

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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This publication contains the collective views of an international group of experts of the WHO Group A *Streptococcus* Vaccine Working Group informed by a consensus building consultation process and does not necessarily represent the decisions or the policies of WHO.

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WHO secretariat

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Page 5: National Institute of Allergy and Infectious Diseases, National Institutes of Health

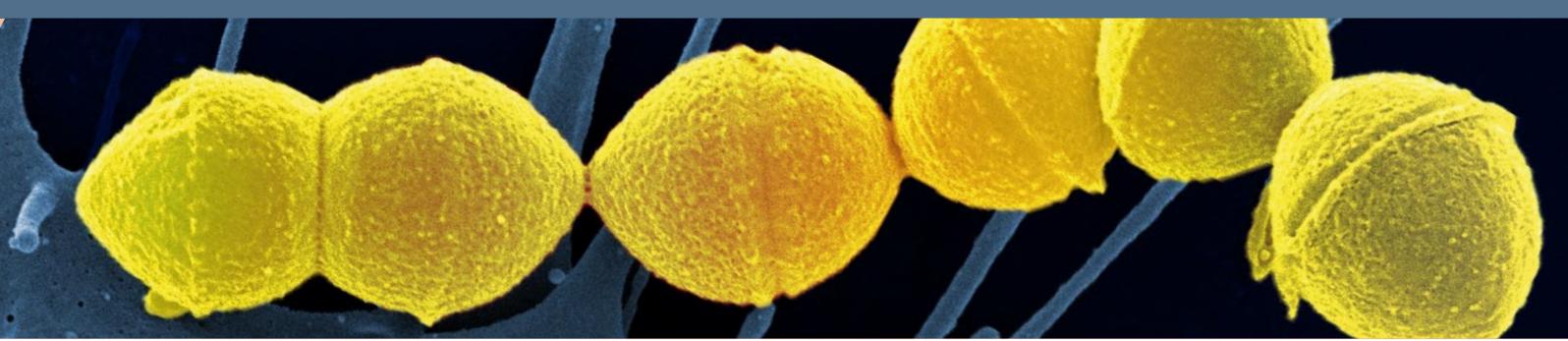
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Page 11: RHD Action



.....> 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-related morbidity and mortality

- Suspected and/or confirmed GAS infections are frequent triggers of antibiotic use, especially in patients presenting with sore throat. Antibiotics are also used for secondary prevention in subjects at risk of complications, in certain cases in household contacts and outbreak management. A GAS vaccine has the potential to reduce overall use of antibiotics, with consequent reductions of selection pressure on pathogenic as well as commensal bacteria. A better characterization of these effects would contribute to more compelling cost-effectiveness and investment case studies. Better estimates of GAS-driven antibiotic use in HIC and LMIC and GAS treatment-related AMR are needed.



.....> **Priorities in vaccine development activities**

Pursue antigen discovery efforts, increasing the number of pipeline vaccine candidates.

- Antigen selection and formulation efforts should aim at addressing global GAS antigenic diversity while minimizing product complexity.

Develop consensus guidance about the appropriate use of safety monitoring tools in candidate vaccine trials

- The due contribution of the analysis of sequence homology between streptococcal and human antigens, of human tissue and antigen immune reactivity and echocardiography to the assessment of candidate vaccines safety should be defined. A comprehensive review of evidence about past safety data from vaccine studies to inform safety monitoring strategies would be valuable.

Characterize immunological surrogates/correlates of protection

- Collaborative efforts towards the generation of relevant non-clinical assays, using open source reference reagents 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. Whether cross-strain/serotype immunity can be generated is an important question. The role of reference laboratories is acknowledged.

Define appropriate pivotal clinical trial design adapted to near-term and long-term strategic goals

- Primary and secondary efficacy endpoint case definitions, adverse events of special interest (AESI) should be defined; standard data collection plans should be developed to support case ascertainment; appropriate trial standards of care should be defined, considering local and WHO recommendations; appropriate trial data dissemination should be ensured.

.....> Key capacities

Define appropriate use of available and future animal models for GAS vaccine safety and efficacy evaluation according to their relevance for human responses

Develop clinically relevant human GAS experimental infection model(s) to support early vaccine proof of concept evaluation

- Clear evidence of efficacy derived from a controlled human infection model could streamline the identification and selection of GAS vaccine candidates most likely to progress through clinical development to large field trials. Such models provide opportunities to dissect immune responses and contribute to establishment of immune correlates of protection. As the outcome of experimental infection may be dependent on the challenge strain and procedures, any positive findings will need to be confirmed in conditions of natural exposure, in the target population.

Establish GAS expert research centres in low- and middle-income countries with Good Clinical Practices (GCP) trial research capacity and appropriate regulatory and ethical oversight; establish baseline rates of efficacy and safety outcomes

- Baseline studies that contribute to improved disease burden estimates provide the opportunity to test and develop standard case definitions and standard data collection methodologies supportive of optimal safety and efficacy evaluation, and support appropriate trial sample size determination. Determining baseline rates of AESI facilitate clinical trials safety data interpretation.

Access low cost vaccine manufacturing under current Good Manufacturing Practices (cGMP) for late stage development and commercial production

Develop standardized immune assay platforms that meet quality requirements

- Clinically relevant high-throughput functional assays able to assess strain-specific and cross-strain immunity should be developed following discovery of surrogates/correlates of protection and pathology with quality-assurance status adapted to vaccine development stage.



.....> **Preparing for policy, commercialization and delivery**

Establish cost-effectiveness and develop research and implementation financial investment scenario(s) to support appropriate funding and policy decision-making at the global and national level, considering the full scope of costs and benefits

- A better understanding of the investment case may encourage responsible stewardship and support for vaccine development and implementation. A comprehensive business case analysis would need to include estimates of research, development and manufacturing costs, market assessments and demand forecast, cost-effectiveness analyses, to support decision-making from manufacturers, research and implementation funders, WHO, and countries. Analyses should consider settings with different disease burden and standards of care for infection prevention, treatment and secondary prophylaxis against long-term adverse outcomes, and public health measures against outbreaks.

Ensure availability, affordability, and acceptability of a functional, cost-effective delivery platform for immunization

- New vaccine development and changes in delivery programs, in particular within the Expanded Programme on Immunization, should inform each other and be mutually responsive. Potential barriers to access and uptake should be understood, taking into account health care providers' perspectives, community acceptance, user concerns. Patient support and advocacy groups should be engaged. Gender issues and vulnerable, most-at-risk groups should be identified. Communication and advocacy plans should be developed accordingly to reduce the risk of missed opportunities to immunize.

Develop effectiveness and safety vigilance platforms for post-implementation surveillance.

- Transmission, strain replacement and the emergence of new virulent strains should be monitored. Monitoring of the impact of vaccine introduction on relevant current practice including reduction of antibiotic use is of particular interest.



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