, a post hoc analysis revealed evidence of cross-protection against GII.2 strains. No significant safety concerns have arisen.

A phase IIb study in infants has been initiated in 2022 and enrolment is proceeding in the US and Latin America; planning for a subsequent phase III study is based on a successful outcome. The effects of co-administration with other paediatric vaccines will also be assessed in the near future. It is anticipated that immunobridging could allow extension to additional age groups. Considerations on a possible efficacy/effectiveness study in older adults are subject to negotiation with authorities. A scientific advisory board has been established, and the company is aiming for approval in the US before 2030. A review of other candidates in development was recently published\(^\text{11}\).

- PDVAC recommended that the developers of the leading norovirus candidate (HilleVax) discuss the proposed phase III clinical design and regulatory strategy with the WHO Regulation and Prequalification team.

13. **Enterotoxigenic E. coli (ETEC) (for information)**

*Lou Bourgeois (PATH)*

Uncertainties surrounding the disease burden and therefore full value of ETEC vaccines have had an impact on donor funding for development of vaccine candidates, although some progress continues to be made. A WHO PPC is available and a stakeholder roadmap that identifies priority activities to enable product development, licensure and global access has been published\(^\text{12}\).

As well as the impact of ETEC infections on mortality, there is accumulating evidence, from field and human infection studies, of their impact on environmental enteric dysfunction (EED), which is likely to have long-term implications for health and development. If EED is preventable by vaccination, this could significantly strengthen the value proposition for ETEC vaccines. In addition, the growing recognition that ETEC is an expanding AMR threat, and the assumption that an effective vaccine may contribute to a reduction in antibiotic use, could also further strengthen the ETEC vaccine value proposition.


Three ETEC vaccine candidates are currently in active clinical development, with one candidate, the parenteral fimbrial tip adhesin (FTA), awaiting funding for a phase II CHIM study. A Shigella–ETEC combination oral vaccine (ShigETEC) has completed initial phase I studies in Europe; a phase II human challenge studies and a phase Ib study in an endemic country (Bangladesh) are scheduled for 2023/2024. Another candidate oral, live-attenuated Shigella–ETEC combination vaccine expressing Shigella serotype-specific O-antigen, as well as CFA/I and LTA2B genes from ETEC (CVD 1208-122), began clinical studies in November 2022.

The most advanced ETEC vaccine candidate is ETVAX, a multivalent vaccine containing four of the most common colonization factors plus an LT toxoid and a dMLT adjuvant, which may also offer some cross-protection against other colonization factors. This candidate demonstrated protective efficacy in Finnish adult travellers and safety and immunogenicity in a dose-finding study in young children and infants in Zambia. It is currently being evaluated in a phase IIb study in 6–23-month-olds in the Gambia, with top-line results expected in March 2024. In addition, progress has been made in developing a vaccine formulation and presentation that is more suitable for implementation in the target populations of young children in LMICs and travellers.

A dual market regulatory strategy may be feasible for ETVAX. Discussions are being held with the FDA on the possibility of using CHIM study data for licensing of a vaccine for travellers. Pending the outcome of the Gambian phase II study, a pivotal phase III trial is projected to take place in Zambia, potentially beginning Q3 2024. Following agreements on technology transfer, ETVAX manufacturing is due to take place in the Republic of Korea.

- PDVAC recommended that the developers of the leading ETEC candidate (Scandinavian Biotech) discuss the proposed phase III clinical design and regulatory strategy with the WHO Regulation and Prequalification team.

14. Next generation rotavirus vaccine (for information)

*Duncan Steele (Bill & Melinda Gates Foundation)*

Global rotavirus surveillance suggests that rotavirus accounts for around 40% of all hospitalizations due to diarrhoeal disease, leading to the deaths of an estimated 200,000 children. Accumulating evidence demonstrates that introduction of vaccination against rotavirus reduces hospitalizations due to rotavirus infection, although the burden of disease remains high.\(^{13}\)

Several next-generation vaccines with improved characteristics, and which may also ease programmatic delivery, are in pre-clinical or early clinical development. However, a phase III trial of NRRV P2-VP8, an injectable non-replicating candidate, was halted due to futility in assessment of superiority to Rotarix\(^{14}\).

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Nevertheless, development of next-generation rotavirus vaccines remains a priority given their potential advantages, including higher efficacy in LMICs.

15. Respiratory syncytial virus (RSV) (for information)

*Erin Sparrow, (WHO); Danny Feikin, (WHO); Heather Zar (University of Cape Town)*

RSV is one of the world’s leading causes of childhood mortality, with 99% of deaths occurring in LMICs. It is the most common cause of paediatric hospitalization due to lower respiratory tract infections (LRTI), and nearly half of RSV-associated deaths occur in infants under 6 months of age. Community-based surveillance initiatives have identified RSV as an important cause of deaths in the community in LMICs. RSV is also a major contributor to the burden on paediatric health services in LMICs. In addition to a reduction in RSV-associated LRTI, RSV prevention has been shown to reduce all-cause medically attended LRTI and antibiotic prescribing.

Given the growing pipeline of RSV immunization candidates, in 2016, SAGE recommended preparations be made for introduction of maternal RSV vaccination and long-acting monoclonal antibodies. A TAG was established in 2017, PPCs have been developed for RSV vaccines and monoclonal antibodies, an R&D roadmap has been published, and regulatory guidelines for vaccines have been made available (regulatory guidelines for monoclonal antibodies for infectious diseases will be published in 2023, with a supplement on RSV to follow in 2024). A VVP for maternal vaccination and RSV monoclonal antibodies is due to be published shortly and an RSV “roadshow” is planned to raise awareness of RSV and RSV immunization products to support national decision-making in the near future. RSV monoclonal antibodies and maternal vaccines were approved in the 2018 Gavi Vaccine Investment Strategy (VIS) for Gavi support for the period 2021-2025 contingent on there being products licensed, a SAGE recommendation, prequalification and affordable pricing. However investments were put on pause due to COVID-19 and a decision to un-pause or re-evaluate the 2018 VIS recommended vaccines is expected in early 2023.

An RSV monoclonal antibody, palivizumab, was licensed in the late 1990s but its high cost restricts use to high-risk groups in mostly high-income countries. In addition, it must be administered once every month during the RSV season, making it programmatically challenging to deliver. A second-generation monoclonal antibody, nirsevimab, has an extended half-life and a single dose can provide protection for

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the duration of an RSV season\textsuperscript{19}; it received EMA approval in late 2022\textsuperscript{20} and FDA authorization is anticipated in 2023. Other RSV monoclonal antibodies are in the pipeline.

More than 20 RSV vaccines are in clinical development\textsuperscript{21}. The most advanced vaccine candidate for is the Pfizer pre-fusion protein F vaccine for maternal immunization and subsequent protection of infants through maternal antibodies. Interim phase III results were positive, with protective efficacy of 69\% against severe RSV infection\textsuperscript{22}, and an FDA submission was accepted for review of evidence in late 2022 with approval anticipated in Q3 2023. The phase III trial includes participants from several Latin American and African countries. The current presentation is a lyophilized single-dose vial and, with BMGF funding, a multi-dose vial presentation is being developed for LMIC markets.

A SAGE working group on RSV will be formed in early 2023 with the view to present to SAGE for policy recommendations in early 2024. Vaccine prequalification is likely to occur by mid-2024 at the earliest. Monoclonal antibodies will follow the medicines prequalification pathway as further described in section 21.

A TAG has been considering likely data needs for policy recommendations. It concluded that the maternal vaccine and monoclonal antibodies should work equally well in LMICs. In women living with HIV, good antibody transfer across the placenta is seen if HIV is well controlled; in addition, the Pfizer vaccine induces high titers of RSV neutralizing antibodies, which should mitigate the effects of suboptimal transplacental transfer observed in uncontrolled HIV, malaria, and other conditions affecting pregnant women in LMICs. In October 2022, SAGE recognized the need for speed and equity, and suggested RSV vaccination had the potential to achieve major impact in LMICs. However, SAGE also recognized the many competing health priorities in LMICs and that the current phase III efficacy trials might not provide sufficient evidence for decision making in these resource constrained settings. Therefore, in parallel with regulatory, policy and financing decisions, SAGE recommended that an additional study be carried out to assess full public health benefits of RSV prevention with a focus on outcomes and trial sites relevant to LMIC context.

In addition, post-marketing studies could be used to examine impacts on long-term morbidity (e.g. wheezing, asthma), antibiotic use, other infections and childhood developmental trajectory.

Current WHO activities include inputting into the design of the full-impact study, drafting of articles on secondary benefits, planning for the RSV roadshow, and continuing monitoring of the vaccine pipeline. As mentioned above a SAGE Working Group on RSV monoclonal antibodies and vaccines will be established in early 2023 to undertake the preparatory technical work for a SAGE decision in early 2024.

\textsuperscript{21} https://www.path.org/resources/rsv-vaccine-and-mab-snapshot/
PDVAC agreed that there is no need to develop an ECVP for RSV vaccines or monoclonal antibodies for maternal immunization or infant populations, given their stage of development (phase III studies completed and regulatory approval in place or application filed). Other technical products for RSV have already been developed as mentioned previously.

PDVAC agreed that the planned studies to assess the full impact of RSV disease prevention in infancy should not delay the introduction of RSV interventions in LMICs, where the greatest burden of severe RSV infection lies. PDVAC fully supported potential accelerator mechanisms that are in discussion, and recommended holding a future PDVAC session on this topic to discuss the activities that are being undertaken to prepare for uptake in LMICs.

PDVAC recommended that Gavi market shaping for RSV monoclonal antibodies be considered (contingent on Vaccine Investment Strategy 2024 discussions).

In the context of IA2030 and immunization throughout the life-course, PDVAC recommended additional information should be sought on the burden of RSV in older adult populations in LMICs (using country-specified definitions), perhaps by leveraging the Global Influenza Surveillance and Response System. This work may lead to an assessment of the value of a combined influenza–RSV vaccine for older populations.

16. Vaccines for sexually transmitted infections (for recommendation)

Carolyn Deal (NIAID, NIH)

More than a million STIs are acquired every day. The importance of interactions between HIV, hepatitis and STIs is widely recognized, with the infections now often being considered collectively in control strategies. WHO PPCs have been produced for herpes simplex virus (HSV) and gonococcal vaccines, while WHO and the US National Institute for Allergy and Infectious Diseases developed an STI vaccine R&D roadmap.

Gonococcal infections are particularly problematic, owing to the repeated rapid development of resistance when new antibiotics are introduced. The US CDC considers Neisseria gonorrhoeae infection to be an urgent threat, and WHO considers it a high priority. Although no gonococcal vaccine exists, retrospective analysis of data from a 4CMenB outer membrane vesicle-based vaccine study in New Zealand identified a decrease in infections with gonococcus (but not Chlamydia) associated with vaccine use, suggesting that this vaccine may be cross-protective against Neisseria gonorrhoeae.

Laboratory studies and other retrospective data analyses have confirmed this cross-protective effect and modelling suggests it could have public health benefits. Prospective phase II and III 4CMenB studies to assess efficacy in prevention of gonococcal infection are now underway and a human challenge study is exploring mucosal immune responses and potential correlates of protection. Notably, the ANRS DOXYVAC

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trial of MenB vaccination and/or preventive antibiotic (doxycycline) use was halted after an interim data analysis owing to the high efficacy associated with both interventions.\textsuperscript{25} Of note, standalone \textit{N. gonorrhoeae} vaccines are also in development and may soon enter clinical trials.

HSV remains the leading cause of genital ulcer disease (GUD) worldwide. An estimated 596.0 million–655.7 million people, 16.0–17.6\% of the world’s population 15–49 years of age, had genital HSV type 1 or HSV type 2 or both. Vaccine development for HSV is mostly at an early stage, with therapeutic vaccines being the most advanced. Two vaccine candidates have completed phase II trials, and a mRNA-based candidate has recently entered a phase I trial. Similarly, vaccine R&D for \textit{Chlamydia} is mostly pre-clinical with just one candidate currently undergoing phase I clinical evaluation.\textsuperscript{26} For \textit{Treponema pallidum} (syphilis), research is at the pre-clinical stage, although a new \textit{in vitro} culture system may accelerate progress.

**Gonococcal vaccines:** What would be the implications (for 4CMenB-containing vaccines) of a positive outcome of the phase II gonococcal studies with the 4CMenB vaccines?

- PDVAC made the following recommendations:
  - Women from LMICs should be included in efficacy studies for vaccines intended to prevent gonococcal infection, particularly in people living with HIV.
  - Developers should consider including AMR-related endpoints in clinical trials, particularly to assess antimicrobial sensitivity and resistance, to better quantify vaccine value.
  - In the consideration of gonococcal vaccine value, data should be generated on other health outcomes resulting from gonococcal infection (e.g. pelvic inflammatory disease, ectopic pregnancy, impairment of fertility, cost to health systems).
  - Evidence should be generated on the value of (and preferences for) a gonococcal vaccine, either as a stand-alone product or as an extension to the 4CMenB indication. A gonococcal indication for a MenB vaccine could increase the likelihood that MenB vaccine is introduced.
  - Discussions with the WHO meningitis vaccine SAGE working group should raise awareness of the potential indication expansion of the 4CMenB vaccine and the GSK ABCWY vaccine candidate.
  - WHO should undertake a landscape analysis of MenB vaccine manufacturers that may be important partners in discussions of a potential indication expansion to include protection against gonococcal infection.

**HSV:** (How) does the development of an mRNA-based candidate affect the feasibility and potential value proposition for an HSV vaccine? Is there anything WHO should/could do to support this innovation?

- The value proposition for therapeutic HSV vaccines, in LMICs, of which an additional new mRNA candidate is one, should be re-evaluated in the context of affordable generic acyclovir.

\textsuperscript{25} https://www.anrs.fr/en/presse/communiques-de-presse/1185/efficacy-meningococcal-b-vaccine-and-preventive-antibiotic

Therapeutic vaccines may have value if they interrupt transmission and value in LMIC settings should also be assessed in light of expanding regional mRNA hubs.

Should we consider a PPC for Chlamydia and, if yes, should we encourage a bivalent gonococcal vaccine?

- PDVAC recommended that the regional prioritization exercise (see above) be used to decide whether a PPC is developed for a Chlamydia–gonococcal bivalent vaccine.

17. Therapeutic HPV vaccines (for recommendation)

_Sami Gottlieb (WHO)_

Vaccination is a key part of WHO’s global strategy to eliminate cervical cancer as a public health problem. The strategy is based on a life-course approach, encompassing primary prevention through prophylactic human papillomavirus (HPV) vaccination in adolescence, secondary prevention based on screening and treatment of cervical precancers, and tertiary prevention based on treatment of invasive cancer. Global implementation targets to achieve elimination have been agreed for 2030.

However, there are major global inequities in access to primary prevention measures, with only 12% of adolescent girls in LMICs receiving two doses of prophylactic HPV vaccine, and to screening, which can be challenging for many LMICs to implement. Therapeutic HPV vaccines could feasibly perform two roles for those not reached by prophylactic vaccination: (1) clearing infection or low-grade lesions; (2) treating high-grade cervical precancers. To date, research has mostly focused on the latter, and on targeting invasive tumours. However, therapeutic HPV vaccines targeting infection and/or low-grade precancers may be more achievable, and several candidates are in phase I or II trials.

An initial WHO consultation in October 2021 discussed the public health need for therapeutic HPV vaccination, particularly in LMICs, and the potential value it could offer by reducing cervical cancer deaths over the next 30–40 years. Early modelling informed a PPC consultation in Nairobi, Kenya, in November 2022 that aimed to clarify the priority public health needs and gaps in cervical cancer prevention in LMICs. It identified two country archetypes – those with some capacity for screening but where programmes were difficult to implement and loss to follow up is high following a positive HPV test, and hence a simpler treatment is needed; and countries where it is difficult to scale up screening at all, so the goal of therapeutic vaccination would be clearance of HPV infection to prevent development of cervical precancers.

As a result, the WHO PPC is likely to include two separate tables, covering vaccines targeting: (1) regression of cervical precancers for women with a positive screening test, and (2) clearance of HPV infections for a broader population of adult women. Modelling suggests that therapeutic HPV vaccines

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could potentially have a large public health impact, but this would decrease as background coverage of existing prevention interventions increases.
Does PDVAC agree with the overall approach of developing two sets of therapeutic HPV vaccine PPCs?:

1. For vaccines causing regression of high-grade cervical pre-cancers, targeting women with a positive cervical cancer test.
2. For vaccines clearing oncogenic HPV infections, targeting adult women through population-based delivery.

- PDVAC agreed that it would be helpful to develop therapeutic vaccine PPCs and FVVAs for the two proposed use cases, based on product attributes that vaccine impact models suggest would have the greatest public health value. The FVVAs may help to clarify which strategy would be most compelling across different health system contexts.
- PDVAC agreed that this therapeutic vaccine is exceptionally within its scope, given the cervical cancer elimination agenda, the substantial burden of HPV infection in LMICs, the need for additional tools beyond prophylactic vaccines, and limitations of current secondary prevention approaches in these regions.

For both PPCs: How best to approach the iterations between the PPCs with the Full Value of Vaccine Assessments

- PDVAC made the following comments:
  - Continued modelling and sensitivity analyses will be important in understanding the value and potential impact of vaccines, as well as critical parameters affecting value and impact (e.g. coverage of other interventions, including women living with HIV, cost-effectiveness).
  - Implementation and delivery considerations will need to be included in the PPCs.
  - The PPCs should be developed in accordance with the modelling results and predicted vaccine value in the context of other innovations.

18. Malaria (for recommendation)

Mary Hamel (WHO) & Lindsey Wu (WHO)

Since 2019, more than 1.2 million children in Ghana, Kenya and Malawi have received at least one dose of RTS,S/AS01 through their childhood immunization programmes as part of the WHO-coordinated Malaria Vaccine Implementation Programme (MVIP). Data from the first 24 months of the pilot implementations have shown that the vaccine is safe and feasible to implement with good uptake despite the novel schedule. Furthermore, there was no impact on uptake of other vaccines, use of insecticide-treated bednets or care-seeking for fever. Hospitalization due to severe malaria fell by 32% and all-cause mortality fell by 9%.

RTS,S/AS01 remains in short supply. A framework has been established for allocation of malaria vaccines, developed with an independent advisory group and through a consultative process. The first key principle is that areas of highest need, that is where children are most likely to die from malaria, should be prioritized.
More than 25 countries have expressed an interest in introducing RTS,S/AS01 and, as of January 2023, 13 submitted applications to Gavi in January 2023 in addition to those already received for Kenya, Malawi and Ghana to expand into comparator areas. Various actions are being taken to address supply constraints, with manufacturing being transferred from GSK to Bharat Biotech in India and GSK committing to provide up to 30 million doses of AS01 adjuvant annually. The possibility of a trial to assess fractional dosing is under consideration.

Preparations are also being made for the review of R21/Matrix-M\textsuperscript{30}candidate vaccine. Recently presented data suggest that R21/Matrix-M may be similarly efficacious to RTS,S/AS01 in preventing clinical malaria in areas of highly seasonal transmission (where the transmission season is largely limited to several months of a year) when provided just prior to the peak transmission season. The ongoing phase III trial is being conducted in five sites in sub-Saharan Africa. Two sites are testing seasonal administration, and three sites are testing standard administration, of which there are 2 sites with year-round low transmission and 1 site with low to moderate transmission.

WHO’s Malaria Vaccine Advisory Committee (MALVAC) has completed its terms of reference and has been sunset as planned. MALVAC developed the first WHO PPC, in 2014; updated malaria vaccine PPCs were published in September 2022\textsuperscript{31}, with goals focused on malaria vaccines to prevent blood-stage infection, reduce morbidity and mortality and reduce community-level transmission. The WHO MPAG remains active with its primary role to advise WHO on all areas of malaria control and elimination; it will advise on the recommended use of the R21/Matrix-M candidate vaccine through the joint SAGE/MPAG process.

Multiple other malaria vaccines are in development, spanning several platforms and targeting a diversity of antigens and life-cycle stages. The pipeline includes pre-erythrocytic, blood-stage and transmission-blocking vaccines, products suitable for pregnant women and \textit{Plasmodium vivax} vaccines. PPCs are being developed for malaria monoclonal antibodies. Their primary use would be prevention of infection in children, with a single dose providing protection in areas of seasonal transmission. Other potential applications include use in pregnant women, in infants hospitalized with severe anaemia before discharge, and in young infants before the age of SAGE vaccination. The benefits of monoclonal antibodies for malaria prevention include single dosage, which is likely to improve adherence compared with chemoprevention and more immediate protection compared to vaccines. Challenges will include the demonstration of safety following repeat administration, technical challenges (e.g. stability, volume required), affordability and identification of suitable delivery strategies. Advanced candidates include

\textsuperscript{30} Datoo MS, Natama HM, Somé A et al. \textit{Efficacy and immunogenicity of R21/Matrix-M vaccine against clinical malaria after 2 years’ follow-up in children in Burkina Faso: a phase 1/2b randomised controlled trial.} Lancet Infect Dis. 2022 Dec;22(12):1728-1736. doi: 10.1016/S1473-3099(22)00442-X.

\textsuperscript{31} https://www.who.int/publications/i/item/9789240057463
CIS43LS, which has demonstrated good efficacy in human challenge and phase II studies, and L9LS, which has been assessed in a challenge model and is undergoing a phase II study.

With the completion of MALVAC, activities related to guidance on early vaccine and monoclonal antibody development will now fall under the purview of PDVAC.

What is needed to advance the pipeline for next-generation products? What role can PDVAC have following sunset of the Malaria Vaccine Advisory Committee (MALVAC)?

- PDVAC strongly recommended that a dedicated technical advisory group (TAG) be formed, and/or expert consultations be convened to address product development issues related to new and next-generation malaria vaccines and monoclonal antibodies. This will be critical to guide overall malaria vaccine and monoclonal development strategy, including development of PPCs and assessment of the relative feasibility/value of vaccine vs monoclonal antibody interventions in different contexts. The expert groups/convenings should report to PDVAC and include at least one or two members of PDVAC.
- PDVAC recommended that the Malaria Vaccine Team, PDR clarifies the remit and oversight mechanisms of the SAGE MPAG WG, and the activities that PDVAC is anticipated to advise on, and communicates to all relevant stakeholders.
- A draft PPC for malaria monoclonal antibodies intended for infants and children is being finalized. PDVAC recommended that an ECVP should be considered for this use case to delineate the data required to inform policy recommendations, particularly in the context of vaccines that are being introduced, or may soon be, and other interventions such as bednets. This is particularly important since WHO prequalification of the monoclonal antibodies will be sought.

19. Improved influenza vaccines (for recommendation)

Chris Chadwick (WHO)

Following the lifting of COVID-19-related restrictions, influenza cases have rebounded, although to date they have not returned to pre-COVID-19 levels. To address this resurgence, in May 2022 WHO issued an updated position paper on the use of influenza vaccines based on October 2021 SAGE recommendations.

Multiple vaccines are in the pipeline, including universal vaccines, details of which are included in a database managed by CIDRAP. Globally, good production capacity exists for both seasonal and pandemic influenza vaccines.

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34 https://www.who.int/publications/i/item/who-wer9719

35 https://ivr.cidrap.umn.edu/universal-influenza-vaccine-technology-landscape
Innovations include multiple nucleic acid-based vaccines, including quadrivalent vaccines, constructs targeting conserved antigens, and combination vaccines also incorporating COVID-19 and RSV antigens. Multivalent vaccines are also being assessed, as illustrated by recent pre-clinical data on a vaccine incorporating haemagglutinin antigens from all 20 known influenza A and B subtypes.\(^\text{36}\)

Multiple global initiatives related to advancing influenza vaccine research and development have been launched. These include the Influenza Vaccines R&D Roadmap (IVR)\(^\text{37}\), which is a 10-year plan with 24 strategic goals and more than 100 milestones; the IVR was developed by the Center for Infectious Disease Research and Policy (CIDRAP) in close collaboration with WHO and other partners. Implementation and monitoring, evaluation and adjustment activities began in 2022.

A WHO PPC for Next-Generation Influenza Vaccines, first published in 2017\(^\text{38}\), is being updated. Work has started on an FVVA, which will align with and inform the updated PPC. Country demand for influenza vaccines remains low, with effectiveness and the duration of protection cited as contributing factors, both of which are addressed in the influenza PPC.

**Is there a need to revise the current WHO PPC for next-generation influenza vaccines?**

- PDVAC recommended revising the existing PPC guidance (developed in 2017) to take into consideration novel platforms, novel antigenic targets and potential correlates of protection, and potential strategies for immunobridging to existing vaccines.

- PDVAC recommended that a TAG, reporting to PDVAC, is set up to revisit and revise the existing PPC. This TAG’s terms of reference should be closely aligned with the activities ongoing to develop an FVVA for improved influenza vaccines to be used in LMICs and also aligned with the IVR strategic goals.


*Marion Menozzi Arnaud (Gavi), Mateusz Hasso-Agopsowicz (WHO), Jean-Pierre Amorij (UNICEF), Courtney Jarrahian (PATH)*

The Vaccine Innovation Prioritization Strategy (VIPS), a collaboration between Gavi, WHO, BMGF, UNICEF and PATH, was established to facilitate the development of cross-cutting immunization technologies with the greatest potential public health impact. Highest priority technologies are currently microarray patches (MAPs), heat-stable vaccines and barcodes on vaccine vials. End-to-end roadmaps and five-year action plans have been developed or are under development for each.

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https://ivr.cidrap.umn.edu

https://www.who.int/publications/i/item/9789241512466
MAPs have multiple potential advantages, including ease of use, compactness, and pain-free administration. They could make it easier to reach zero-dose and under-immunized populations, accelerate vaccine roll-out in a pandemic, and offer a potential platform for adult vaccination. Which benefit is most important is likely to vary from antigen to antigen and across different settings. Increasing volumes of clinical data are being published across a range of antigens, with several phase II studies in progress or planned.

For LMICs, measles–rubella (MR) MAPs are the lead candidate. A preliminary list of 12 priority vaccine targets has been developed and will be published for public consultation. Papers have been published on MR-MAP development\(^\text{39}\), MR-MAP global demand\(^\text{40}\) and hepatitis B birth dose vaccine-MAP cost-effectiveness\(^\text{41}\); others are in preparation on investment in MAP manufacturing and MAP quality attributes.

Challenges include uncertainties with regard to country demand, technical and regulatory risks in product development, and the large upfront investment required to establish production facilities. The latter will need to be in place before licensing trials, suggesting that prequalification of the first MR-MAP products is unlikely before 2029.

Different potential use cases for MR-MAPs have been outlined, including administration by health workers, community health workers, caregivers or by vaccine recipients themselves, with vaccination taking place in facilities, through outreach or in other settings – including in the home. Multi-stakeholder country engagement is being undertaken, starting with Indonesia and Ethiopia, to understand what MAP properties are most valued and which use cases might be considered. In neither country was self-administration seen as a likely approach, at least initially.

Potential demand for MR-MAPs has been modelled for 2030–2040 and an initial FVVA has been developed. Analyses suggest that MAPs have a potential to reduce morbidity and mortality significantly, with cost-effectiveness varying by setting. Costs per DALY saved in LMICs are estimated to be similar to newly introduced vaccines. Cost of manufacturing has a major influence on cost-effectiveness, so establishing a manufacturing base in a low-cost setting could have a major impact.

Are the mentioned activities appropriate to accelerate the development of vaccine microarray patches (MAPs)?

- While there have been activities to assess country-level interest, product preferences and demand for measles–rubella MAPs (MR-MAPs), PDVAC noted that further information is needed.

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\(^{40}\) Ko M, Malvoti S, Cherian T et al. Estimating the future global dose demand for Measles-Rubella microarray patches. medRxiv 2022.08.11.22278665; doi: https://doi.org/10.1101/2022.08.11.22278665

to understand likely speed of uptake and anticipated market penetration (currently the demand forecast relies on a number of assumptions, not on actual consumer data).

- PDVAC recommended prioritizing the willingness-to-pay analysis in the context of existing vaccines (at the country level) as this is critical to drive the supply side and encourage entrants with products that are affordably priced.

How can we design a sustainable mechanism to engage with countries to inform product development and prepare for country uptake?

- PDVAC was supportive of advancing vaccine-MAPs in general, potentially for high-income country indications in the first instance (for example, flu-MAPs or COVID-MAPs) to de-risk investment, establish regulatory precedence and build acceptability. This approach will likely ultimately accelerate the development and use of MR-MAPs and other vaccine-MAPs that could bring significant coverage and equity benefits to LMICs.

21. Monoclonal antibodies (for recommendation)

Erin Sparrow (WHO), Veysel Kayser (consultant), Theodore Ruel (IMPAACT), Shelly Malhotra (IAVI)

Monoclonal antibodies have been developed for prevention of disease caused by several pathogens, including COVID-19, C. difficile, anthrax, rabies and RSV, and multiple products are in the pipeline for other pathogens. The cost and dose of monoclonal antibodies for disease prevention vary considerably. Their advantages include the fact they are fast-acting and have an excellent safety profile. Disadvantages include their high cost, short half-life (although an increasing number of extended half-life (Fc-modified) mAbs in development), the need for administration by trained healthcare workers and complex clinical development.

To encourage innovation, PPCs have been developed for monoclonal antibodies for HIV prevention and RSV, and are in preparation for malaria prevention in infants and young children. Generic, i.e., product agnostic WHO norms and standards “guidelines on the nonclinical and clinical evaluation of monoclonal antibodies and related biological products intended for the prevention or treatment of human infectious diseases” is close to finalization and disease-specific supplements are planned. Monoclonal antibodies follow the medicines prequalification pathway.

Many factors drive the high cost of monoclonal antibodies, which are challenging to develop and manufacture. Although the field is marked by much innovation, it may not be possible to address all the cost drivers to achieve affordability in LMICs. Nevertheless, new antibody engineering technologies, formulation strategies and delivery approaches may create new opportunities and potential applications.

One potential use of monoclonal antibodies may be in postnatal HIV prophylaxis, to further lower rates of mother-to-child transmission. A consultation has highlighted several drawbacks to current drug-based strategies to prevent mother-to-child transmission, which contribute to continuing infection of young infants.
infants, including an estimated 160,000 new paediatric infections in 2021, almost half of which occur during breastfeeding.

There is some support for the use of monoclonal antibodies as a “safety net” and alternative to drug-based post-natal prophylaxis. This includes data from non-human primate studies, safety data in children, and proof-of-concept clinical data in adults. In addition, longer acting monoclonal antibodies offering broader protection at lower doses are on the horizon.

Several phase I studies are underway or planned, including in LMICs. Modelling suggests that monoclonal antibody postnatal prophylaxis could reduce vertical HIV transmission by up to 42% depending on setting and is likely to be cost-effective. Further stakeholder consultations are required to assess feasibility and acceptability. In addition, a workshop in March 2023 will discuss business model innovation and ways to further reduce the costs of monoclonal antibodies.

Would it be feasible to develop a generic PPC for infectious disease monoclonal antibodies for prophylactic use?

- PDVAC did not consider that a generic PPC for infectious disease monoclonal antibodies would be feasible, given pathogen-specific differences. However, there is currently no guidance regarding minimum requirements for programmatic suitability for monoclonal antibodies targeting infectious diseases in LMICs, as there is for vaccines in the form of the WHO Programmatic Suitability for Prequalification guidance. PDVAC recommended that development of an analogous document for monoclonal antibodies should be considered to guide developers. This guidance should be developed with input from the WHO prequalification team and be informed by commonalities across the various existing PPCs for monoclonal antibodies for infectious disease prevention. Disease-specific supplements would be important tools to guide development.

Long-acting prophylactic monoclonal antibodies will be prequalified by WHO as medicines but may used like vaccines within routine immunization programmes. However, medicine prequalification does not follow the same programmatic suitability requirements as vaccine prequalification; as an example, a monoclonal antibody given intravenously can be prequalified through the medicines pathway, but an intravenous vaccine would not be considered suitable for vaccine prequalification. This could have detrimental implications on decisions for introduction, post-licensure, if the monoclonal antibody is not suitable for use, and feasible to deploy within the immunization programme.

In addition, the reliance on a National Regulatory Authority that is considered ML3 for prequalification is not applicable to medicines; whereas it is a pre-requisite for vaccines. WHO’s Prequalification of Medicines Programme offers two pathways for the prequalification of monoclonal antibodies, of which there are 2 types: Biotherapeutic products BTPs, i.e. (novel) products not claimed to be similar biotherapeutic products) and similar biotherapeutic products (SBPs, i.e. biosimilars):

- **full assessment** of SBPs that have been registered by a non-stringent regulatory authority (SRA), based on a Reference biotherapeutic product (RBP) that has been approved by an SRA; and
- abridged assessment of BTPs, or their corresponding SBPs as applicable, that have been approved by a stringent regulatory authority (SRA) and that are marketed in the country of registration.

BTPs (developed as stand alone products) and not approved by an SRA do not fall within the scope of the Prequalification of Medicines programme, therefore all monoclonal antibodies intended for WHO PQ must be approved by an SRA.

**Is there a need for technical products (e.g. a research roadmap) to guide development of HIV monoclonal antibodies for paediatric use?**

- The existing WHO PPC for monoclonal antibodies for HIV prevention is broad, with multiple target populations described. PDVAC concluded that additional and specific guidance is needed to advance HIV monoclonal antibodies for neonatal and paediatric use, given their unique delivery settings and constraints in LMICs. PDVAC recommended that this guidance consider issues such as the implications of HIV seropositivity due to antibody infusion, dose volumes, route of delivery and compatibility with the EPI or other delivery schedule. Given resource constraints, PDVAC recommended that IVB work with other WHO initiatives that could lead the development of such guidance.

- PDVAC noted that data on user preferences and acceptability (drug versus monoclonal antibody) would be helpful.

### 22. Role of vaccines in reducing AMR (for recommendation)

**Mateusz Hasso-Agopsowicz (WHO), Padmini Srikantiah (BMGF)**

The potential of vaccination to reduce antibiotic use, a key driver of antimicrobial resistance (AMR), is included within FVVAs. The value proposition in this area includes fewer drug-resistant infections, reduced antibiotic use for syndromic conditions for which vaccine targeted pathogens contribute to the frequency of events, and economic benefits; the extent of benefits will vary by pathogen.

Although vaccination is seen as a critical tool in the battle against AMR, the potential of vaccination has arguably yet to be fully prioritized. An action framework developed as an IA2030 annex focuses on three objectives: increasing use of existing vaccines; developing new vaccines that contribute to AMR control; and expanding and sharing knowledge on vaccination to address AMR.

For WHO AMR priority pathogens, 61 candidates are in active development, but there are multiple pathogens for which no candidates currently exist. Four pathogen types and recommended strategies have been distinguished:

- Where vaccines exist, increase coverage and promote introduction.
- Where vaccines are in late-stage development, accelerate development and prepare for introduction.
- Where vaccines are in early-stage development, continue development and generate data on AMR impacts.
Where there are limited or no vaccine candidates, focus on other control and prevention measures.

In 2019, an estimated 1.27 million deaths were attributable to bacterial AMR and 4.95 million deaths were associated with bacterial AMR. Modelling suggests that a significant proportion of these deaths could be averted were vaccines available, including more than 123,000 deaths associated with drug-resistant S. pneumoniae and 118,000 deaths from TB. There have been two studies with RSV interventions (RSV and monoclonal antibodies that have demonstrated a reduction in use of anti-microbial prescriptions).

One AMR priority pathogen is Klebsiella pneumoniae. It is responsible for a substantial disease burden, including an estimated 790,000 deaths in 2019, much of it due to resistant infections, and with the greatest impact in young children in LMICs. In neonates, K. pneumoniae is the leading infectious disease killer globally and 87% of deaths are AMR-related. The CHAMPS study, which is analysing child deaths in seven countries in Africa and Asia, estimates that K. pneumoniae contributes to 45% of all neonatal infectious disease deaths. Older people are also at particular risk, including in high-income countries.

K. pneumoniae has been prioritized for new vaccine development by BMGF, focusing on maternal vaccination with a conjugate vaccine. The most promising targets for vaccine development are LPS O-antigens and capsular K antigens. Activities include sero-epidemiology of neonatal K. pneumoniae infections and genomic sequencing of isolates, development of animal models, and definition of correlates of protection. Currently, five vaccines are in pre-clinical development and one has entered clinical trials. CARB-X has also prioritized K. pneumoniae and is supporting two vaccine projects.

Are the mentioned activities appropriate to articulate and leverage the role of vaccines in reducing AMR?

PDVAC noted that, while quantifying the impact of vaccines is an essential component of vaccine value and part of the FVVA—regulators currently do not consider evaluation of AMR endpoints as a priority in their scientific advice; the review of regulators focuses on benefit/risk assessment for individuals. The most feasible AMR endpoint to include in the context of an efficacy trial is reduction in antibiotic use as a secondary or exploratory measure. The greatest value of AMR endpoints may be for post-licensure reimbursement/recommendation decisions by the HTA agency or NITAG rather than the regulator.

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45 Joseph A. Lewnard, et al. Prevention of antimicrobial prescribing among infants following maternal vaccination against respiratory syncytial virus | PNAS
- PDVAC recommended engaging with regulators to socialize the need to collect data on antibiotic use and other potential indicators during phase II-III clinical development as evidence of potential impact on AMR, which could be very important for policy and financing decisions and country uptake.
- PDVAC noted that it would be useful to model how the evolution of resistance might be affected by vaccine introduction and the consequent reductions in antibiotic use and prevention of resistant infections.
- PDVAC recommended that WHO convenes regulators and other stakeholders to map out what studies and evidence generation are needed post-licensure to demonstrate impact on AMR, for example as part of phase IV effectiveness studies. This may identify some additional indicators that can be feasibly measured pre-licensure.

**What is an appropriate mechanism to build awareness and increase urgency of the burden of *Klebsiella pneumoniae* and need for a vaccine?**

- PDVAC noted that initial findings from the regional pathogen prioritization exercise (see above) suggest that *Klebsiella* is an important pathogen for vaccine development.
- PDVAC recommended that PDR consider developing a VVP for *Klebsiella pneumoniae* as a tool to communicate current understanding of disease burden, existing interventions and vaccine research gaps.
- PDVAC suggested that the serotype distribution in populations at greatest risk (neonates and older adults) should inform vaccine design.