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WHO Preferred Product Characteristics for Group A *Streptococcus* Vaccines

DEPARTMENT OF IMMUNIZATION, VACCINES AND BIOLOGICALS

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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.