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# Group A *Streptococcus* Vaccine Development Technology ROADMAP

Priority activities for development, testing, licensure and global availability of Group A *Streptococcus* vaccines

2018

World Health Organization

GROUP A *STREPTOCOCCUS* VACCINE TECHNOLOGY ROADMAP

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## WHO secretariat

Martin Friede, Johan Vekemans.

## Image credits

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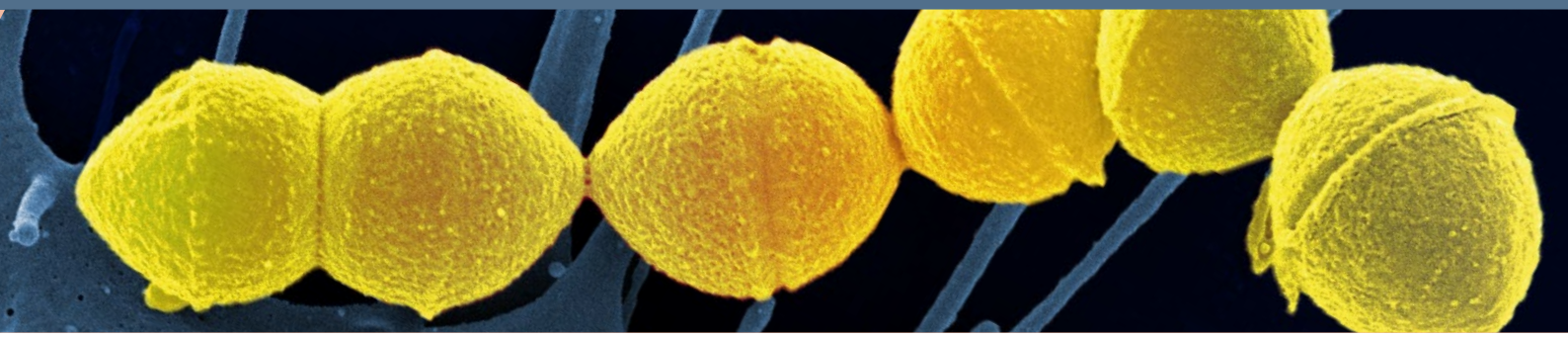

## Background on Technology Roadmaps

Vaccine development technology roadmaps produced by the World Health Organization (WHO) aim to provide a strategic framework outlining priority activities for vaccine researchers, funders and product developers, to accelerate the pathway to availability of vaccines in specific priority disease areas, addressing globally unmet medical needs.

The present roadmap states the WHO vision and strategic goals for group A *Streptococcus* (GAS) vaccine development. The document was written with input from academic groups, industry, regulators, financing bodies and public health agencies, among others. This document is not intended to be product- or product type-specific. WHO encourages implementation of the roadmap by the GAS vaccine research community. Progress in the field will be monitored, and the document will be updated if there are significant changes impacting the vision, strategic goals or priority activities.

## Introduction

*Streptococcus pyogenes* or group A *Streptococcus* (GAS) is a Gram-positive bacterium that expresses an array of virulence factors associated with a very broad spectrum of clinical manifestations in humans, its sole host and reservoir. GAS is one of the top infectious disease causes of death and disability worldwide, often affecting young people, mostly in low- and middle-income countries (LMIC). The pharyngeal mucosa and the skin represent the major anatomical sites responsible for maintaining the human reservoir of GAS and for human-to-human transmission.

Pharyngitis and impetigo are responsible for the greatest number of symptomatic GAS infections each year. GAS also causes invasive infections such as cellulitis, peritonsillar or retropharyngeal abscesses, necrotizing fasciitis, septic arthritis, and sepsis. GAS can produce an array of superantigens that can cause scarlet fever and streptococcal toxic shock syndrome, the latter of which has a high case fatality rate. The immune response to GAS infection can lead to self-targeted immune reactions, including acute rheumatic fever (ARF), chronic rheumatic heart disease (RHD) and post-streptococcal glomerulonephritis (PSGN), which itself may have a causative role in chronic renal impairment sometimes leading to end-stage renal failure. RHD, a sequela of ARF, is characterized by progressive valvular heart disease, frequently affecting young adults. The relative contribution of pharyngitis

and skin infections in the causal pathway leading to long-term complications is not well defined. In addition to cardiac and renal disease, cellulitis is a major contributor to economic, social, and health utilization burden of GAS disease. GAS also complicates pregnancy, with frequently unfavorable maternal and/or fetal outcomes. Women with sometimes subclinical pre-existing RHD may deteriorate during pregnancy because of hemodynamic changes, and RHD may account for a substantial proportion of maternal mortality in low income countries. GAS is also a leading cause of puerperal and neonatal sepsis. Outbreaks of GAS-related disease occur in closed, semi-closed as well as community settings.

Current prevention strategies have been unsuccessful in driving a reduction in the massive burden of GAS disease in LMIC, where the bulk of disease burden is presently concentrated. In high-income countries (HIC), while an important decline in RF, RHD and PSGN has been seen over the past half century, associated with economic development and antibiotic treatment of GAS clinical infections, adverse outcomes, especially invasive and toxin-mediated disease, however, remain, and young children, pregnant women and the elderly are particularly at risk. Rising trends in invasive disease and scarlet fever have been reported from some HIC.

Sore throat is a frequent trigger of antibiotic use, both in children and adults. While only a fraction of sore throats are related to GAS pharyngitis, the justification for antibiotic prescription is, in the great majority of cases, related to the perceived need to prevent GAS-related complications. Unjustifiably, although GAS remains universally susceptible to beta-lactams, broad-spectrum antibiotic use for suspected or confirmed GAS infection is widespread. This massive sore throat-driven antibiotic use contributes to the increasing global threat of antimicrobial resistance (AMR) by exposing other commensal bacteria to antibiotics.

Altogether, GAS infections have important economic, social, and health utilization consequences globally. Prevention of GAS infections and their immune-mediated complications through use of safe and effective GAS vaccines is, therefore, an important public health goal. A GAS vaccine may have the potential to massively reduce sore throat-associated antibiotic use. A key consideration in the use of GAS vaccines as part of a prevention strategy relates to the diversity in geographic distribution of GAS strains. GAS strains are most commonly categorized according to the variation in the nucleotide sequence of the N-terminal region of the emm gene that encodes the cell surface M virulence protein. Several GAS vaccine candidates are in various stages of pre-clinical and clinical development, including M protein-based vaccines (targeting the variable N-terminal sequence or the more conserved repeat region), and non-M protein antigens.


## 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 LMIC, the value of a vaccine, primarily for prevention of GAS pharyngitis, skin infections, cellulitis and invasive disease and associated antibiotic use in HIC, is also highlighted.

## Near-term strategic goals

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

## Long-term strategic goal

**To develop safe, globally effective and affordable GAS vaccines 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.**

While the long-term goal highlights the need for GAS vaccines capable of addressing the wide spectrum of disease and health-economic burden, the near-term strategic goal highlights the opportunity to reach proof of concept rapidly and prioritize vaccine candidate approaches for later evaluation. Pharyngitis and skin infections are assumed to be primary intermediates on the causal pathway to secondary immune-mediated GAS-related diseases, and key drivers of the global health and economic burden.

## Research priorities

### Improve global estimates of disease burden and better characterize the epidemiology of GAS infection

- Research is needed to better quantify and characterize the age and geographical distribution of key GAS disease syndromes, and priority should be placed on determining incidence of ARF and onset of new RHD in young people, puerperal and neonatal sepsis, and GAS-attributable mortality. A better understanding of transmission dynamics, the ecological reservoir, genetic diversity and molecular epidemiology is important. Surveillance programs should be developed.

### Further describe the spectrum of natural disease history

- Better estimates of the potential impact of prevention of GAS pharyngitis and skin infection on other severe disease entities would help inform the relative importance of the proposed near-term vaccine development strategic goals. A better quantification of the contribution of GAS infections and PSGN to end-stage kidney disease is needed. The determinants of transmission, including the role of asymptomatic carriage, should be better understood, informing the potential community impact of various vaccine use scenario.

### Drive improved understanding of GAS-related secondary immune-mediated diseases

- A better understanding of the drivers of immune-mediated diseases that occur after natural exposure would help inform vaccine development strategies. The role of repeated infections and the importance of their nature and severity is of particular interest.

### Define the consequences of GAS-associated antibiotic use, and estimate the impact of vaccine use on antibiotic use and antimicrobial resistance-