BMJ Global Health

Research opportunities for the primordial prevention of rheumatic fever and rheumatic heart disease—streptococcal vaccine development: a national heart, lung and blood institute workshop report

Alma Fulurija,[1,2] Madeleine W Cunningham,[3] Natalia Korotkova,[4] Mary Y. Masterson ,[5] Geetha P. Bansal,[6] Michael G. Baker,[7] Jeffrey W. Cannon,[2,8] Jonathan R. Carapetis,[1,2,9] Andrew C. Steer[10]

To cite: Fulurija A, Cunningham MW, Korotkova N, *et al*. Research opportunities for the primordial prevention of rheumatic fever and rheumatic heart disease—streptococcal vaccine development: a national heart, lung and blood institute workshop report. *BMJ Glob Health* 2023;**8**:e013534. doi:10.1136/bmjgh-2023-013534

Handling editor Seye Abimbola

Received 28 July 2023
Accepted 1 November 2023

For numbered affiliations see end of article.

Correspondence to
Dr Alma Fulurija; alma.fulurija@telethonkids.org.au

ABSTRACT

Streptococcus pyogenes, also known as group A streptococcus (StrepA), is a bacterium that causes a range of human diseases, including pharyngitis, impetigo, invasive infections, and post-infection immune sequelae such as rheumatic fever and rheumatic heart disease. StrepA infections cause some of the highest burden of disease and death in mostly young populations in low-resource settings. Despite decades of effort, there is still no licensed StrepA vaccine, which if developed, could be a cost-effective way to reduce the incidence of disease. Several challenges, including technical and regulatory hurdles, safety concerns and a lack of investment have hindered StrepA vaccine development. Barriers to developing a StrepA vaccine must be overcome in the future by prioritising key areas of research including greater understanding of StrepA immunobiology and autoimmunity risk, better animal models that mimic human disease, expanding the StrepA vaccine pipeline and supporting vaccine clinical trials. The development of a StrepA vaccine is a complex and challenging process that requires significant resources and investment. Given the global burden of StrepA infections and the potential for a vaccine to save lives and livelihoods, StrepA vaccine development is an area of research that deserves considerable support. This report summarises the findings of the Primordial Prevention Working Group-VAX, which was convened in November 2021 by the National Heart, Lung, and Blood Institute. The focus of this report is to identify research gaps within the current StrepA vaccine landscape and find opportunities and develop priorities to promote the rapid and successful advancement of StrepA vaccines.

SUMMARY BOX

- ⇒ Despite the availability of antibiotic treatment, disease burden attributed to group A streptococcus (StrepA) infections remains high, particularly in low-income and middle-income countries (LMICs), highlighting the need for disease prevention and vaccination as a potentially cost-effective and feasible option.
- ⇒ The StrepA vaccine pipeline is sparse, and there has been little investment in the development of StrepA vaccines in the last few decades, largely due to technical hurdles and regulatory concerns around safety.
- ⇒ There is a need for greater investment into the research and development pipeline for StrepA vaccines particularly in LMIC, to progress current advanced candidates to clinical proof of concept studies, and to identify new vaccine targets to prevent the initial acute stages of StrepA infection.
- ⇒ There is a need for greater investment in development of sentinel sites with strong disease surveillance to support future vaccine trials, especially in the LMICs.
- ⇒ There is a need to better understand StrepA immunobiology and natural protection from StrepA disease, thereby offering avenues to identify natural correlates of protection that could be induced by a vaccine.
- ⇒ Research opportunities also exist to develop better animal models of StrepA disease that recapitulate key features of human infection, but also clinical trials to be able to address the potential safety concerns surrounding StrepA vaccine development. Human challenge models offer a pathway for early and rapid assessment of vaccine efficacy.
- ⇒ Limited understanding of pathogenesis associated with StrepA infections, and a lack of suitable animal models has contributed to the minimal number of candidates in development.

INTRODUCTION

Group A Streptococcus (*Streptococcus pyogenes*; StrepA) is a highly infectious obligate human pathogen that can cause a diverse array of infections such as pharyngitis, impetigo, toxic shock syndrome and acute glomerulonephritis.[1–3] StrepA infections can lead to significant morbidity and mortality, particularly in vulnerable populations such as young children and elderly adults. In 2019, the Institute for Health Metrics and Evaluation Global Burden of Disease study estimated there to

be >600 million cases of pharyngitis globally (mainly affecting young children), leading to 500 000 deaths annually.[4] Repeated infections can trigger autoimmune sequelae such as acute rheumatic fever (ARF) and rheumatic heart disease (RHD) which affects nearly 40 million individuals globally and results in >300 000 RHD-related deaths.[1 5–7]

Traditionally, primordial prevention encompasses interventions and strategies that reduce the risk of disease presentation. Vaccine and social behavioural measures strongly influence risk to infectious disease exposure (eg, polio, smallpox, influenza) and management of diseases due to lifestyle choices (eg, obesity, hypertension, diabetes). Some chronic conditions have early origins in childhood when habits are formed that can potentially lead to irrevocable and undesirable health conditions. The early onset of StrepA-associated pharyngitis can result in the development of RHD if not adequately addressed.[4] Therefore, timely diagnosis remains a core issue among LMICs. StrepA was first identified almost 150 years ago and despite decades of effort, there is still no licensed vaccine due to technical, financial and regulatory challenges.

During a workshop held by the National Heart Lung Blood Institute on 'Eradication of Rheumatic Heart Disease: Assessing Research Challenges and Opportunities' in November 2021, the Primordial Prevention Working Group (PPWG) focused on social determinants of health (PPWG-SDH) and vaccine development efforts (PPWG-VAX) that can be applied to prevent or reduce the subsequent sequelae that progresses to RHD.

The focus of this report is to present the identified research gaps within the current StrepA vaccine landscape and find opportunities to promote the rapid and successful advancement of StrepA vaccines within the following key research areas:

1. Basic science studies of disease pathogenesis and progression, including potential biomarkers of risk and poor outcomes.
2. Revitalisation of the StrepA vaccine development pipeline including discovery of novel vaccine candidates and identification of correlates of protection (COP).
3. Development of a dedicated global network to support StrepA surveillance, vaccine trials and manufacturing.
4. Development and implementation of interdisciplinary approaches to promote equitable access to vaccines.

This paper provides a summary of the proceedings of the PPWG-VAX and proposes a list of key opportunities that should be considered when advancing StrepA vaccine development, which is complementary to the PPWG-SDH recommendations.

KEY RESEARCH TOPIC 1

Basic science studies of disease pathogenesis and progression

StrepA vaccine development requires a thorough understanding of the mechanisms of StrepA pathogenesis, immunobiology, host–pathogen immunogenetics, and a multidisciplinary approach that integrates basic science research, preclinical studies and clinical trials. The key basic science areas needed to advance StrepA vaccines include:

1. StrepA biology and the host immune response to StrepA.
   a. Understanding StrepA virulence factors, their contribution to pathogenesis, as well as the identification of new vaccine targets and biomarkers of risk and poor outcomes.
   b. Comprehensive knowledge of the host immune response to StrepA infection (immune state/disease state) and immune mechanisms of protection against StrepA.
   c. Understanding of global evolution dynamics of StrepA and disease associations.
2. Development of appropriate preclinical animal models.
3. Human challenge studies and efficacious clinical trials.

StrepA biology and the host immune response to StrepA infection

An ideal StrepA vaccine would induce an immune response that prevents colonisation or rapidly clears the acute infection, without causing excessive inflammation or tissue damage. Therefore, studying the biology of StrepA and the host immune response to StrepA infection is essential to identify vaccine targets and understanding how the immune system can be harnessed to protect against StrepA infections. This research can inform the design of vaccine candidates that are effective against a broad range of globally circulating StrepA strains and associated diseases and induce a robust and protective immune response without causing harmful side effects.

StrepA has evolved several strategies that allow the evasion or subversion of the host immune response, enabling it to establish and maintain infections.[8 9] StrepA proteins with immune evasion properties include M protein, hyaluronic acid capsule, streptolysin O (SLO) and S (SLS), DNases, adhesins, proteases and pyrogenic toxins.[8 10]

Characterisation of immune evasion strategies is critical to inform the development of effective vaccines and therapeutics against StrepA to enhance the host immune response and limit the ability of StrepA to establish and maintain infections.

Currently, there is incomplete understanding of the role and function of StrepA antigens in host responses.

Preclinical animal models

Animal models are useful tools to study disease pathogenesis, optimise vaccine design and formulation, understand immune responses, assess vaccine safety, and evaluate vaccine effectiveness prior to initiating clinical trials. Animal studies are often required by regulatory agencies to provide important data on safety and efficacy to support regulatory approval. These models have been used extensively to study the pathogenesis of StrepA infections[11 12]

and to evaluate the efficacy of vaccines.[13–20] However, the current models have several limitations including species-specific differences and a lack of host specificity, given that StrepA is a human-specific pathogen.

To date, there is no single model that can accurately mimic the pathophysiology of human diseases caused by StrepA. This issue significantly restricts the use of animal models for assessment of StrepA vaccine efficacy in humans. Most StrepA vaccines have been evaluated in mouse models of systemic disease or subcutaneous infection and focused on the prevention of deaths in animals and bacterial clearance. It is unclear if these models can serve as surrogates for human infection, since the initial target indication for a StrepA vaccine is acute pharyngeal infection, and a limited number of StrepA strains colonise the mouse nasopharynx. Extensive strain diversity, combined with an incomplete understanding of the strains that are representatives of the population, constitute another challenge for evaluation of StrepA vaccines.

The non-human primate (NHP) model of pharyngitis is considered the current standard as it most closely mimics human pharyngitis.[19] However, high costs, ethical concerns and technical challenges[21] associated with working and maintaining these animals limit the use of NHPs for vaccine studies.

Currently, there is no animal model that completely recapitulates ARF/RHD, which are uniquely human diseases. Lewis rats remain the only available model to investigate the pathogenesis of ARF/RHD and assess the safety of StrepA vaccine candidates.[22–24] The Lewis rat model reflects early events that lead to cardiac valvular pathology, but it does not follow the natural course of StrepA infection. It can be used to investigate the autoimmune process involved in immune-mediated StrepA disease following immunisation with streptococcal antigens such as the M protein,[25] and has shown that repeated streptococcal infections are required to produce the autoimmune and inflammatory manifestations and electrophysiological changes in the heart.[26] The model has also been used to study brain sequelae and chorea symptoms after group A streptococcal immunisation.[27]

Novel animal models that more accurately mimic the spectrum of StrepA disease in humans are urgently required, to provide a preclinical platform for vaccine safety and efficacy evaluations prior to clinical trials.

Human challenge studies and clinical trials

Recently a human challenge model for StrepA has been developed by Osowicki and colleagues.[28 29] Importantly, critical to vaccine development efforts, the successful establishment of a human challenge model for StrepA paves the way to establish an early indication of vaccine efficacy and establish vaccine COP.

Human challenge models have contributed directly to regulatory approval of vaccines for other pathogens including for typhoid.[30 31] For current StrepA vaccines, the human challenge model is limited in that it does not reflect the target population (young children and infants) and is performed in a primed adult population with pre-existing StrepA immune responses. The role of such a model in later phase evaluation and approval of StrepA vaccines is yet to be determined and will be informed by results from future trials. Nevertheless, human challenge models have potential as an important tool for vaccine development in humans.

Progression of StrepA vaccine candidates through the clinical development pathway into proof-of-concept phase 2b trials and then phase 3 licensing trials in the target population will be critical to future distribution of safe and effective vaccines. While straightforward, with potentially modest sample sizes for efficacy studies of pharyngitis in preschool aged children, there are several challenges that lie ahead and will need careful consideration throughout the clinical development pathway. These include the lack of a correlate of immune protection, safety concerns regarding induction of ARF by a vaccine (or when a vaccinated individual is next exposed to StrepA), debate concerning the target population and target indication, and questions around whether prevention of StrepA pharyngitis will necessarily lead to prevention of ARF and RHD.

Gaps

Several gaps exist in the state of understanding of the biology, pathogenesis and immunology of StrepA and include the following:

1. A lack of animal models that mimic the full spectrum of human disease caused by StrepA, making it difficult to fully evaluate vaccine candidates.
2. A lack of understanding of the host immune response to StrepA and StrepA immune evasion mechanisms: better understanding of these aspects will allow for identification of new vaccine targets and protective immune responses that can inform and improve vaccine design.
3. Further validation of the human challenge model for StrepA, including diverse strains, will inform vaccine formulation and dose, as well as COP in humans.
4. Lack of vaccine candidates progressed into clinical trials and an unclear clinical development pathway to licensure for StrepA vaccines.
5. Lack of knowledge relating to biomarkers for ARF risk and poor outcomes of ARF including severe RHD.

Opportunities

The PPWG-VAX has recognised the need for the following studies to address identified gaps:

1. Natural infection studies to assess disease pathogenesis and characteristics of immunity, including detailed longitudinal cohort studies to better understand recurrent infections and immune mechanisms involved in acute infection and autoimmune disease.
2. Molecular characterisation of StrepA isolates causing symptomatic versus asymptomatic infection (carriage).
3. Longitudinal studies of StrepA transmission dynamics in different settings.

4. Development of appropriate preclinical animal models of acute StrepA infection (pharyngitis, skin).
5. Further development and refinement of the human challenge model to study host immune responses at the mucosal site and systemically.
6. Support to accelerate vaccine candidates into clinical trials.

KEY RESEARCH TOPIC 2

Revitalisation of the StrepA vaccine development pipeline including discovery of novel vaccine candidates and identify COP

The history of StrepA vaccine development dates back over 100 years. Vaccine strategies have included whole cells, pyrogenic toxins, M protein and non-M protein as vaccine targets.[10 32–34] The most direct evidence of vaccine prevention of human StrepA infection came from a series of human challenge studies held in the late 1960–1970s,[35–38] where several studies showed that type-specific immunity was achievable after vaccination with M protein extract, but high reactogenicity was reported. Unfortunately, a report of an increase in cases of ARF in vaccinees[39] contributed to a US Federal ban on testing in humans that remained in effect until 2006.

StrepA vaccine development has been impeded by several factors including significant strain diversity and antigenic variability, diverse geographical distribution of serotypes, and the lack of definitive correlates of human immune protection. Another critical issue is a lack of understanding of the molecular mechanisms that lead to autoantibody and autoreactive T cell recognition of human proteins in the case of ARF/RHD and the immune cross-reactive StrepA epitopes involved in the disease process.[40 41]Vaccine design must consider maximum coverage, efficacy and above all, safety. Long-term immunity should also be expected from StrepA vaccines, and it will be most important to establish immunity that will prevent ARF and RHD. It is anticipated that preventing acute StrepA infections will result in the prevention of ARF/RHD, therefore StrepA pharyngitis is an accepted first target indication for StrepA vaccines.[42] Furthermore, identification of biomarkers of ARF risk is important to help identify individuals more likely to develop StrepA immune sequelae. One potential biomarker was identified in patients with ARF, RHD and Sydenham chorea.[43] N-acetylglucosamine-specific IgG2 antibodies were significantly elevated only in RHD and Sydenham chorea but was not elevated over normal levels in children with acute streptococcal pharyngitis.

Despite the challenges, ongoing efforts are continuing to develop a safe and effective vaccine against StrepA, and although the vaccine pipeline is sparse due to limited investment, there are several StrepA vaccine candidates entering or in clinical studies.[33]

StrepA vaccine pipeline

A vaccine to prevent StrepA pharyngitis must be broadly effective while avoiding the induction of cross-reactive autoantibodies. Early vaccine design relied on purified M protein; the major surface-associated virulence factor which elicited protective antibodies in early trials. However more recently several non-M proteins and the main constitutive component of the StrepA cell wall, the Lancefield group A carbohydrate (GAC), have been shown to be protective in preclinical animal models.[10 16 33] The highly conserved nature of non-M proteins and GAC across various serotypes and lack of evidence of tissue cross reactivity of vaccines comprising these proteins, makes them an attractive target for vaccine development, along with epitopes from M protein.[10 44–46] Problems can arise if vaccines do not induce sufficiently strong bactericidal or opsonising antibodies required for systemic clearance of StrepA. Thus, vaccine antigens able to induce protective immune responses that opsonize the bacteria and target it for immune clearance are desirable.[47] Conversely, for StrepA, an upper respiratory pathogen, mucosal immunity is relevant and likely to be required to prevent infection, which has been more difficult to generate and maintain than systemic immunity.

Multiple StrepA vaccines candidates are in development (table 1). M protein vaccines target either the N-terminal variable region (eg, StrepAnova) or the conserved C-region of the M protein (eg, Combivax, StreptInCor), a major surface-associated virulence factor which elicited protective antibodies in early trials.[10 44 45 48] The advantage of N-terminal region M protein vaccine design is that immunity is type specific; however, this has a major limitation due to the genetic diversity (>260 types) of StrepA. To overcome this and achieve broader coverage against circulating StrepA serotypes, vaccines were designed based on epitopes from the highly conserved C region of the M protein believing the vaccine would be cross-protective.[16] Although the only demonstrated correlate of protection for StrepA vaccines is M protein, certain amino acid sequences have been associated with a risk of inducing ARF.[40] As outlined previously, a critical need for StrepA vaccine development is a better understanding of the immune mechanisms that drive ARF/RHD, and characterisation of the StrepA proteins involved, so that appropriate vaccines can be designed and will be safe.

Strategies targeting other immunodominant, conserved StrepA antigens were also employed, since highly conserved StrepA proteins appear to possess a lower potential for antibody cross-reactivity.[49–53] Several of these antigens were combined into multicomponent vaccines containing combinations of non-M protein antigens including the peptidases SpyCEP and C5a, SLO, adhesion and division protein SpyAD, arginine deiminase, trigger factor, pilus protein, pyrogenic exotoxins and GAC, and showed protection from StrepA infection in animal models.[13 14 17 19 54–60]

Conversely, a limitation of GAC, is that the N-acetylglucosamine (GlcNAc) side chains have been implicated in

Table 1 Current StrepA vaccine development pipeline

Vaccine class	Vaccine candidate	Vaccine design	Adjuvant	Vaccine developer	Stage of development
Non-M protein vaccines					
Type specific	StreptAnova	30-valent N-terminal epitope fusion proteins[45 93]	Alum	University of Tennessee Research Foundation, USA	Completed phase I
C' repeat region of M protein	StreptInCor	55aa peptide derived from the C-terminal M5 protein[17 94 95]	Alum	University of Sao Paulo, Brazil	Preclinical
	J8 CombiVax	12aa peptide derived from P145 conserved region of M protein+20 aa peptide derived from SpyCEP[14 96]	Alum	Griffith University, Australia	Phase 1
	P*17 CombiVax	20aa peptide derived from P145 + 20aa peptide derived from SpyCEP[14 97]	Alum	Griffith University, Australia	Phase 1
Non-M protein vaccines					
Conserved proteins and GAC	4-Combo	SpyCEP, SLO, SpyAD, GAC[49 50 55]	Alum	GSK Vaccines for Global Health, Italy	Preclinical
	5-Combo	TF, ADI, SLO, SpyCEP, ScpA[19 56]	SMQ	University of Queensland, Australia	Preclinical
	TeeVax	T antigen fusion proteins[58 73]	Alum	University of Auckland, New Zealand	Preclinical
	Vax-A1	modified GAC conjugated to SpyAD ScpA, SLO[63]	Alum	Vaxcyte, USA	Preclinical
		Undisclosed	Undisclosed	Moderna, USA	Preclinical
		Undisclosed—based on GAC[64]	Undisclosed	Rhapseda, UK	Preclinical
		Based on a SpeA,-SpeB fusion protein[59 60]	Undisclosed	Vaxform, USA	Preclinical

ADI, arginine deiminase; GAC, group A carbohydrate; ScpA, Streptococcal C5a peptidase; SLO, streptolysin O; Spe, streptococcal pyrogenic exotoxin ; SpyAD, S. pyogenes adhesion and division protein; SpyCEP, Streptococcal cell envelope protease; TF, Trigger Factor.

provoking autoimmune cross-reactivity in RHD.[61] The presence of antibodies to GAC in patients with ARF has been reported[43]; however, it is important to mention that vaccines containing GAC have not caused cross reactivity.[46] Therefore, a glycoconjugate vaccine based on the modified polyrhamnose backbone lacking GlcNAc sidechains is also being explored as a vaccine and has demonstrated protection in animal models without evidence of cross reactivity to human tissues.[51 62–64] Table 1 summarises the limited StrepA vaccine pipeline and status of development.

Mucosal immunity

StrepA vaccines in development rely on their ability to induce broadly neutralising systemic immune responses to several immunodominant proteins. Acute infection occurs at the mucosa in the nasopharynx. It is plausible that mucosal vaccines may confer better protection against StrepA at the site of infection, thus preventing infection and colonisation. There are few mucosal vaccines in development, although delivery of the conserved M protein CombiVax vaccine intranasally, after a systemic priming dose, induced robust mucosal responses and protected mice from StrepA challenge.[13] Similarly, expression of the StrepA pilus in *Lactobacillus lactis* generated protective immune responses.[65 66]

The limited research into StrepA mucosal vaccines is related to insufficient understanding of the host–bacteria interaction and mucosal immune responses to StrepA, the lack of suitable experimental models that fully recapitulate human infection by StrepA, and effective delivery systems that protect vaccine antigens from degradation. Furthermore, the use of vaccine adjuvants for design of more effective StrepA vaccines has been limited. Unfortunately, few adjuvants are approved for use in humans, and no mucosal adjuvant formulations have been licensed.

Current vaccine strategies do not target StrepA at mucosal sites, and there is a need for greater understanding of mucosal immune responses that are protective and longer lasting, to inform next generation vaccine strategies.

Autoreactive antibodies and safety

Autoreactive antibodies induced by proteins or antigens from StrepA can potentially induce cross-reactive

antibodies that mistakenly attack healthy tissues and organs in the body. In some cases, such immune responses can cause tissue damage and inflammation, resulting in autoimmune disorders such as ARF.[40] Importantly, T cells, that cross-react with heart proteins or other antigens have been reported.[67 68] CD4+ T cells can help B cells to induce cross-reactive autoantibodies. Cytotoxic CD8+ T cells can attack valve tissues particularly in women who are at risk for the development chronic rheumatic heart valve disease.[69] The development of invasive or autoimmune diseases could also indicate defects in follicular T cell functionality.[70] Therefore, the risk of acquiring these autoimmune disorders due to cross-reactive antibodies and T cells induced by StrepA proteins varies among individuals and depends on multiple factors, such as genetic predisposition including HLA, previous exposure to StrepA, and some StrepA proteins which may even have protective effects against autoimmune diseases. Characterisation and testing of vaccine candidates that have minimal likelihood of inducing autoreactive antibodies are essential to ensure both safety and lasting immunity against StrepA.

Correlates of protection

Limited understanding of mechanisms of immunity to StrepA remains a significant impediment to vaccine development both in terms of identifying optimal antigenic targets of vaccination and developing assays that act as CoP. Although immunity to StrepA is not well understood, antibody-mediated bactericidal and opsonophagocytic activity are thought to be important protective immune mechanisms. Such assays have been suggested to correlate with protection[71 72] and type-specific M protein vaccines were shown to induce stronger type-specific protection than other StrepA antigens with opsonic activity.[72 73] In addition, T cell mediated responses may also contribute to protection. CD4+ T cells provide needed signals to activate B cells in order to generate protective antibodies. Both CD4+ T cell mediated and humoral responses should be evaluated to determine the impact and efficacy of related vaccine development efforts.

CoP assays are an important aspect of vaccine development and once identified could replace the need for clinical endpoints in vaccine efficacy trials. Frost *et al* recently highlighted the lack of CoP and the need to establish standardised CoP assays.[74] Identification of CoP requires clinical trials of StrepA vaccines and natural infection studies. At present, there are knowledge gaps hindering the development of humoral and T-cell mediated assays including better understanding immunity to StrepA in humans, availability of quality biobanks and demonstration of vaccine efficacy with a clinical endpoint.

Gaps

To address these identified barriers, several research gaps have been identified including:

1. Need to address vaccine safety and efficacy before widespread utilisation, including better understanding of natural infection and immunity in adults and children.
2. Need to identify correlates of vaccine induced protection both in the blood, and at the mucosa, compared with natural correlates of immunity/disease.

Opportunities

The PPWG-VAX has recognised the following opportunities to address identified gaps

1. Investment in StrepA vaccine pipeline; particularly discovery research to identify new vaccine targets.
2. Development of mucosal vaccine strategies to target infection at mucosal sites versus systemic protection with bactericidal and opsonic clearance.
3. Identification of vaccine CoP at mucosal and systemic sites.

KEY RESEARCH TOPIC 3

Development of a dedicated global network to support StrepA surveillance and vaccine trials

Vaccine developers and decision-makers require high quality disease burden data to guide vaccine development and to help prioritise public health measures as well as commercial investment. Therefore, disease surveillance plays a critical role in supporting the development and licensure of vaccines. Well-established disease surveillance networks are necessary to (1) understand the burden of disease, (2) assess vaccine efficacy, (3) allow early detection of adverse events, (4) identify breakthrough infections, (5) determine impact of vaccines on transmission, (6) detect vaccine safety signals and (7) facilitate post-licensure surveillance.

Disease surveillance is indispensable in vaccine trials, as this provides real-time data on disease incidence, vaccine effectiveness, safety monitoring and impact on disease transmission. By closely monitoring the target disease and vaccinated populations, surveillance systems contribute to the overall success of vaccine development, evaluation and post-approval monitoring, ensuring public health protection, informing policy-makers and promoting evidence-based immunisation practices.

StrepA disease surveillance and vaccine trials

The first attempt to quantify the global burden of StrepA diseases was published as recently as 2005, which highlights the under-recognition of StrepA diseases as a global health priority; an example is the disconnect between RHD burden and the relatively modest research and development investment efforts into RHD, making it one of the most neglected of all infectious diseases.[75] While more recent epidemiological data, including an update of the GBD Study, have contributed to improved estimates of the burden of RHD,[76] there remains a lack of a strategic approach to collecting and analysing critical epidemiological data from LMIC.

A 'data purpose matrix' was recently developed outlining how a strategic approach could help prioritise StrepA disease burden data required for different purposes and audiences in order to accelerate vaccine development.[77] The matrix identifies how data can be used to assist with advocacy, regulatory, policy and financing strategy at each stage of vaccine development and provides detailed guidance for the specific StrepA surveillance data that should be prioritised for each disease endpoint.

A global coordinated network that has the capacity to gather geographically diverse national StrepA disease burden data across the spectrum of StrepA diseases, and more accurately estimate the burden of disease would be a valuable proposition and would critically support future StrepA vaccine trials.

Priorities for StrepA disease surveillance

As outlined in the WHO technical road map, the most immediate priority is to progress to vaccine efficacy studies using StrepA pharyngitis and skin infections as primary endpoints, and pharyngitis is a suitable first target indication, endorsed by WHO. Vaccine effectiveness against endpoints such as ARF, RHD, post-streptococcal glomerulonephritis and invasive disease will require post-licensure evaluation,; hence, a priority is to establish reliable ongoing surveillance mechanisms for these conditions in a range of settings, ready for when licensed vaccines become available.

The priority areas that must be addressed in order to establish quality StrepA disease surveillance includes understanding the disease pathogenesis, epidemiology and transmission dynamics, clinical trials, post-licensure studies, efforts to harmonisation protocols and data collection, antimicrobial considerations such as antibiotic use, and economic evaluation (figure 1).

Hence the most urgent priority is to progress to vaccine efficacy studies using StrepA pharyngitis and skin infections as primary endpoints and to establish reliable ongoing surveillance mechanisms for StrepA in a range of settings is a priority.

Gaps

To address the barriers identified above, several research gaps have been identified including:

1. Need to improve global estimates of disease burden and characterisation of StrepA epidemiology.
2. Need to improve the understanding of StrepA-related secondary immune mediated diseases.
3. Need to understand the ramifications of StrepA associated antibiotic use and the potential impacts of vaccine use on antibiotic consumption and antimicrobial resistance (AMR).
4. Need to build global networks to facilitate the above activities.

Opportunities

In alignment with these goals, the PPWG-VAX recognises the following opportunities:

1. Implement standardised surveillance protocols to promote data harmonisation between sites.
2. Characterise immunological surrogates/COP during clinical trials.
3. Develop guidance documents for the appropriate use of safety monitoring tools in vaccine trials.
4. Develop effectiveness and safety platforms for postimplementation surveillance.
5. Define appropriate clinical trial design adapted to near-term (pharyngitis) and long-term (ARF/RHD) endpoints.

KEY RESEARCH TOPIC 4

Development and implementation of interdisciplinary approaches to promote equitable access to vaccines

Development and implementation of interdisciplinary approaches and multistakeholder collaborations are essential for promoting equitable access to vaccines.

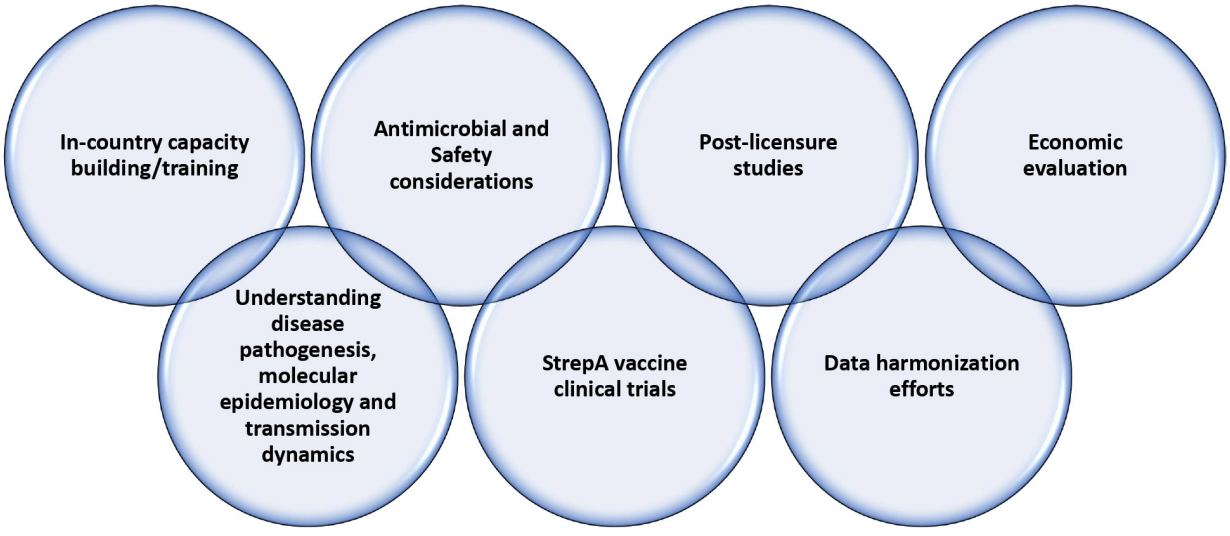

Figure 1 Research priorities for surveillance sites.

Table 2 Examples of vaccine introduction in LMICs after vaccine licensure[98 99]

Vaccine	Time of licensure	First implementation in LMICs
Pneumococcal conjugate vaccine (PCV)	2000	Rwanda: 2009; Kenya: 2011; Ghana: 2012
Rotavirus vaccine	2006	Nicaragua: 2006; Brazil 2006, South Africa 2009, Mali 2015, Malawi, 2015, India: introduction over several years
Human papilloma virus (HPV) vaccine	2006	Bhutan: 2010; Rwanda: 2007; Uganda: 2007; Cambodia: 2007
Hepatitis B vaccine	1981	China: 1992; Indonesia: 2000; Nigeria: 2004
Meningococcal conjugate vaccines	2005, 2010	Burkina Faso, Mali, and Niger in 2010
HiB polysaccharide vaccine HiB conjugate vaccines	1985 1987	Ghana: 2002 GAVI HIB initiative>2005
Malaria vaccine	2018 (approved for pilot introduction)	Ghana, Kenya, Malawi 2019

Through fostering collaborations and strong relationships, we can build capacity and capabilities, address inequities, analyse comprehensive data, optimise resources, and contribute to more effective and equitable vaccine access, reducing the impact of infectious diseases. Understanding the barriers/enablers to vaccine development and implementation, and the needs of key stakeholder and policy-makers early during development will facilitate accelerated progress towards licensure and implementation of safe and effective StrepA vaccines.

Prior studies have demonstrated that more is needed to ensure equitable access and distribution of vaccines than simply identifying candidate vaccines that are safe and effective. There are many examples of vaccines that took years, or even decades, to be available population-wide, long after they were confirmed as safe and effective vaccines (table 2). Multiple factors influence vaccine access and distribution, which could be addressed earlier in the vaccine development pipeline to proactively overcome these barriers. These include assessing the potential market size for vaccine distribution, the health-economic impact of vaccination compared with other prevention strategies, and the funding mechanisms for vaccine supply and administration. Therefore, there is a need to proactively circumvent potential impediments faced preventing the rapid uptake of and equitable access to safe and effective vaccines.

Time from licensure to implementation for paediatric vaccines in LMIC can vary based on several factors, including the specific vaccine, country context, healthcare infrastructure and financing. For example, rotavirus vaccine, first licensed in 2006, was implemented in Nicaragua shortly after licensure, but other countries introduced the vaccine over several years.[78] Pneumococcal conjugate vaccines, first licensed for use in 2000, a decade or more to implement with introduction in Rwanda in 2009, Kenya in 2011 and in Ghana 2012. The human papillomavirus vaccine was licensed in 2006 and varied in time to implementation, with Bhutan introducing the vaccine in 2010. Global initiatives, such as GAVI The Vaccine Alliance (formerly The Global Alliance for Vaccines and Immunization), The Bill and Melinda Gates Foundation (BMGF) and PATH, play crucial roles in accelerating the introduction of new vaccines in LMIC by providing support and resources.

Learnings from COVID-19 vaccine development

The accelerated development and deployment of COVID-19 vaccines are a testament to the effectiveness of collaborative efforts among stakeholders. Several factors contributed to this acceleration including global collaboration efforts as the scientific community, governments, industry and regulatory agencies came together to share data, knowledge and resources.[79 80] This collaboration allowed scientists to combine expertise and work towards a common goal, expediting the vaccine development process. Governments and international organisations also invested significant financial resources into research and development efforts, enabling the rapid scale-up of manufacturing capabilities before regulatory approval, and regulators provided expedited review processes. The pandemic demonstrated how interdisciplinary approaches and multistakeholder collaborations can progress vaccines from the preclinical phase to implementation rapidly. For Strep A vaccines, what is needed is recognition of the serious burden of StrepA infections to help bring the 'enablers' together.

The PPWG-VAX WG believes that multidisciplinary partnerships with industry and non-industry stakeholders, and decision-makers will enable the development of a coordinated and strategic approach that includes consultations about known and unknown barriers. This dialogue will constructively support the vaccine pipeline, thereby creating the infrastructure to share applicable information directly with policy-makers (eg, national immunization and technical advisory groups; NITAGS) and funders (such as GAVI, BMGF) to continue progress. Community partnerships will also be essential, as will the efforts of governments to prioritise access to vaccines above other competing interests. These collaborative efforts would require the inclusion of groups with lived experiences of StrepA diseases, particularly RHD and

invasive diseases, which would be critical to informing and fostering the development of contextually relevant strategic approaches.

Health economic evaluation and financing

The StrepA Vaccine Global Consortium developed the first Full Value of Vaccines Assessment for StrepA. This included return on investment analyses on the development, manufacture, and distribution of vaccines from a commercial perspective, cost-effectiveness analyses on the adoption of vaccines from a public health sector perspective, and social return on investment analyses on the global uptake of vaccines from a societal perspective. All analyses indicated that StrepA vaccines would generate a favourable return on investment.

Vaccination was predicted to avert billions of cases of superficial disease (pharyngitis and impetigo) and millions of cases of severe disease (invasive disease and RHD) occurring in 30 global birth cohorts from 2022. Vaccination costs in line with those for other pathogens (eg, pneumococcus and meningococcus) were estimated to be cost-effective from a health sector perspective, and vaccination could result in total societal benefits in the trillions of US dollars range. On a commercial side, the risk-adjusted net present values for investment in StrepA vaccine development, manufacture and sale were found to be positive, indicating significant profits, across several scenarios.[81] However, there were a number of uncertain factors, in addition to vaccine specific parameters such as efficacy and duration of protection, including country-specific vaccine adoption rates and market size, manufacturing costs, and baseline health and economic burdens of disease now and in the future.[82] In addition, funding mechanisms for procurement and administration of StrepA vaccines was not investigated. These issues are interactive in nature: adoption rates depend on vaccine unit costs and unit costs depend on market size to benefit from economies of scale. They, therefore, warrant further discussion.

Social determinants of health applicable to vaccines

ARF and RHD distribution is highly patterned by SDH with the highest rates in LMIC[83] and among those living in relative poverty in high-income countries.[84 85] Unfortunately, these are the populations who have the lowest coverage of existing routine vaccines of childhood.[86–88] This is another manifestation of the inverse care law where those in greatest need are least well served. Delivering high coverage with StrepA vaccines will therefore need well-developed strategies and programmes that draw on the best available evidence about what works to achieve high coverage with existing vaccines delivered to these population and in these settings.

Multiple systematic reviews have summarised the evidence about how to achieve high immunisation coverage. Only a minority have focused on low-income and middle-income countries and populations living in relative poverty[89–92] One of these systematic reviews found supportive evidence for providing information on immunisation to parents and other community members, health education at facilities, immunisation reminders, regular immunisation outreach with and without household incentives, home visits and integration of immunisation with other services.[89] A systematic review of articles on factors influencing under-5 childhood immunisation uptake in Africa concluded that immunisation health education intervention among pregnant women would hopefully improve childhood immunisation uptake.[90] A qualitative evidence synthesis of factors that influence parents' views and practices on immunisation in Africa categorised caregiver views and practices about immunisation into five themes, including the need to address a lack of knowledge and information.[91] One study specifically reviewed the evidence about mobile phone reminders for improving routine childhood immunisation in low-income and middle-income countries.[92] It found that such reminders, particularly combined with voice message, SMS and phone calls appears to have modest effectiveness.

There will be importance research questions to investigate before, during and after the introduction of StrepA vaccines to support achieving high vaccine coverage across eligible groups. The nature of these questions will depend on those who are ultimately identified to receive these vaccines. It will be important to understand community perspectives on the importance of RF and other StrepA diseases, views on the effectiveness of vaccines, and who they think should receive it. It will be important to identify approaches to ensure interventions can be delivered effectively to low-income households and groups where disease rates are highest.

Gaps

To address the previously outlined barriers, several research gaps have been identified including the need:

1. To engage with key industry and non-industry stakeholders, and with decision-makers, to develop a co-ordinated and strategic approach to support StrepA vaccine development to understand:
   - The barriers (and enablers) of progressing the vaccine development pipeline in consultation with vaccine developers, biotech and industry.
   - The appetite of policy-makers (eg, NITAGS) and their needs for decision-making and funding.
2. To understand how to foster decision-making among politicians, bureaucrats, funding agencies, industry and other stakeholders, with a view to ensuring that development and implementation of StrepA vaccines are given due prominence.
3. For greater engagement and advocacy on StrepA vaccine development.
4. For better accuracy in disease burden estimates of the local, regional, and global burdens, including economic and social burdens of disease directly and indirectly caused by StrepA such as AMR.

5. Understanding the global transmission dynamics of StrepA infections.
6. To further develop health economic value and develop models of financing for StrepA vaccines.

Opportunities

The PPWG-VAX WG has recognised the following opportunities to address the previously identified gaps:

1. Further development of the business case/economic evaluation for StrepA vaccines and dissemination more broadly to key policy-makers, industry and non-industry stakeholders.
2. 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.
3. Ensure the availability, affordability and acceptability of a functional, cost-effective delivery platform for immunisation.
4. Enable access to low-cost vaccine manufacturing under current Good Manufacturing Practices for late-stage development and commercial production.
5. Enlist the support of people with lived experience of StrepA diseases, particularly RHD and invasive disease, as critical members of research and translation partnerships, learning from experience with other diseases such as HIV.

CONCLUSION

To facilitate StrepA vaccine development, several scientific approaches need to be effectively harmonised and facilitated beyond the early discovery of targets and preclinical studies. Workshop participants recognised the central need to develop partnerships for clinical trials of new candidates, and the creation of LMIC Centers of Excellence (CoE) to generate a thorough understanding of disease burden and genetic heterogeneity to inform vaccine development. Eventually, these CoEs, where researchers can conduct disease burden studies, understand immunopathogenesis across the lifespan, and learn from monitoring and surveillance of community outbreaks, can serve as centres for clinical trials to measure efficacy and safety in the short-midterm and longer-term vaccine impact. Validation of a human infection model, in which naïve consented humans are infected with StepA and longitudinally followed for a specified timeframe, was also considered a priority area to potentially accelerate vaccine development into the future. This would broaden the research communities understanding of the natural progression of the disease.

Workshop participants prioritised identifying intersectional research areas related to vaccines, SDH and primary prevention approaches for interdisciplinary investigations, and implementation efforts. Clearly, it will be important to develop interventions/screening practices focused on key at-risk populations. Early diagnostic methods and investigating whether different vaccines may be needed for symptomatic versus asymptomatic patients will require the primary prevention and other SDH researchers to assist with suitable vaccine target discovery, and identification of appropriate setting for vaccine deployment. This will require working with policy-makers and public health practitioners for optimal delivery of vaccines to at-risk populations.

Author affiliations
[1]Wesfarmers Centre for Vaccines and Infectious Diseases, Telethon Kids Institute, Nedlands, Western Australia, Australia
[2]Centre for Child Health Research, The University of Western Australia, Perth, Western Australia, Australia
[3]Department of Microbiology and Immunology, The University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA
[4]Department of Microbiology, Immunology and Molecular Genetics, University of Kentucky, Lexington, Kentucky, USA
[5]Center for Translation Research and Implementation Science (CTRIS), National Heart Lung and Blood Institute, Bethesda, Maryland, USA
[6]John E Fogarty International Center, Bethesda, Maryland, USA
[7]Department of Public Health, University of Otago Wellington, Wellington, New Zealand
[8]Department of Global Health and Population, Harvard University T H Chan School of Public Health, Boston, Massachusetts, USA
[9]Department of Infectious Diseases, Perth Children's Hospital, Nedlands, Western Australia, Australia
[10]Infection, Immunity and Global Health, Murdoch Children's Research Institute, Parkville, Victoria, Australia

Contributors The coauthors contributed equally to this work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Disclaimer The contents and views expressed in this report are those of the authors and do not necessarily reflect the official views of the National Heart, Lung, and Blood Institute, Fogarty International Center, National Institutes of Health, United States Government, or the affiliated institutions.

Competing interests MWC, JRC and ACS have received funding support from the National Institutes of Health. MWC received fees as a consultant for Vaxform Incorporated, Serum India Institute and Pfizer Incorporated. MWC is the Chief Scientific Officer and co-founder, with financial interest, in Moleculera Labs, a commercial laboratory for diagnostic testing of autoantibodies against the heart and brain.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article.

ORCID iD
Mary Y. Masterson http://orcid.org/0000-0002-3369-9183

REFERENCES

1 Carapetis JR, Steer AC, Mulholland EK, *et al*. The global burden of group A streptococcal diseases. *The Lancet Infectious Diseases* 2005;5:685–94.
2 Ralph AP, Carapetis JR. Group a streptococcal diseases and their global burden. *Curr Top Microbiol Immunol* 2013;368:1–27.

3 Walker MJ, Barnett TC, McArthur JD, *et al*. Disease manifestations and pathogenic mechanisms of group A streptococcus. *Clin Microbiol Rev* 2014;27:264–301.
4 Miller KM, Carapetis JR, Van Beneden CA, *et al*. The global burden of sore throat and group A streptococcus pharyngitis: a systematic review and meta-analysis. *eClinicalMedicine* 2022;48:101458.
5 Craik N, Hla T, Cannon J, *et al*. Global disease burden of Streptococcus Pyogenes. In: Ferretti JJ, Stevens DL, Fischetti VA, eds. *Streptococcus pyogenes: Basic Biology to Clinical Manifestations*. 2nd edn. Oklahoma City (OK), 2022.
6 Watkins DA, Johnson CO, Colquhoun SM, *et al*. Global, regional, and national burden of rheumatic heart disease, 1990–2015. *N Engl J Med* 2017;377:713–22.
7 Cho KH, Port GC, Caparon M. Genetics of group A streptococci. *Microbiol Spectr* 2019;7.
8 Brouwer S, Rivera-Hernandez T, Curren BF, *et al*. Author correction: pathogenesis, epidemiology and control of group A streptococcus infection. *Nat Rev Microbiol* 2023;21:619.
9 Lannes-Costa PS, de Oliveira JSS, da Silva Santos G, *et al*. A current review of pathogenicity determinants of streptococcus SP. *J Appl Microbiol* 2021;131:1600–20.
10 Dale JB, Walker MJ. Update on group A streptococcal vaccine development. *Curr Opin Infect Dis* 2020;33:244–50.
11 Gogos A, Federle MJ. Modeling streptococcus pyogenes pharyngeal colonization in the mouse. *Front Cell Infect Microbiol* 2019;9:137.
12 Watson ME, Neely MN, Caparon MG. Animal models of Streptococcus Pyogenes infection. In: Ferretti JJ, Stevens DL, Fischetti VA, eds. *Streptococcus pyogenes: Basic Biology to Clinical Manifestations*. Oklahoma City (OK), 2016.
13 Ozberk V, Reynolds S, Huo Y, *et al*. Prime-pull immunization with a bivalent M-protein and spy-CEP peptide vaccine adjuvanted with CAF(R)01 liposomes induces both mucosal and peripheral protection from covR/S mutant streptococcus pyogenes. *mBio* 2021;12:e03537-20.
14 Reynolds S, Pandey M, Dooley J, *et al*. Preclinical safety and immunogenicity of streptococcus pyogenes (Strep A) peptide vaccines. *Sci Rep* 2021;11:127.
15 Bessen D, Fischetti VA. Synthetic peptide vaccine against mucosal colonization by group A streptococci. I. protection against a heterologous M serotype with shared C repeat region epitopes. *J Immunol* 1990;145:1251–6.
16 Batzloff MR, Hayman WA, Davies MR, *et al*. Protection against group A streptococcus by immunization with J8-diphtheria toxoid: contribution of J8- and diphtheria toxoid-specific antibodies to protection. *J Infect Dis* 2003;187:1598–608.
17 Postol E, Alencar R, Higa FT, *et al*. Streptincor: a candidate vaccine EPITOPE against S. Pyogenes infections induces protection in outbred mice. *PLoS One* 2013;8:e60969.
18 Rivera-Hernandez T, Rhyme MS, Cork AJ, *et al*. Vaccine-induced Th1-type response protects against invasive group A streptococcus infection in the absence of opsonizing antibodies. *mBio* 2020;11:e00122-20.
19 Rivera-Hernandez T, Carnathan DG, Jones S, *et al*. An experimental group A streptococcus vaccine that reduces pharyngitis and tonsillitis in a nonhuman primate model. *mBio* 2019;10:e00693-19.
20 Rivera-Hernandez T, Walker MJ. Humanized plasminogen mouse model to study group A streptococcus invasive disease. *Methods Mol Biol* 2020;2136:309–16.
21 Lemaitre J, Naninck T, Delache B, *et al*. Non-human primate models of human respiratory infections. *Mol Immunol* 2021;135:147–64.
22 Rush CM, Govan BL, Sikder S, *et al*. Animal models to investigate the pathogenesis of rheumatic heart disease. *Front Pediatr* 2014;2:116.
23 Sikder S, Price G, Alim MA, *et al*. Group A streptococcal M-protein specific antibodies and T-cells drive the pathology observed in the rat autoimmune Valvulitis model. *Autoimmunity* 2019;52:78–87.
24 Rafeek RA, Hamlin AS, Andronicos NM, *et al*. Characterization of an experimental model to determine streptococcal M protein-induced autoimmune cardiac and neurobehavioral abnormalities. *Immunol Cell Biol* 2022;100:653–66.
25 Quinn A, Kosanke S, Fischetti VA, *et al*. Induction of autoimmune valvular heart disease by recombinant streptococcal M protein. *Infect Immun* 2001;69:4072–8.
26 Gorton D, Sikder S, Williams NL, *et al*. Repeat exposure to group A streptococcal M protein exacerbates cardiac damage in a rat model of rheumatic heart disease. *Autoimmunity* 2016;49:563–70.
27 Brimberg L, Benhar I, Mascaro-Blanco A, *et al*. Behavioral, pharmacological, and immunological abnormalities after streptococcal exposure: a novel rat model of Sydenham chorea and related neuropsychiatric disorders. *Neuropsychopharmacology* 2012;37:2076–87.
28 Osowicki J, Azzopardi KI, Fabri L, *et al*. A controlled human infection model of streptococcus pyogenes pharyngitis (CHIVAS-M75): an observational, dose-finding study. *Lancet Microbe* 2021;2:e291–9.
29 Osowicki J, Azzopardi KI, McIntyre L, *et al*. A controlled human infection model of group A streptococcus pharyngitis: which strain and why? mSphere *mSphere* 2019;4:e00647-18.
30 Sekhar A, Kang G. Human challenge trials in vaccine development. *Semin Immunol* 2020;50:101429.
31 Cooper MM, Loiseau C, McCarthy JS, *et al*. Human challenge models: tools to accelerate the development of malaria vaccines. *Expert Rev Vaccines* 2019;18:241–51.
32 Steer AC, Law I, Matatolu L, *et al*. Global Emm type distribution of group A streptococci: systematic review and implications for vaccine development. *Lancet Infect Dis* 2009;9:611–6.
33 Walkinshaw DR, Wright MEE, Mullin AE, *et al*. The streptococcus pyogenes vaccine landscape. *NPJ Vaccines* 2023;8:16.
34 Harbison-Price N, Rivera-Hernandez T, Osowicki J, *et al*. Current approaches to vaccine development of Streptococcus Pyogenes. In: Ferretti JJ, Stevens DL, Fischetti VA, eds. *Streptococcus pyogenes: Basic Biology to Clinical Manifestations*. 2nd edn. Oklahoma City (OK), 2022.
35 D'Alessandri R, Plotkin G, Kluge RM, *et al*. Protective studies with group A streptococcal M protein vaccine. III. challenge of volunteers after systemic or intranasal immunization with type 3 or type 12 group A streptococcus. *J Infect Dis* 1978;138:712–8.
36 Fox EN, Waldman RH, Wittner MK, *et al*. Protective study with a group A streptococcal M protein vaccine. Infectivity challenge of human volunteers.. *J Clin Invest* 1973;52:1885–92.
37 Polly SM, Waldman RH, High P, *et al*. Protective studies with a group A streptococcal M protein vaccine. II. challange of Volenteers after local immunization in the upper respiratory tract. *J Infect Dis* 1975;131:217–24.
38 Waldman RH, Lee JD, Polly SM, *et al*. Group A streptococcal M protein vaccine: protection following immunization via the respiratory tract. *Dev Biol Stand* 1975;28:429–34.
39 Massell BF, Honikman LH, Amezcua J. Rheumatic fever following streptococcal vaccination. report of three cases. *JAMA* 1969;207:1115–9.
40 Carapetis JR, Beaton A, Cunningham MW, *et al*. Acute rheumatic fever and rheumatic heart disease. *Nat Rev Dis Primers* 2016;2:15084.
41 Cunningham MW. Pathogenesis of group A streptococcal infections. *Clin Microbiol Rev* 2000;13:470–511.
42 Vekemans J, Gouvea-Reis F, Kim JH, *et al*. The path to group A streptococcus vaccines: world health organization research and development technology roadmap and preferred product characteristics. *Clin Infect Dis* 2019;69:877–83.
43 Kirvan CA, Canini H, Swedo SE, *et al*. Igg2 rules: N-acetyl-beta-D-Glucosamine-specific Igg2 and Th17/Th1 cooperation may promote the pathogenesis of acute rheumatic heart disease and be a biomarker of the autoimmune sequelae of streptococcus pyogenes *Front Cardiovasc Med* 2022;9:919700.
44 Kotloff KL, Corretti M, Palmer K, *et al*. Safety and immunogenicity of a recombinant multivalent group a streptococcal vaccine in healthy adults: phase 1 trial. *JAMA* 2004;292:709–15.
45 Pastural É, McNeil SA, MacKinnon-Cameron D, *et al*. Safety and Immunogenicity of a 30-Valent M protein-based group a Streptococcal vaccine in healthy adult volunteers: a randomized, controlled phase I study. *Vaccine* 2020;38:1384–92.
46 Sabharwal H, Michon F, Nelson D, *et al*. Group A Streptococcus (GAS) carbohydrate as an immunogen for protection against GAS infection. *J Infect Dis* 2006;193:129–35.
47 Beachey EH, Cunningham MW. Type specific inhibition of preopsonization versus immunoprecipitation by streptococcal M proteins. *Infect Immun* 1973;8:19–24.
48 Sekuloski S, Batzloff MR, Griffin P, *et al*. Evaluation of safety and immunogenicity of a group A streptococcus vaccine candidate (Mj8Vax) in a randomized clinical trial. *PLoS One* 2018;13:e0198658.
49 Bensi G, Mora M, Tuscano G, *et al*. Multi high-throughput approach for highly selective identification of vaccine candidates: the group A streptococcus case. *Mol Cell Proteomics* 2012;11:M111.015693.
50 Di Benedetto R, Mancini F, Carducci M, *et al*. Rational design of a glycoconjugate vaccine against group A *streptococcus*. *Int J Mol Sci* 2020;21:8558.
51 Gao NJ, Rodas Lima E, Nizet V. Immunobiology of the classical lancefield group A streptococcal carbohydrate antigen. *Infect Immun* 2021;89:e00292-21.
52 Davies MR, McIntyre L, Mutreja A, *et al*. Author correction: atlas of group A streptococcal vaccine candidates compiled using large-scale comparative genomics. *Nat Genet* 2019;51:1295.

53 Henningham A, Gillen CM, Walker MJ. Group a streptococcal vaccine candidates: potential for the development of a human vaccine. *Curr Top Microbiol Immunol* 2013;368:207–42.
54 Cleary PP, Matsuka YV, Huynh T, *et al*. Immunization with C5A Peptidase from either group A or B Streptococci enhances clearance of group A streptococci from intranasally infected mice. *Vaccine* 2004;22:4332–41.
55 Kabanova A, Margarit I, Berti F, *et al*. Evaluation of a group A streptococcus synthetic oligosaccharide as vaccine candidate. *Vaccine* 2010;29:104–14.
56 Rivera-Hernandez T, Pandey M, Henningham A, *et al*. Differing efficacies of lead group A streptococcal vaccine candidates and full-length M protein in cutaneous and invasive disease models. *mBio* 2016;7:e00618-16.
57 Guerino MT, Postol E, Demarchi LMF, *et al*. HLA class II transgenic mice develop a safe and long lasting immune response against streptincor, an anti-group A streptococcus vaccine candidate. *Vaccine* 2011;29:8250–6.
58 Loh JMS, Rivera-Hernandez T, McGregor R, *et al*. A multivalent T-antigen-based vaccine for group A streptococcus. *Sci Rep* 2021;11:4353.
59 Morefield G, Touhey G, Lu F, *et al*. Development of a recombinant fusion protein vaccine formulation to protect against streptococcus pyogenes. *Vaccine* 2014;32:3810–5.
60 HogenEsch H, Dunham A, Burlet E, *et al*. Preclinical safety study of a recombinant streptococcus pyogenes vaccine formulated with aluminum adjuvant. *J Appl Toxicol* 2017;37:222–30.
61 Galvin JE, Hemric ME, Ward K, *et al*. Cytotoxic monoclonal antibody from rheumatic carditis reacts with human endothelium: implications in rheumatic heart disease. *J Clin Invest* 2000;106:217–24.
62 van Sorge NM, Cole JN, Kuipers K, *et al*. The classical Lancefield antigen of group a streptococcus is a virulence determinant with implications for vaccine design. *Cell Host Microbe* 2014;15:729–40.
63 Gao NJ, Uchiyama S, Pill L, *et al*. Site-specific conjugation of cell wall polyrhamnose to protein spyad envisioning a safe universal group A streptococcal vaccine. *Infectious Microbes and Diseases* 2020;3:87–100.
64 Burns K, Dorfmueller HC, Wren BW, *et al*. Progress towards a glycoconjugate vaccine against group A streptococcus. *NPJ Vaccines* 2023;8:48.
65 Loh JMS, Lorenz N, Tsai CJ-Y, *et al*. Mucosal vaccination with Pili from group A streptococcus expressed on lactococcus lactis generates protective immune responses. *Sci Rep* 2017;7:7174.
66 AH JK, Pilapitiya D, Tsai CJ, *et al*. Expanding strain coverage of a group A streptococcus pilus-expressing lactococcus lactis mucosal vaccine. *Immunol Cell Biol* 2023.
67 Ellis NMJ, Li Y, Hildebrand W, *et al*. T cell Mimicry and EPITOPE specificity of cross-reactive T cell clones from rheumatic heart disease. *J Immunol* 2005;175:5448–56.
68 Faé KC, da Silva DD, Oshiro SE, *et al*. Mimicry in recognition of cardiac myosin peptides by heart-intralesional T cell clones from rheumatic heart disease. *J Immunol* 2006;176:5662–70.
69 Passos LSA, Jha PK, Becker-Greene D, *et al*. Prothymosin alpha: a novel contributor to estradiol receptor alpha-mediated Cd8(+) T-cell pathogenic responses and recognition of type 1 collagen in rheumatic heart valve disease. *Circulation* 2022;145:531–48.
70 Dan JM, Havenar-Daughton C, Kendric K, *et al*. Recurrent group A *Streptococcus* Tonsillitis is an Immunosusceptibility disease involving antibody deficiency and aberrant T_{FH} cells. *Sci Transl Med* 2019;11:eaau3776.
71 Tsoi SK, Smeesters PR, Frost HRC, *et al*. Correlates of protection for M protein-based vaccines against group A streptococcus. *J Immunol Res* 2015;2015:167089.
72 Frost HR, Sanderson-Smith M, Walker M, *et al*. Group A streptococcal M-like proteins: from pathogenesis to vaccine potential. *FEMS Microbiol Rev* 2018;42:193–204.
73 Tsai J-YC, Loh JMS, Clow F, *et al*. The group A streptococcus serotype M2 pilus plays a role in host cell adhesion and immune evasion. *Mol Microbiol* 2017;103:282–98.
74 Frost H, Excler JL, Sriskandan S, *et al*. Correlates of immunity to group A streptococcus: a pathway to vaccine development. *NPJ Vaccines* 2023;8:1.
75 Macleod CK, Bright P, Steer AC, *et al*. Neglecting the neglected: the objective evidence of underfunding in rheumatic heart disease. *Trans R Soc Trop Med Hyg* 2019;113:287–90.
76 Roth GA, Mensah GA, Johnson CO, *et al*. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study. *J Am Coll Cardiol* 2020;76:2982–3021.
77 Moore HC, Cannon JW, Kaslow DC, *et al*. A systematic framework for prioritizing burden of disease data required for vaccine development and implementation: the case for group A streptococcal diseases. *Clin Infect Dis* 2022;75:1245–54.
78 Abou-Nader AJ, Sauer MA, Steele AD, *et al*. Global Rotavirus vaccine introductions and coverage: 2006 - 2016. *Hum Vaccin Immunother* 2018;14:2281–96.
79 Druedahl LC, Minssen T, Price WN. Collaboration in times of crisis: a study on COVID-19 vaccine R&Amp;Amp;Amp;Amp;Amp;D partnerships. *Vaccine* 2021;39:6291–5.
80 Bloom DE, Cadarette D, Ferranna M, *et al*. How new models of vaccine development for COVID-19 have helped address an epic public health crisis. *Health Aff (Millwood)* 2021;40:410–8.
81 IVB master deck. n.d. Available: who.int
82 WHO expert review of group A streptococcus vaccines. 2022.
83 Ou Z, Yu D, Liang Y, *et al*. Global burden of rheumatic heart disease: trends from 1990 to 2019. *Arthritis Res Ther* 2022;24:138.
84 Bennett J, Zhang J, Leung W, *et al*. Rising ethnic inequalities in acute rheumatic fever and rheumatic heart disease, New Zealand, 2000-2018. *Emerg Infect Dis* 2021;27:36–46.
85 Katzenellenbogen JM, Bond-Smith D, Seth RJ, *et al*. Contemporary incidence and prevalence of rheumatic fever and rheumatic heart disease in Australia using linked data: the case for policy change. *J Am Heart Assoc* 2020;9:e016851.
86 Jackson J, Sonneveld N, Rashid H, *et al*. Vaccine preventable diseases and vaccination coverage in aboriginal and Torres Strait Islander people. *Commun Dis Intell (2018)* 2016;47.
87 Gbd R. Measuring routine childhood vaccination coverage in 204 countries and territories, 1980-2019: a systematic analysis for the global burden of disease study 2020, release 1. *Lancet* 2021;398:503–21.
88 Sinclair O, Grant C. New Zealand's immunisation policy fails again and entrenches ethnic disparities. *The New Zealand Medical Journal (Online)* 2021;134:92–5.
89 Oyo-Ita A, Wiysonge CS, Oringanje C, *et al*. Interventions for improving coverage of childhood Immunisation in Low- and middle-income countries. *Cochrane Database Syst Rev* 2016;7:CD008145.
90 Galadima AN, Zulkefli NAM, Said SM, *et al*. Factors influencing childhood Immunisation uptake in Africa: a systematic review. *BMC Public Health* 2021;21:1475.
91 Mavundza EJ, Cooper S, Wiysonge CS. Wiysonge CS: a systematic review of factors that influence parents' views and practices around routine childhood vaccination in Africa: a qualitative evidence synthesis. *Vaccines (Basel)* 2023;11:563.
92 Yunusa U, Garba SN, Umar AB, *et al*. Mobile phone reminders for enhancing uptake, completeness and timeliness of routine childhood immunization in low and middle income countries: a systematic review and meta-analysis. *Vaccine* 2021;39:209–21.
93 Dale JB, Penfound TA, Chiang EY, *et al*. New 30-Valent M protein-based vaccine evokes cross-opsonic antibodies against non-vaccine serotypes of group A streptococci. *Vaccine* 2011;29:8175–8.
94 Guilherme L, Postol E, Ferreira FM, *et al*. Streptincor: a model of anti-streptococcus pyogenes vaccine reviewed. *Auto Immun Highlights* 2013;4:81–5.
95 Postol E, Sá-Rocha LC, Sampaio RO, *et al*. Group A streptococcus adsorbed vaccine: repeated intramuscular dose toxicity test in minipigs. *Sci Rep* 2019;9:9733.
96 Pandey M, Powell J, Calcutt A, *et al*. Physicochemical characterisation, immunogenicity and protective efficacy of a lead streptococcal vaccine: progress towards phase I trial. *Sci Rep* 2017;7:13786.
97 Nordström T, Pandey M, Calcutt A, *et al*. Enhancing vaccine efficacy by engineering a complex synthetic peptide to become a super Immunogen. *J Immunol* 2017;199:2794–802.
98 Guignard A, Praet N, Jusot V, *et al*. Introducing new vaccines in low- and middle-income countries: challenges and approaches. *Expert Rev Vaccines* 2019;18:119–31.
99 Feikin DR, Flannery B, Hamel MJ, *et al*. Vaccines for children in Low- and middle-income countries. In: Black RE, Laxminarayan R, Temmerman M, et al, eds. *Reproductive, Maternal, Newborn, and Child Health: Disease Control Priorities* Third Edition (Volume 2). edn. 2016: