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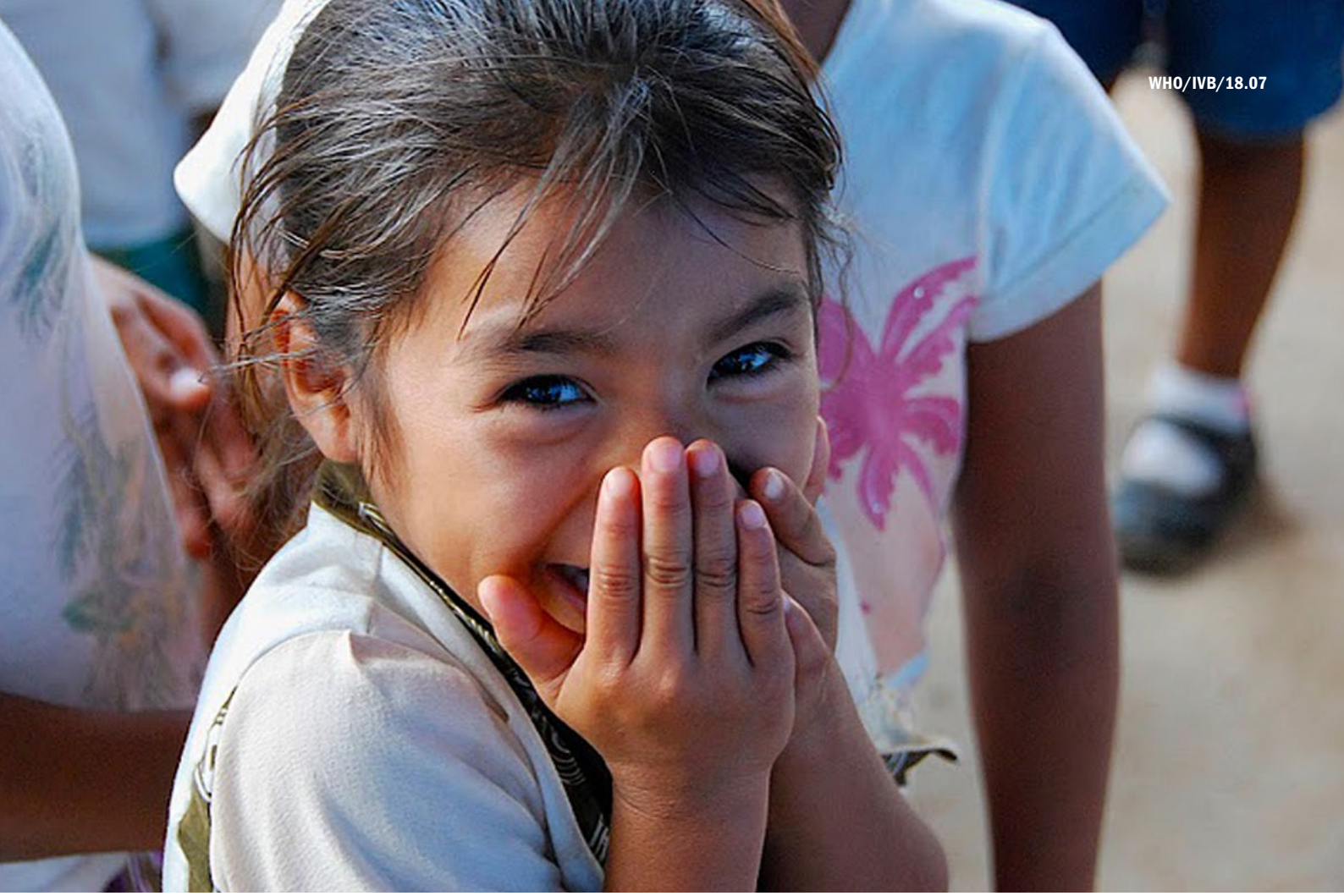

# WHO Preferred Product Characteristics for Group A *Streptococcus* Vaccines

*DEPARTMENT OF IMMUNIZATION, VACCINES AND BIOLOGICALS*

Family, Womens's and Children's Health (FWC)

World Health Organization

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## WHO Secretariat

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# A. INTRODUCTION

## I. Background and purpose

Vaccine preferred product characteristics (PPCs) published by the World Health Organisation (WHO) describe preferred parameters pertaining to vaccine indications, target population, data collected for safety and efficacy evaluation, research and development (R&D) and immunization strategies. Selected disease areas are identified as WHO priorities based on the unmet public health need for vaccines, technical feasibility assessment and suitability for use in low- and middle-income countries.

The PPCs are intended to encourage innovation and the development of vaccines for use in settings most relevant to the global unmet public health need. They do not include minimally acceptable characteristics and it is important to note that if a vaccine does not meet the PPC criteria, it could still be assessed by WHO for policy recommendation. Any group A *Streptococcus* (GAS) vaccine that becomes licensed and potentially available will undergo evidence-based assessment for policy recommendations by the Strategic Advisory Group of Experts (SAGE) on Immunization.

The primary target audience for WHO PPCs is any entity intending to eventually seek WHO policy recommendation and prequalification for their products. WHO preferences can be useful to all those involved in vaccine development activities, including academic groups, funders and manufacturers.

WHO PPCs intend to provide early guidance on vaccine development strategies and targets, and are to be updated regularly to account for innovations or any other change in the identified need and R&D landscape. WHO PPCs do not override existing WHO guidance on vaccine development. Useful links to existing documents are provided in Appendix 1.

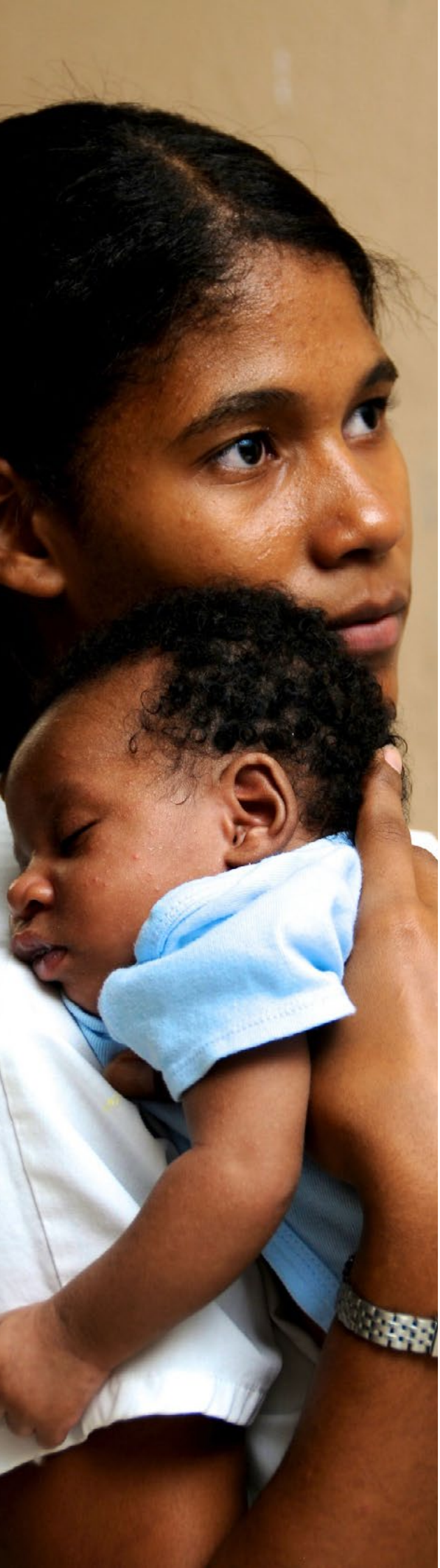
## II. Public health need for GAS vaccines

GAS infection is a major cause of death and disability globally, with an estimated number of annual deaths exceeding 500,000 *(1, 2)*. GAS causes a diverse spectrum of disease. Infection in the oropharyngeal mucosae and the skin is ubiquitous, and constitute the primary transmission reservoirs. The detailed determinants of transmission are unknown. An estimated 600 million cases of pharyngitis occur every year *(1, 2)*. Impetigo is also very frequent. GAS also causes severe local infections such as cellulitis, peritonsillar or retropharyngeal abscesses, necrotizing fasciitis as well as distant infections (septic arthritis) and sepsis. An estimated 160,000 annual deaths have been attributed to GAS invasive disease *(1, 2)*. Pregnant women, neonates, the elderly, and those with skin breakdown are particularly susceptible to invasive GAS disease. GAS has the potential to release toxins, inducing diseases such as scarlet fever and streptococcal toxic shock syndrome, which carries a very high case fatality rate *(3, 4)*.

Post-infection immune responses can lead to immune-mediated diseases. Acute rheumatic fever (ARF) can turn into rheumatic heart disease (RHD), and post-streptococcal glomerulonephritis (PSGN) can also occur and potentially lead to end-stage renal disease. RHD disease is often only detected at a late stage, with a high mortality rate. Characteristic valvular disease can cause secondary complications and strokes *(5, 6)*. RHD affects an estimated 33 million people worldwide, with about 319,000 deaths per year, and 10.5 million disability-adjusted life-years (DALYs) lost due to RHD *(3)*. ARF and RHD affect children, adolescent and young adults, cause premature disability and death, and deeply impact economies. RHD disproportionally affects women, with adverse pregnancy-associated complications.

Low- and middle-income countries (LMIC) bear the vast majority of the global disease burden *(1–3)*. Timely and complete antibiotic treatment of GAS pharyngitis will prevent most cases of subsequent ARF, but primary prevention of ARF based on antibiotic treatment of GAS pharyngitis has not been successful in reducing the population level burden of ARF and RHD in the context of resource-constrained health systems *(7)*. Untreated infections frequently result in substantial long term sequelae due to ARF, RHD and PSGN – often only detected at a late stage. The complexity of case ascertainment may be responsible for an under-estimation of the disease burden. The morbidity and mortality related to acute invasive disease is substantial, especially in vulnerable persons with old age, obesity or diabetes, among pregnant or peripartum women, and in newborn babies. GAS was the leading cause of maternal sepsis (in turn, the leading direct cause of maternal death) in the UK between 2006 and 2008 *(8, 9)*, and is a leading cause of early neonatal sepsis in Kenya *(10)*. Outbreaks of GAS-related diseases such as invasive infections with high mortality rates have been reported in both HIC and LMIC *(11, 12)*. In many countries, inappropriate treatment of sore throat with antibiotics, almost all of which are targeted at treating possible GAS pharyngitis, leads to a massive amount of antibiotic use, which in turn has a substantial impact on emergence of antimicrobial resistance among multiple bacterial species *(13, 14)*. The indirect burden related to antibiotic use, which contributes to the emergence of antimicrobial resistance, need to be considered in the evaluation of the medical need for a GAS vaccine.

There is currently no available primary prevention strategy of GAS suitable for global disease control. The overall disease burden from a variety of severe disease manifestations justifies a GAS vaccine to be an important public health goal.



## III. WHO vision and strategic goals for GAS vaccines

### Vision

**A safe, globally effective and affordable GAS vaccine is needed to prevent and potentially eliminate acute GAS infections (pharyngitis, skin infections, cellulitis, invasive disease) and associated antibiotic use, immune-mediated sequelae (kidney disease, rheumatic fever and rheumatic heart disease) and associated mortality.**

While the medical need of a GAS vaccine is highest in high endemicity LMICs, the value of a vaccine, primarily for prevention of GAS pharyngitis, skin infections and invasive disease and associated antibiotic use in HIC, is also highlighted.

### Near-term strategic goals

**To demonstrate favourable safety and proof of efficacy of a candidate vaccine against GAS pharyngitis and skin infections in children.**

### Long-term strategic goal

**To develop a safe, globally effective and affordable GAS vaccine for prevention of acute infections (pharyngitis, skin infections, cellulitis, invasive disease) and associated antibiotic use, and secondary immune-mediated sequelae (kidney disease, rheumatic fever and rheumatic heart disease) and associated mortality.**

# IV. Clinical research and development considerations

## 1. Vaccine construct, antigen target, formulation

Vaccine candidates in development include constructs targeting antigens that are highly polymorphic in the GAS population, such as those including the N terminal proportion of the M protein (encoded in the *emm* gene), on which the serotyping nomenclature is based. The M protein is a leading immunogenic target antigen including the N-terminal hyper-variable region and the more conserved C-repeat region closer to the cell surface. Although *emm* type-specific vaccines may provide some cross-protection against non-vaccine serotypes, multivalent or chimeric constructs will be required for polymorphic targets. Conserved antigen candidates including the conserved C-repeat region of the M protein, or non-M protein antigens, which may be surface expressed or secreted, have also been identified and are considered for vaccine development. Further research is needed to evaluate the scope of antigen diversity across geographic regions *(15, 16)*. Whether the same vaccine constructs will be appropriate for different geographical regions remains to be evaluated *(17)*. Cross-immunity affecting other, non-group A streptococci including group C/G and group B streptococci, should also be considered, depending on the distribution of target antigen expression across the various streptococcal groups.

Multi-component vaccines may be necessary and acceptable, but complexity should be kept to the minimum necessary to address public health goals, in order to contain the required investments and manufacturing costs. Various models may contribute to evidence generation for justification of the inclusion of single elements in multi-component vaccines. In vitro immunogenicity/bacterial killing assays, experimental animal and human infection models may be valuable to inform antigen selection, and further development of these tools is desirable.

A programmatically suitable formulation for IM or SC injection using standard volumes for injection would be acceptable. Product development strategies targeting pain-free delivery, would be welcomed. Mucosal delivery via the oral or nasal route should also be considered, as well as dermal delivery platforms with potential for reduced reactogenicity and ease of administration.

The potential for candidate vaccines to induce immune memory, which may be boosted by recall responses upon natural (re-)exposure, providing long term protection, will be critical. The presence of an adjuvant in the vaccine formulation if safe and justified, would be acceptable. Adjuvants with extended, favourable safety demonstrated will be preferred.

## 2. Target population

GAS affects all populations. Skin and pharyngeal infections remain common in both high- and low- income settings. In temperate climate/high-income settings, first infection – usually pharyngitis – typically occurs during pre-school or early school age. In tropical/low-income settings, the first infection is more commonly of the skin, and occurs at younger ages.

An immunization schedule providing protection starting during early childhood is therefore desirable. The optimal vaccination age may vary according to regional disease epidemiology. Inclusion in the Expanded Programme of Immunization (EPI) is desirable when considering logistic practicality and feasibility of delivery, and the early risk of skin infection in LMIC. In

high-income settings, a later schedule may be appropriate. The existing EPI schedule provides vaccines very early in life, and already includes several injections per visit. The EPI schedule is evolving to adopt a life-course approach and will include later visits during the second year of life, school age and in adolescence. Epidemiologically and immunologically appropriate ages for vaccination, linked to the provision of other vaccines or preventive childhood interventions may be explored and utilized when evaluating candidate vaccines. The need for boosters to maintain protection against an ongoing risk later in life should be determined.

The role of vaccination of adults, including individuals at increased risk of severe GAS disease, – i.e., pregnant women, people living with HIV, diabetes, obesity, malignancies or other immunosuppressive conditions, the elderly, should be defined.

The role of maternal immunization during pregnancy to prevent GAS puerperal sepsis and invasive infections in neonates and young infants should be considered.

The role of vaccine campaigns to interrupt transmission in high-risk populations and outbreaks of GAS-related diseases should be further investigated.

## 3. Efficacy evaluation

Sound considerations about possible vaccine development pathways have been presented elsewhere *(18)*.

Animal infection models have been developed but further evidence is needed to confirm their usefulness to predict immune responses in humans *(19)*.

Human experimental models of pharyngeal infections have been used in the past. Further research is required to determine clinical relevance. This research platform may be useful to filter down candidates worthy of further evaluation in studies with bigger sample size and contribute to the characterization of immune correlates of protection.

Pharyngitis and skin infections, being frequent, obligate intermediates on the causal pathway to more severe complications, constitute relevant and feasible early development vaccine efficacy trial endpoints. Provided favourable safety is established, initial licensure may justifiably be based on prevention of such more frequent disease syndromes that constitute a significant part of the disease burden and are recognized primary antecedent infections for more severe complications. Options for evaluation of vaccines against invasive infections, especially cellulitis and sepsis, should be considered.

The impact of vaccination on late immune-mediated disease syndromes may, depending on evidence generated, justifiably be evaluated only after initial licensure. Conditional licensure with agreed post-approval commitments may be an approval pathway to consider.

Standard case definitions of various relevant efficacy endpoints should be defined. Sample size and duration of follow-up should be based on evidence-based background rates of disease endpoints and targeted vaccine efficacy levels.

The vaccine impact on bacterial carriage, and potential for induction of herd immunity, should be characterized. The risk of bacterial population replacement with loss of protection through selective prevention of vaccine strains or serotypes will need to be evaluated. Further work is

required to determine the optimal methodology to assess the potential for vaccines to interrupt transmission, an important goal of vaccine strategies.

Different vaccine efficacy evaluation pathways may need to be considered in different geographical areas, according to regional predominant disease syndromes and age distribution, health economic considerations and public health priorities. High incidence of skin infections are seen in LMIC, starting very early in life. Interaction with scabies and how to account for it in vaccine evaluation and use should be further characterized.

Pharyngitis is a significant driver of antibiotic use globally and thereby a contributor to development of antibiotic resistance. The potential for vaccines to significantly reduce antibiotic use for the treatment of pharyngitis may constitute an important health economic benefit of GAS vaccine. The motivation for antibiotic treatment of sore throat is almost entirely driven by the possibility of GAS infection, which causes only 5–30% of pharyngitis cases. The volume of antibiotic use for treatment of GAS skin infection and cellulitis is not well characterized, but a significant vaccine-related reduction will constitute a further health economic driver. Antibiotic use should be monitored in large scale vaccine evaluation studies. Mathematical modelling may contribute to the estimate of the role of GAS vaccines in prevention of antibiotic exposure, emergence of microbial resistance, and vaccine preventable antibiotic resistance-related disease burden.

Further evidence is desirable to better inform target vaccine efficacy levels presented as part of the PPC tables, which have been developed by analogy and qualitative value assessment. The wide susceptibility age range, frequency of exposure, risk of escape variant selection, justify setting rather high target efficacy levels for pharyngitis and skin infection, as well as the need to reach a level of efficacy that provides the potential to impact standards of care and reduce antibiotic use. The value of preventing severe outcomes justify lowering target protection levels. Impact modelling could valuably inform how these preferences are set.

## 4. Safety evaluation

One vaccination study conducted in the 1960s among siblings of RF patients suggested a crude M protein vaccine preparation might have led to an increased susceptibility to ARF upon subsequent infection *(20)*. Since, thousands of individuals have been vaccinated with GAS constructs in other studies, with no emerging evidence of vaccine-induced auto-immunity *(20)*.

As a minimum, standard procedures for monitoring of vaccine-related adverse events should be implemented. The appropriate use of additional safety monitoring precautions should be considered. The optimal use of the following tools to contribute to appropriate selection of antigen and safety monitoring strategy should be better defined: GAS and human antigen sequence comparison studies, antigen molecular mimicry studies, animal vaccination studies, evaluation of vaccine-induced T- and B-cell effectors reactivity to human tissues; testing of immune serum for the presence of antibodies targeting human antigens. The role of cardiac echography, urine and blood analyses should be defined, taking into account baseline variability and the possibility of incidental, non-clinically significant findings. Safety endpoints need to be appropriately predefined; case ascertainment methodologies, individual stopping and group halting rules should be clearly detailed in study protocols.

## 5. Value proposition

An effective GAS vaccine is an important public health priority given the importance of the disease burden. GAS causes disability and deaths in the young adult population and other age groups, and has high direct and indirect impact on health economic systems. This should be better captured in a comprehensive global health value proposition analysis. A GAS vaccine value proposition analysis would aim to capture the public health and economic impact of vaccine use and investments needed to reach functional vaccine implementation in health systems. The value proposition assessment aims to support optimal stewardship of responsible investments. The main drivers of the value proposition are: vaccine-preventable burden of disease, cost of research and development, vaccine price, cost of implementation, impact on health systems. As the epidemiology vary between high-, and low- and middle-income countries, various health-economic scenarios need to be considered. The potential impact of vaccine introduction on standard medical practice including reduction of antibiotic use should be considered. Mathematical modelling can be a useful support in decision-making during clinical development, when interpreting available data, and upon policy decision on implementation and prioritization.

# B. PREFERRED PRODUCT CHARACTERISTICS FOR GAS VACCINES

| Parameter | Preferred Characteristic | Notes |
|---|---|---|
| **Indication** | Prevention of GAS-related pharyngitis, superficial skin infections, cellulitis, toxin-mediated disease, invasive infections and associated antibiotic use, secondary rheumatic fever, rheumatic heart disease and post-streptococcal glomerulonephritis. | Prevention of pharyngitis and skin infections would constitute relevant and feasible early vaccine development targets. See efficacy sections for further considerations on efficacy evaluation. |
| **Target population for primary immunization** | Primary schedule: infants and/or young children. | Further evidence is needed to define the optimal vaccination age according to epidemiological setting, and whether GAS vaccination would be most appropriately introduced in early infancy, or require later, early childhood doses, and late booster doses.<br>Research should determine the role of primary immunization in the following special circumstances:<br>• Secondary prevention in subjects at increased risk of RHD<br>• Immunization of adults at increased risk of cellulitis or severe invasive disease such as elders, individuals with diabetes, obesity, or other immune suppressive conditions<br>• Women, including pregnant women, for prevention of puerperal and neonatal sepsis<br>• Immunization campaigns for interruption of outbreaks of GAS-related disease |
| **Schedule, primary immunization and boosting** | No more than three doses required for primary immunization | Research should determine the required number of doses and schedule for primary immunization, and the requirements for booster doses. Boosting around school age, young adulthood and/or pregnancy, elderly could be proposed. Considering the age distribution of the disease burden, several booster doses may be required and acceptable. |

| Parameter | Preferred Characteristic | Notes |
|---|---|---|
| **Efficacy targets** | Preferences for target efficacy differ according to the severity of the target disease syndrome<br>• 80% protection against non-severe, non-invasive, confirmed GAS disease<br>• 70% protection against confirmed GAS cellulitis and other invasive infections<br>• 50% protection against long-term immune-mediated sequelae | Lower limits of acceptable vaccine efficacy are not defined here. Long-term protection is required given the age distribution of the disease risk. The preferred minimal follow-up time for efficacy evaluation is 2 years.<br>Appropriate efficacy endpoint case definitions and ascertainment methodologies for vaccine trials should be defined.<br>A strategy including pre-defined stage-gate criteria should be developed with the aim to minimize risk and accelerate vaccine development, and promote responsible research investment:<br>• The availability of a clinically relevant human experimental infection model may be very valuable.<br>• Early proof of concept focusing on more frequent, less severe endpoints (with pharyngitis and skin infection as a priority) should establish the potential protective profile.<br>• Vaccine efficacy against cellulitis and other invasive infections will require larger sample size.<br>• The impact on longer term, less frequent, severe complications, may need to be evaluated in pilot implementation or post-licensure studies.<br>The vaccine impact on carriage and transmission should be characterized. |
| **Strain and serotype coverage** | Efficacy targets are set irrespectively of strain/serotype considerations. The vaccine composition should ensure that a vast majority (preference for at least 90%) of the current disease-causing isolates from the region targeted for use are prevented. | The role of variation over time and potential for bacterial population replacement should be characterized.<br>Further research is needed to determine role of immune assays to infer strain/serotype specificity of protection. |
| **Safety** | Safety and reactogenicity profile at least as favourable as current WHO-recommended routine vaccines. | As a minimum, a standard safety monitoring plan should be implemented as part of clinical development efforts.<br>The appropriate use of additional safety monitoring tools including human antigen immune reactivity testing and echocardiography should be pre-defined, considering the risk of unspecific, coincidental findings, especially if multiple comparisons are planned.<br>The intensity of safety investigations should be tailored to the amount of accrued evidence about the safety profile. Safety endpoints of interest should be protocol defined and supported by sample size analyses. |
| **Adjuvant requirement** | Evidence should be generated to justify adjuvant inclusion in the formulation. | Adjuvants with established, favourable safety profiles are preferred over new adjuvants. |

| Parameter | Preferred Characteristic | Notes |
|---|---|---|
| **Immuno-genicity** | Established correlate/surrogate of protection based on a validated assay measuring immune effector levels/ functionality. | The longevity of the immune response should be characterized, and the relationship to duration of protection should be investigated.<br>Collaborative efforts towards the generation of relevant non-clinical assays, using open source reference reagents (including immune sera) with international standards of quality may greatly contribute to comparability assessments, generation of a regulatory acceptable correlate of protection, ultimately supporting immune bridging steps, clinical development plan simplification and accelerating the pathway to licensure. The role of reference laboratories is acknowledged. |
| **Non-interference** | Demonstration of favourable safety and immunologic non-interference upon co-administration with recommended other vaccines if used in the same target population. | |
| **Route of administration** | Injectable (IM or SC) using standard volumes for injection as specified in programmatic suitability for PQ or needle-free delivery. | The role of pain-free mucosal delivery via the pharynx or nasopharynx, and dermal delivery, should be considered. Preference for IM or SC over ID. |
| **Registration, prequalification and programmatic suitability** | The vaccine should be prequalified according to the process outlined in Procedures for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies. WHO-defined criteria for programmatic suitability of vaccines should be met (Appendix 1). | |
| **Value proposition** | Dosage, regimen and cost of goods amenable to affordable supply. The vaccine should be cost-effective and price should not be a barrier to access including in LMIC. | Reduction of antibiotic use in routine practice would be of high added value. The vaccine impact on health systems, economic impact and other aspects of implementation science should be evaluated in large trials, pre- or post-approval, as practicable. |

# Appendix 1

## USEFUL LINKS

1. WHO PPCs do not override existing WHO guidance on vaccine presentation, packaging, thermostability, formulation and disposal, addressed in documents from the WHO Vaccine Presentation and Packaging Advisory Group (VPPAG): http://www.who.int/immunization/policy/committees/vppag/en/index2.html.
2. Guidance about the WHO Prequalification (PQ) process which assesses vaccine quality, safety, efficacy and suitability for use in low and middle-income countries (for Programmatic Suitability for Prequalification (PSPQ) criteria is also available elsewhere: http://apps.who.int/iris/bitstream/10665/76537/1/WHO_IVB_12.10_eng.pdf.
3. Guidance on WHO regulatory expectations about clinical evaluation of vaccines can be found elsewhere: http://www.who.int/biologicals/expert_committee/WHO_TRS_1004_web_Annex_9.pdf

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