WHO expert review of Group A Streptococcus vaccines

1st joint expert consultation of
Product Development for Vaccines Advisory Committee (PDVAC) and
Immunization and Vaccines Related Implementation
Research Advisory Committee (IVIR-AC):
Hybrid (in person/on-line) meeting, London, United Kingdom, 30 September 2022

Participants: The hybrid meeting was attended by 59 participants, including PDVAC, IVIR-AC, and SAVAC (Strep A Vaccine Global Consortium) members; WHO staff; country representatives; industry professionals; and funders. See list of participants

Meeting Structure: To ensure the expertise of each committee could be appropriately utilized in the context of a combined consultation, the meeting was divided into two parts. Part 1 focused on the objectives for PDVAC; part 2 on the objectives for IVIR-AC. This document summarizes the outcomes and recommendations of both sets of deliberations.

Meeting materials are posted here

Executive Summary

Group A Streptococcus (GAS) infections result in a broad spectrum of acute and chronic clinical symptoms and sequelae, which collectively account for more than 500,000 deaths, of which 328,000 are due to rheumatic heart disease (RHD), and 1.8 million new cases each year, globally. Post-infection immune responses can lead to immune-mediated diseases; acute rheumatic fever (ARF) can lead to RHD, and post-streptococcal glomerulonephritis (PSGN) can also occur and potentially lead to end-stage renal disease. An estimated 200,000 annual deaths have been attributed to GAS invasive disease, (eg, sepsis, empyema, deep skin infections). The epidemiology of many of the GAS-related diseases varies by region, and populations from low- and middle-income countries (LMICs) are at greatest risk of severe disease and death due to GAS infection.

The 2018 World Health Assembly (WHA) resolution on rheumatic heart disease and rheumatic fever prompted the development and publication of two critical guidance documents, the *WHO Preferred Product Characteristics (PPC) for Group A Streptococcus Vaccines*[1] and the *WHO Group A Streptococcus Vaccine Development Technology ROADMAP*[2], which aim to inform, advance and accelerate GAS vaccine Research and Development (R&D). In addition, the *Strep A Vaccine Global Consortium* (SAVAC) initiated a parallel effort to develop a *Full Value of Vaccines Assessment* (FVVA) for novel GAS vaccines. This FVVA Report has been developed using the WHO FVVA framework and aims to assess and communicate the full value of vaccination against GAS infection, particularly in LICs and MICs—accounting for not only the individual health benefits, but also population-based indirect and broader socioeconomic impacts—from the perspective of multiple stakeholders.

To ensure the 2018 WHO PPC and Roadmap documents remain current and relevant, **PDVAC** reviewed the progress towards achieving the activities within the existing Research and Development (R&D)

[1] https://apps.who.int/iris/bitstream/handle/10665/279142/WHO-IVB-18.07-eng.pdf
[2] https://apps.who.int/iris/handle/10665/279392

Roadmap, including evidence generated as part of the FVVA, in the context of the current GAS vaccine pipeline.

In preparation for the FVVA upcoming publication, **IVIR-AC** reviewed the FVVA analytical framework, quantitative methods and results, and evaluated their strength, relevance, and applicability toward demonstrating the full potential value of a novel GAS vaccine.

The **over-arching objectives of this joint meeting** were to: 1) review recent advances in GAS Vaccine R&D and the soon to be published FVVA; and 2) agree on key priorities to ensure the WHO GAS vaccine PPC and Vaccine Development Technology Roadmap, and the FVVA developed by SAVAC are current, appropriate and relevant.

Specifically:

- PDVAC was invited to review recent progress in GAS Vaccine R&D and to provide recommendations on the need to update the current WHO PPC and R&D Roadmap on GAS vaccines. Questions to PDVAC included:
  - Is there a need for more than one PPC, given the breadth of clinical outcomes encompassed by the current PPC?
  - In the context of the current GAS pipeline, and the progress in defining the FVVA for GAS vaccines, which elements of the current WHO PPC and Vaccine Development Technology Roadmap guidance documents require updating?
  - Are there specific recommendations for vaccine product parameters that PDVAC recommends for inclusion, or critical roadmap activities that should be initiated as a priority?

- IVIR-AC was invited to review quantitative methods supporting the development of the GAS FVVA and discuss its relevance and applicability, by:
  - Confirming the strength, relevance, and applicability of the preliminary results and quantitative methods which serve as the basis for the FVVA analytical framework.
  - Determining which additional studies, if any, may complement or broaden the initial GAS FVVA analyses.
  - Identifying ways to communicate the FVVA work to GAS vaccine R&D stakeholders.

Part I - PDVAC Consultation

Key discussion points

GAS vaccine development carries a range of uncertainties that have contributed to the limited interest and investment by vaccine manufacturers. Given the broad spectrum of diseases caused by GAS infection, several indications and potential clinical endpoints have public health relevance. That said, the relative importance (value proposition) of these indications and clinical endpoints vary by context, as does the feasibility and probability of technical and regulatory success of evaluating GAS vaccines for those indications and endpoints.

A primary intent of WHO PPCs and Roadmaps is to offer guidance to vaccine manufacturers and funders on the preferred product attributes and research priorities and needs, respectively, for LMIC use. When relevant, these global guidance documents also acknowledge and consider that vaccine development and use in HICs can be initially more compelling for vaccine manufacturers, and may be a necessary step on

the pathway to developing fit-for-purpose vaccines for LMIC use. This issue was presented as the backdrop for the discussion on GAS vaccines, given that the initial HIC indication for licensure would likely focus on pharyngitis and/or impetigo - which are not currently considered a significant public health concern in many LMICs - but are a feature of GAS pathogenesis that can lead to serious chronic and fatal conditions such as invasive disease, ARF and RHD, particularly in LMIC contexts.

The current PPC has a broad indication (currently defined as prevention of GAS-related pharyngitis, superficial skin infections, cellulitis, toxin-mediated disease, invasive infections and associated antibiotic use, secondary ARF, RHD and PSGN) that does not differentiate the indications (and associated clinical endpoints) that would differ depending upon the epidemiologic and socio-economic context of GAS vaccine use. An alternative to the current PPC could be one in which PPC elements are defined by context-specific indications for use. Discussions included stratifying the PPCs by indication and target population, revisiting the original efficacy targets, and defining primary endpoints and secondary endpoints supported by appropriate case definitions. PDVAC considered the risk of separate PPCs for HIC and LMIC use cases, as doing so could increase the likelihood that vaccines developed for HIC use might not be fit-for-purpose for LMIC use, which in turn would further increase existing equity gaps between HICs and LMICs.

As a precursor to a revised PPC document, PDVAC considered the utility of a *GAS Vaccine Development and Regulatory Strategy* document that describes an optimized pathway of vaccine (clinical and product) development and regulatory approvals through incrementally expanded indications, target populations, and contexts of use. Such a document would outline the steps to achieve initial licensure for the relatively more feasible indication(s), for example pharyngitis likely in HICs, and then describe how such an initial pathway to vaccine development and market approval forms the basis for, and ultimately accelerates, vaccine development and licensure for the more relevant indication(s) for use in LMICs, including through post-licensure effectiveness studies for LMIC endpoints such as RHF and/or RHD. Such an integrated vaccine development and regulatory strategy document could form the foundation for a revised PPC document that **articulates the needs of a GAS vaccine for both HIC and LMIC contexts**, with the clear intent to uphold the critical goal of ensuring timely data and evidence, and timely development of fit-for-purpose vaccines for use in LMICs.

The Roadmap discussion was highly predicated on the outcomes of the PPC discussion, including clarity on the vaccine target indications and populations, to identify critical research that is needed to develop and deliver GAS vaccines. For inclusion in the revised Roadmap, there is a need to better understand and articulate disease burden, identify biomarkers that may correlate with protection and with vaccine safety, understand the mechanisms of disease transmission, and interventions in different contexts, and better formulate a targeted advocacy plan to create awareness around GAS vaccines and the range and complexity of GAS disease over the life-course.

Final discussions looked toward immediate next steps and how to implement PDVAC recommendations. SAVAC 2.0 may provide a platform to develop the integrated product development and regulatory strategy document that informs the updated PPC and Roadmap.

PDVAC conclusions and recommendations:

Is there a need for more than one PPC, given the breadth of clinical outcomes encompassed by the current PPC?

- PDVAC recommends that PPCs are developed for the individual priority GAS indications. For example, a PPC for a vaccine targeted to prevention of pharyngitis and/or scarlet fever, predominately for use in HICs, and a PPC (one or more) for a vaccine targeted to a priority indication for use in LMICs.
- It will be important to include all use cases within the same PPC document to describe the priority indications and target populations in different contexts. While an indication for pharyngitis may offer the quickest and least costly path to achieve initial licensure, the compelling public health and socio-economic value of GAS vaccines will be through prevention or reduction in other more severe disease outcomes. As such, it will be important to convey the considerations for GAS vaccine uptake in LMICs and to position the various GAS indications along the spectrum of GAS disease.

In the context of the current GAS pipeline, and the progress in defining the FVVA for GAS vaccines, which elements of the current WHO PPC and Vaccine Development Technology Roadmap guidance documents require updating?

- For the PPC:
- The immediate task is to determine which indications are a priority for PPC development. The indications will differ by target population, efficacy target, case definition, clinical endpoint and other parameters. The priority indications should be determined by the public health and socio-economic value that GAS vaccines against the proposed indication could offer.
- It will be important to quantify the contribution of the GAS vaccine indication to reduction in anti-microbial resistance (in both GAS and other pathogens in the vaccine value assessment).
- PDVAC recommended the drafting of an integrated vaccine development and regulatory framework document, to lay out the initial and subsequent indications for GAS, and considerations such as case definitions, clinical endpoints and efficacy targets for each. This kind of strategic document could be a critical component of the GAS roadmap to lay out the pathway to licensure and use in LMICs, that may include initial licensure in HICs. It will serve as a basis for prioritizing the indications for PPC development, and will ultimately facilitate and accelerate the PPC work.

- For the Roadmap:
- To accelerate and rationalize GAS vaccine development, maintain focus on the identification of surrogate markers of protection as well as identification of the relevant pathogen-specific virulence factors that need to be targeted to prevent different disease entities, depending on the PPC, and highlight the importance of this in the revised roadmap.

- It will be critical to continue to advocate for comprehensive GAS burden estimates in LMICs to inform the value of GAS vaccines. Identifying and mapping advocacy objectives by indication and target group, including a community engagement plan to generate demand, was also highlighted as critical.
- The critical need for need for appropriate post-marketing surveillance systems should be highlighted and consideration be given to the feasibility and cost of setting up such post-marketing surveillance systems in LMICs. It will be important to quantify the contribution of the GAS vaccine indication to reduction in anti-microbial resistance, as well as GAS transmission and subsequent disease, particularly in the context of other interventions.

Are there specific recommendations for vaccine product parameters that PDVAC recommends for inclusion, or critical roadmap activities that should be initiated as a priority?

- PDVAC recommended the development of a 'data purpose matrix' to identify 'what data are needed when' along the product development pathway, to support planning and advocacy for funding, stakeholder consultation, policy consideration, and use. This tool could be a useful framework for identifying key activities to include in the roadmap.
- Given the striking paucity of private sector investment and partnership in GAS vaccine R&D, despite the apparent inordinate burden of disease, it will be informative to consult with manufacturers to identify, understand, and develop strategic priorities to overcome barriers and create incentives to investing in GAS vaccines.

PDVAC encouraged SAVAC and the PDVAC secretariat at WHO to consider a creative partnership with each other to undertake the activities proposed. It may be feasible to incorporate many of these activities in SAVAC 2.0, and for SAVAC to lead, with WHO/PDVAC oversight and/or implementation of some, if not all, of the above recommendations.

Part 2 – IVIRAC Consultation

Streptococcus pyogenes, also known as Group A Strep (GAS), is a human- exclusive Gram-positive pathogen responsible for a broad array of infections resulting in > 500,000 death annually. Estimated healthcare and societal costs[3] associated with invasive GAS disease and acute upper respiratory infections in the United States are estimated at $5.33-$6.86 billion annually.[4] Theoretically, all Strep A infections and resulting immune-mediated complications are vaccine-preventable, yet after decades of research, a licensed vaccine remains elusive. Antibiotics are typically the first line of treatment for GAS, yet overuse remains a global concern; antibiotic treatment does not ensure prevention of future GAS complications; and a lack of knowledge and/or limited access to antibiotics are added complications in resource poor settings where disease and societal impact may be the highest.

Given the high health and economic burden of Strep A diseases globally and the growing complications with antibiotic over-use, greater investment in the development and delivery of safe and effective Strep A vaccines is warranted. To support this aim, SAVAC developed the *Full Value of Vaccines Assessment (FVVA)* Report which illustrates the full value of a novel GAS vaccine to reduce the health, social, and economic impact of GAS infections, conditions and disease states.

Several analyses support the FVVA, including disease burden and vaccine impact modelling, economic burden and vaccine cost-effectiveness modelling, full societal benefit and return on investment analyses, among others. IVIR-AC reviewed the methodologies and analytical approaches for disease burden, vaccine impact modeling and cost-effectiveness and provided a critical evaluation of their quantitative strength, relevance and utility toward establishing the full value of a novel GAS vaccine.

IVIR-AC conclusions

[3] costs incurred from out-patient or hospitalization and management of long-term sequelae; productivity losses resulting from acute illness, long-term disability, and mortality.

[4] Andrejko K, et.al. *Health-Economic Value of Vaccination Against Group A Streptococcus in the United States*. Clin Infect Dis. 2022 Mar 23;74(6):983-992. doi: 10.1093/cid/ciab597. https://pubmed.ncbi.nlm.nih.gov/34192307/ (accessed 05 Nov 2022)

The committee commended the team for generating robust estimates overall, establishing important new evidence on a hypothetical GAS vaccine adhering to the WHO Preferred Product Characteristics (PPC), and expanding the current knowledge base of GAS vaccines in general. The analytical approach presented was comprehensive in nature, covering the health sector and societal and commercial perspectives while also addressing key questions around disease burden, potential impact of a vaccine, and economic consequences. IVIR-AC found the estimates robust to support a global and business investment case for a hypothetical GAS vaccine.

IVIR-AC recommendations:

Can IVIR-AC confirm the strength, relevance, and applicability of the preliminary results and quantitative methods of the FVVA analytical framework?

- The committee agrees with the analytical approach adopted for the burden of disease assessment, vaccine impact modeling, and cost-effectiveness analysis of a hypothetical GAS vaccine based on the WHO PPC. A static model is appropriate at this stage, assuming there is no impact on transmission. However, it may be important to tease out the different disease endpoints for the overall impact and adjust the model accordingly.
- Further clarification is needed for some of the assumptions, including:
    - The probability and CFRs for different health outcomes of GAS infection, including Acute Rheumatic Fever (ARF) and Rheumatic heart disease (RHD), and how they vary by age/country.
    - The rationale for the two vaccine waning scenarios (i.e., full efficacy for 10 years and linear waning over 20 years), as this has a potential impact on long-term economic benefits through RHD prevention. Consider assuming exponential waning instead of full efficacy for 10 years.

Are there any additional studies which may complement or broaden the initial GAS FVVA analyses?

- Adopt a gender-based modelling approach and/or sensitivity analysis in low- and middle-income countries (LMICs). For example, incorporate gender variations in RHD morbidity and mortality. Gender differentials are also reflected in labor force participation rates in LMICs, which are a key driver of productivity losses.
- Undertake a full probabilistic sensitivity analysis sampling from probability distributions for the uncertainty in the natural history of disease progression and disease outcomes.
- Analyze whether country- and age-specific rates of Strep A burden are changing over time. If so, a sensitivity analysis is needed for the time frame of introduction for the vaccine impact model.
- Revisit the assumption that vaccine coverage is the same for ages 0 to 5, especially the assumption that measles-containing-vaccine second dose (MCV2) coverage is an appropriate proxy for vaccine coverage at age 5.
- Clearly illustrate the economic burden of GAS infections (and its uncertainty) by plotting the different disease outcomes on the same y-axes separately for high-income, upper-middle income, low-middle income, and lower-income countries.
- Benchmark the success probability of the hypothetical vaccine against recently developed similar types of vaccines, if available, to help stakeholders understand the level of uncertainty.
- Consider incorporating the (small) likelihood and costs associated with AEFI in the economic model.

What are potential considerations and approaches for communicating the FVVA work to GAS vaccine R&D stakeholders?

- Although the thresholds used by the FVVA, such as 1 x gross domestic product (GDP) per capita for the Cost Effectiveness Analysis and 3 x GDP/capita for the Cost Benefit Analysis are fine for global investment decisions, they should not be used for individual country investment decisions where the vaccines are funded by national health budgets.
- It would be useful to clarify the key assumptions of the WHO PPC in future presentations, especially vaccine efficacy against different clinical endpoints.