HHS Public Access

Author manuscript

Curr Opin Infect Dis. Author manuscript; available in PMC 2021 June 01.

Published in final edited form as:

Curr Opin Infect Dis. 2020 June ; 33(3): 244–250. doi:10.1097/QCO.0000000000000644.

Update on Group A Streptococcal Vaccine Development

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Abstract

Purpose of the review: There is a global need for safe, effective, and affordable vaccines to prevent group A streptococcal infections and their most serious complications. The aim of this review is to highlight the recent progress in the identification of promising vaccine antigens and new approaches to vaccine design that address the complexities of group A streptococcal pathogenesis and epidemiology.

Recent findings: Combination vaccines containing multiple shared, cross-protective antigens have proven efficacious in mouse and non-human primate models of infection. The development of complex multivalent M protein-based vaccines is continuing and several have progressed through early-stage human clinical trials. Formulations of vaccines containing universal T cell epitopes, TLR agonists and other adjuvants more potent than alum have been shown to enhance protective immunogenicity. Although the group A streptococcal vaccine antigen landscape is populated with a number of potential candidates, the clinical development of vaccines has been impeded by a number of factors. There are now concerted global efforts to raise awareness about the need for group A streptococcal vaccines and to support progress toward eventual commercialization and licensure.

Summary: Pre-clinical antigen discovery, vaccine formulation, and efficacy studies in animal models have progressed significantly in recent years. There is now a need to move promising candidates through the clinical development pathway to establish their efficacy in preventing group A streptococcal infections and their complications.

Keywords

Streptococcus pyogenes; vaccine; pharyngitis; acute rheumatic fever; rheumatic heart disease; group A *Streptococcus*; Strep A

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Conflicts of Interest:

Dr. Dale is the inventor of certain technologies related to the development of group A streptococcal vaccines. The technology has been licensed from the University of Tennessee Research Corporation to Vaxent, LLC. Dr. Dale is the Chief Scientific Officer and a member of Vaxent. Dr. Walker holds an intellectual property interest in Strep A antigens ADI and TF.

Introduction

Group A streptococcus (Strep A) is a ubiquitous human-specific pathogen responsible for a wide array of infections. Uncomplicated infections, such as pharyngitis and impetigo, account for the greatest global burden of disease, affecting millions of children annually [1]. Serious invasive infections, which include necrotizing fasciitis, streptococcal toxic shock syndrome, puerperal sepsis and pneumonia, are not as common but are associated with significant morbidity and mortality [2, 3]. Post-streptococcal glomerulonephritis (PSGN) and acute rheumatic fever (ARF) are immune-mediated diseases that may follow seemingly uncomplicated infections. On a global level, rheumatic heart disease (RHD) is associated with the greatest disease burden because it primarily affects children and young adults, is associated with excess mortality, and often results in debilitating heart disease when individuals reach their prime productive years [4]. Theoretically all Strep A infections and thus their immune-mediated complications are vaccine-preventable, yet after decades of research there is not a licensed vaccine.

Strep A vaccine development has been ongoing for decades. In the 1940's, over 4000 young adults were injected with whole killed bacteria and monitored for Strep A infections [5]. The vaccines were highly reactogenic and did not prevent disease. Based on these early observations, investigators in the 1960's vaccinated adult volunteers with fractions of cell walls or partially purified M proteins which were also reactogenic and did not produce consistent immune responses [6, 7]. To achieve immunizing doses of partially purified M antigens, Massell repeatedly injected children with lower amounts of the toxic preparations [8]. The authors later concluded that the immunized children experienced a higher attack rate of ARF compared to historical control subjects [9]. Whether this was causally related to the vaccine is still debated. Nonetheless, in 1978 the controversy resulted in a US FDA ban on subsequent vaccine trials which was eventually overturned 30 years later. Prior to the FDA ban, more precise methods were used to purify M proteins used in landmark studies in the 1970's undertaken by Fox and colleagues. They demonstrated that immunization, either subcutaneously or via the mucosal route, could prevent infection with the homologous M type of Strep A after challenge infections delivered to the pharynx and tonsils [10, 11]. Beachey and his co-workers also conducted limited human studies of a highly purified M protein preparation which was free of toxicity and elicited type-specific bactericidal antibodies [12].

More recent vaccine development efforts have taken advantage of genomics, proteomics, reverse vaccinology and precisely defined antigen/epitope content of vaccines. Vaccine candidates include N-terminal M peptides configured in recombinant multivalent proteins, conserved M epitopes from the central region of the M protein, cell wall carbohydrate, and multiple secreted and cell surface proteins, many of which have defined roles as determinants of virulence and pathogenesis (Table 1). In this review, we provide an update of the current status of Strep A vaccine development, describe the impediments to the clinical development of promising vaccine candidates, and highlight ongoing international efforts to overcome the barriers preventing the eventual licensing of safe, affordable, and effective vaccines.

Landscape of Strep A Vaccine Antigens: Non-M Protein Vaccine Candidates

Carbohydrate vaccines.

Carbohydrate capsule antigens have been incorporated into a number of vaccines targeting streptococcal species, notably *Streptococcus pneumoniae* and *Streptococcus agalactiae*. However, the capsule of Strep A is composed of hyaluronic acid, which is also produced in human tissues and recognized as a self-antigen, thus ruling this molecule out as a vaccine component [13, 14]. Another important polysaccharide constituent of Strep A is the group A carbohydrate (GAC), which comprises approximately 50% of the cell wall. GAC is composed of a [→3)α-Rha(1→2)α-Rha(1→] polyrhamnose backbone with an β-d-N-acetylglucosamine (1→3) side chain attached to each α−1,2–linked rhamnose [15]. Up to 25% of the N-acetylglucosamine side chains have recently been shown to be decorated with glycerol phosphate [16]. The vaccine potential of purified GAC was initially examined by conjugating to tetanus toxoid. Mice immunized with this conjugate were protected against systemic and intranasal challenge [17]. However, the N-acetylglucosamine side chain of GAC has been suggested as a trigger for post-infection sequel caused by Strep A [18]. To address this issue, a Strep A glycosyltransferase *gacI* knock-out, unable to incorporate N-acetylglucosamine into the GAC polymer, was used to prepare polyrhamnose for vaccine studies. This antigen, coupled to a pneumococcal carrier protein, generated antibodies that provided passive protection in mice [19]. Subsequently, GAC lacking the N-acetylglucosamine side chain, conjugated to Strep A ADI, was formulated with alum and used in active immunization studies in mice. Immunised mice were protected from cutaneous Strep A challenge, but were not protected against invasive Strep A infection [20].

Multi-component vaccines.

Numerous studies have identified Strep A antigens with protective efficacy in one or more mouse vaccine models (summarized in [21–24]; Table 1). These candidate Strep A vaccine antigens are asymmetrically distributed across serotypes and display varying levels of amino acid sequence variation [23]. More recent efforts have focused on the development of multi-component Strep A vaccines that offer the promise of broader strain coverage and enhanced efficacy. Here, we briefly highlight four non-M protein multi-component vaccines with demonstrated efficacy in animal models. Using a combination of proteomics, immune-array, and flow cytometry, a combination of 3 Strep A proteins (SpyCEP, SpyAD, SLO) was identified that provided significant protection in intranasal and intraperitoneal challenge models against 4 different Strep A M types [25]. Several of these individual vaccine antigens have also been incorporated into other experimental multi-component vaccines. A 5-component vaccine (ADI, TF, C5a peptidase, SpyCEP and SLO; designated Combo5), was formulated in alum and assessed in murine vaccine models. Immunized mice were protected from cutaneous Strep A challenge, but were not protected against invasive Strep A infection [20]. Using the same invasive disease model, the capacity of 6 experimental adjuvants to improve the protective efficacy of Combo5 was assessed. Several novel adjuvants containing the saponin QS21 were found to significantly improve protection afforded by the Combo5 vaccine in comparison to alum, likely by providing a more balanced Th1/Th2-type immune response [26]. Combo5 formulated in alum has also been assessed in a non-human primate model of pharyngitis, where it was observed to reduce symptoms of pharyngitis and

tonsillitis, but did not prevent Strep A colonization [27]. Pooled human immunoglobulin (intravenous immunoglobulin G, IVIG) is used to treat Strep A invasive disease. Reglinski et al. identified several Strep A surface antigens reactive with this human immunoglobulin [28]. The Spy7 vaccine, incorporating 7 selected antigens (C5a peptidase, oligopeptide-binding protein, pullulanase, nucleoside-binding protein, hypothetical membrane associated protein Spy0762, cell surface protein Spy0651 and SpyAD), was formulated in Freund's adjuvant and used in vaccine studies. Spy7 vaccination demonstrated significantly reduced dissemination of serotype M1 and M3 GAS [29]. The capacity of Spy7 to generate protection using an adjuvant suitable for human use, such as alum, was not reported. Finally, a 5-component vaccine designated 5CP (sortase A, C5a peptidase, SpyAD, SpyCEP and SLO) has been formulated with CpG-oligodeoxynucleotides as adjuvant and used for intranasal immunization studies. This vaccine protected against intranasal, skin and systemic challenge [30].

M Protein Vaccines

Multivalent M protein-based vaccines.

M protein of Strep A is a major virulence determinant of the bacteria, and contains protective epitopes that elicit antibodies that opsonize the bacteria and promote phagocytic killing. There are now >200 *emm* types that are defined by the 5' *emm* gene sequence that encodes the N-terminus, or hypervariable region (HVR), of the mature protein [31]. Previous studies indicating that the HVR contains epitopes that evoke antibodies with the greatest bactericidal activity and are also least likely to elicit potentially harmful tissue cross-reactive antibodies prompted studies of recombinant multivalent subunit vaccines containing 4–30 different HVR M peptides [32–36]. The most recent 30-valent vaccine was formulated to contain M types that are prevalent in the US, Canada, and Europe with the potential to provide immunity against ~85% of cases of pharyngitis and invasive infections in these geographic locations [36]. The 30-valent vaccine (StreptAnova™) was recently evaluated in a phase 1 study in adult participants and was shown to be safe, well-tolerated, and immunogenic without eliciting autoimmunity [37]. Using a different approach, N-terminal M peptides have been expressed by *L. lactis* and used as mucosal immunogens which protected mice from mucosal challenge infections [38, 39]. This approach could prove to be a low-cost method of vaccine production in low- and middle-income countries.

The perceived limitations of the multivalent M protein vaccine approach concern potential vaccine coverage in low- and middle-income countries and disadvantaged populations in high income countries where the diversity of M types is greatest and where children and young adults are at greatest risk for ARF/RHD [40–42]. Although the prospect of developing broadly protective vaccines containing N-terminal HVR peptides seem daunting given the number of different *emm* sequence types, recent investigations suggests that not all M types are immunologically distinct. Studies have shown that M proteins may be clustered based on sequence and functional activity related to the binding of specific host proteins [43]. The analysis of 175 different M sequences showed that 143 *emm* types were closely related in sequence and function and could be grouped into 16 *emm* clusters. M proteins that were unrelated to others accounted for 32 single M clusters. Coupled with the observation

from pre-clinical studies that the 30-valent vaccine antisera opsonized a significant number of non-vaccine *emm* types of Strep A and that the cross-opsonized M types were located in clusters where at least one vaccine peptide was represented, the authors concluded that M antibody-mediated immunity was likely cluster-specific as well as M protein specific [43]. The concept of cluster-specific immunity was supported by studies employing computational structure-based design of vaccines. Vaccines formulated to include a minimum number of structurally defined peptides from one cluster generated functional opsonic antibodies against most of the non-vaccine M types of Strep A in the same cluster [44]. Additionally, M antibodies elicited following natural infection were cross-opsonic against members of the same M cluster, adding support to the concept of cluster-specific rather than strictly M type-specific immunity [45].

Immunological similarities among N-terminal regions of the M proteins are most likely related to structural constraints imposed by the binding of specific host proteins, which enhances the virulence of Strep A. The complement regulatory proteins C4 binding protein (C4BP) and factor H (FH) are negative regulators of complement activation that bind to the HVR of many M proteins. Co-crystallization studies of HVR peptides with C4BP have defined at least two C4BP binding motifs contained within 44 different M proteins [46]. The hypothesis is that sequence variants within the N-terminal regions of the M proteins evolved under immune pressure but were constrained in the context of maintaining the common virulence property of binding complement regulatory proteins. Exploiting similarities in sequence and structure within the HVR of M proteins, guided by computational analysis of peptide structures, may lead to the development of broadly protective vaccines [47].

M protein vaccines containing conserved C-repeat epitopes.

Formulating vaccines that contain conserved M protein sequences present in the middle of the mature proteins (C-repeat region, CRR) is another approach that aims to circumvent the issue of sequence variation within the HVR [48]. StreptInCor is a peptide vaccine that contains T and B cell epitopes of the M protein CRR and elicits protective immunity in mice [49]. Pre-clinical toxicity studies have recently been completed in preparation for phase 1 clinical trials of this vaccine [50]. J8 (and related peptides J14 and p145) has been identified as a minimal B cell epitope from a segment of the CRR and elicits protective immunity in mice against mucosal, soft tissue, and systemic infections, independent of M type [51, 52]. The J8 epitope of the M protein does not appear to be immunodominant following natural infection [53]; however, the J8 peptide coupled to diphtheria toxoid (DT) evokes antibodies in mice that promote opsonization and phagocytosis [51]. J8-DT adjuvanted with alum was recently evaluated in a phase 1 study in adults and found to be immunogenic and well-tolerated [54]. The J8 peptide fused to the universal T cell epitope PADRE synthesized as an anionic lipopeptide and formulated with chitosan nanoparticles was highly immunogenic in mice, indicating the contributions of T cell help and the lipid component of the vaccine [55]. The J14 parent peptide, p145, has been structurally engineered using systematic amino acid replacements to become a “super immunogen” that resulted in more potent immune responses and protection of mice [56]. Enhanced immunogenicity of J14 was observed when the peptide was formulated with c-di-AMP or BPPCysMPEG as adjuvants and delivered via the mucosal route using lipopeptide nano carriers [57]. Using a novel approach to vaccine

design and production, three repeats of the J14 peptide were fused to ten different N-terminal M peptides to which a Gram-positive sortase motif (LPETG) was added on the C-terminus [58]. *S. aureus* sortase A was used to efficiently conjugate the TLR-2 agonist FSL-1 to the multivalent vaccine protein. The vaccine elicited high-titere antibodies that conferred protection in mice against challenge infections with M1 Strep A.

Impediments to Strep A Vaccine Development and Current Efforts to Overcome The Barriers

Although there has been substantial progress in understanding the molecular pathogenesis of Strep A infections and the pre-clinical identification of a number of potential vaccine candidates, the clinical development of safe and effective vaccines is impeded. The impediments include 1) the absence of defined human immune correlates of protection which could support the down-selection of candidate antigens, 2) inadequate animal models of infection, 3) the uncertainty about a market for a Strep A vaccine in high-income countries, 4) lack of commercial interest and reluctance to invest, 5) the complexity of the epidemiology of Strep A infections and concerns about potential efficacy and vaccine coverage, and 6) perceptions of the risk of autoimmune complications triggered by the vaccines.

Although the barriers are formidable, there are now concerted global efforts to support the clinical pathways needed to identify viable Strep A vaccine candidates. In 2018 the World Health Assembly adopted a Global Resolution calling for better control and prevention of Strep A infections and RHD [59]. The World Health Organization (WHO) subsequently sponsored the publication of two consensus documents, a Group A Streptococcal Vaccine Research and Development Roadmap and a Preferred Product Characteristics document [60]. In 2019, with Wellcome Trust support, a Strep A Vaccine Consortium was formed (named SAVAC – the Strep A Vaccine Consortium), and in that same year the Government of Australia committed AU$35 million to support Strep A vaccine’s progress into a Phase 2b efficacy trial against pharyngitis within 5 years. Investigators have developed a human challenge model of streptococcal pharyngitis that may prove to be pivotal in generating proof-of-concept data for selecting efficacious vaccines to enter clinical development [61]. SAVAC is working with the WHO to develop a Public Health Value Proposition that outlines the global health investment benefits as well as the industry business case for a Strep A vaccine.

Conclusions

The world needs a safe, effective, and affordable vaccine to prevent Strep A infections and their most serious complications, most importantly acute rheumatic fever, rheumatic heart disease, and invasive disease, all of which are associated with greater than 500,000 premature deaths per year [1]. Investigators have made significant progress in discovering a broad array of potential vaccine candidates but clinical development has been impeded for multiple reasons. Concerted global efforts supporting vaccine development and implementation of strategies to identify and fill gaps in the processes are ongoing and may ultimately result in commercial or NGO investment necessary for licensure.

Financial Support:

Dr. Dale receives research funds from the US Public Health Service, United States, NIH grant RO1 AI-132117 and from the American Heart Association, Strategically Focused Research Network (Children's). Dr. Walker receives funds from the Australian National Health and Medical Research Council for Strep A vaccine development.

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Key points:

1. Multicomponent Strep A vaccines have proven efficacious in animal models of infection.
2. Clinical development of safe and effective StrepA vaccines is currently impeded.
3. The WHO Assembly has adopted a Global Resolution calling for better control and prevention of Strep A infections and RHD.

Table 1.

Summary of group A streptococcal vaccine candidates in various stages of development.

Vaccine	Pre-clinical (mouse model)	Proof of concept in non-human primate or human challenge	Phase 1	Phase 2	Phase 3	References
Carbohydrate						
Group A carbohydrate	X					17, 18
Modified group A carbohydrate	X					19
Multicomponent						
GSK 3 component vaccine SpyCEP, SpyAD, SLO	X					25
Combo5 ADI, TF, C5a peptidase, SpyCEP, SLO	X	X				20, 27
Spy7 SpyAD, C5a peptidase, Spy0762, Spy0651, oligopeptide binding protein, pullulanase, nucleoside-binding protein	X					28, 29
5CP SpyCEP, SLO, SpyAD, C5a peptidase, sortase A	X					30
M protein-based						
Purified M protein	X	X	X			10, 11, 12
Multivalent HVR (4, 6, 8 valent)	X					32, 33, 34
23 valent HVR			X	X		35
30 valent HVR StreptAnova			X			36, 37
StreptInCor	X					49, 50
J8/J14/p145	X		X			52, 54
10 valent HVR-J14 combination	X					58
Other vaccine antigens	X					21–24