Prospects for a Group A Streptococcal Vaccine: Rationale, Feasibility, and Obstacles—Report of a National Institute of Allergy and Infectious Diseases Workshop

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Infections due to group A streptococci (GAS) represent a public health problem of major proportions in both developing and developed countries. Currently available methods of prevention are either inadequate or ineffective, as attested to by the morbidity and mortality associated with this ubiquitous pathogen worldwide. Advances in molecular biology have shed new light on the pathogenesis of GAS infections and have identified a number of virulence factors as potential vaccine targets. Therefore, the National Institute of Allergy and Infectious Diseases convened an expert workshop in March 2004 to review the available data and to explore the microbiologic, immunologic, epidemiologic, and economic issues involved in development and implementation of a safe and effective GAS vaccine. Participants included scientists and clinicians involved in GAS research, as well as representatives of United States federal agencies (Centers for Disease Control and Prevention, Food and Drug Administration, Department of Defense, and National Institute of Allergy and Infectious Diseases), the World Health Organization, and the pharmaceutical industry. This report summarizes the deliberations of the workshop.

There has long been interest in developing a safe and effective group A streptococcal (GAS) vaccine to reduce the morbidity, mortality and economic burden from GAS diseases and their sequelae. Advances in molecular biology, including the cloning and sequencing of the genomes of several prevalent GAS serotypes and genotypes, have shed new light on the pathogenesis of GAS infections and have identified a number of virulence factors as potential vaccine targets. Because vaccine research is now progressing on a number of fronts, a workshop was convened to prepare a plan for further clinical development of vaccines and their implementation by integrating scientific, clinical, and public health information. The following summary includes highlights of the discussion. The full meeting agenda and list of participants may be found at the National Institutes of Health Web site (http://www.niaid.nih.gov/dmid/meetings/).

GAS infections: worldwide and domestic burden of disease. GAS are associated with a spectrum of clinical manifestations ranging from upper respiratory tract infections (e.g., pharyngitis) and skin infections (e.g., impetigo) to invasive diseases (e.g., cellulitis, bacteremia, pneumonia, necrotizing fasciitis, and streptococcal toxic shock syndrome [STSS]) and nonsuppurative sequelae (e.g., acute rheumatic fever [ARF] and poststreptococcal glomerulonephritis). An independent review commissioned by the World Health Organization recently concluded that a minimum of 517,000 deaths annually are attributable to GAS globally, with approximately one-third of those deaths (163,000) related to invasive GAS disease and the remainder (354,000) related to nonsuppurative sequelae of GAS infections (Jonathan Carapetis, University of Melbourne, Australia, personal communication). Table 1 summarizes the estimated global burden of disease. More than 90% of cases of GAS-associated upper respiratory tract and skin infections, ARF, and poststreptococcal glomerulonephritis occur in less-developed countries.

The impact of GAS-associated pharyngitis on the US health care system is considerable. Acute pharyngitis accounted for 11 million office visits in 2000 [1]. GAS is the most common bacterial cause of acute pharyngitis, estimated to be the source of 15%–30% of cases in children and ~10% of cases in adults [2, 3]. Although the incidence of ARF in the United States has decreased during the past 50
The incidence of invasive GAS, as detected by the Active Bacterial Core surveillance, ranges from 3.1 to 3.8 cases per 100,000 population, with a case-fatality rate of 11.7%–14.8%. Because of the greater incidence and higher case-fatality rate, the estimated number of deaths that occur each year in the United States due to invasive GAS infections is ~6-fold the estimated number of deaths due to invasive meningococcal disease (a mean of 1340 deaths per year due to GAS infection, compared with 223 deaths per year due to Neisseria meningitidis infection). Moreover, the distribution of disease and death among the 2 extremes of age differs for meningococcal and GAS infections. In 2002, the projected number of cases and deaths due to invasive meningococcal disease among US residents aged ≤17 years were 855 and 43, respectively. The projected number of cases and deaths due to GAS infection among this same younger age group were 1409 and 53, respectively. A much greater difference was noted among elderly individuals (≥65 years old). The estimated numbers of cases in this group were 212 and 3147 for N. meningitidis and GAS, respectively, and the projected number of deaths were 71 and 806, respectively.

**Rationale**

Although the organism remains uniformly susceptible to penicillin, currently available methods of prevention of GAS disease are inadequate. So-called primary prevention of ARF (i.e., prompt diagnosis and treatment of acute streptococcal pharyngitis) is beneficial in individual cases but has not been effective in control of the disease in developing countries in which it is highly prevalent, nor has it been demonstrated to prevent acute glomerulonephritis. Secondary prevention of ARF (i.e., continuous antimicrobial prophylaxis in patients who have experienced an attack) is cost-beneficial but requires a compliant patient and/or family and a well-developed public health infrastructure to assure fidelity and maintain registries. At present, there is no effective method of preventing life-threatening GAS-associated invasive infection. These facts have spurred renewed interest in vaccine development.

It is of interest to compare the impact of GAS disease with that of a disease associated with a pathogen for which immunization is currently employed—namely, meningococcal disease. The incidence of meningococcal disease in the United States is 0.5–1.1 cases per 100,000 population, with a case fatality rate of 8.4%–12.2%. In comparison, the incidence of invasive GAS, as detected by the Active Bacterial Core surveillance, ranges from 3.1 to 3.8 cases per 100,000 population, with a case-fatality rate of 11.7%–14.8%. Because of the greater incidence and higher case-fatality rate, the estimated number of deaths that occur each year in the United States due to invasive GAS infections is ~6-fold the estimated number of deaths due to invasive meningococcal disease (a mean of 1340 deaths per year due to GAS infection, compared with 223 deaths per year due to Neisseria meningitidis infection). Moreover, the distribution of disease and death among the 2 extremes of age differs for meningococcal and GAS infections. In 2002, the projected number of cases and deaths due to invasive meningococcal disease among US residents aged ≤17 years were 855 and 43, respectively. The projected number of cases and deaths due to GAS infection among this same younger age group were 1409 and 53, respectively. A much greater difference was noted among elderly individuals (≥65 years old). The estimated numbers of cases in this group were 212 and 3147 for N. meningitidis and GAS, respectively, and the projected number of deaths were 71 and 806, respectively.

**Immunologic characteristics, pathogenesis, and vaccine development.** Understanding the pathogenesis of GAS infections will provide rational approaches for the development of GAS vaccines. However, GAS virulence determinants are as varied as the pathological findings associated with infection. Streptococci are able to adhere to and colonize skin, oral-nasal mucosa, and tonsils and are able to disseminate to other organs. The spectrum of genes that encode and express virulence determinants by any single strain is also highly variable and is likely to be the product of horizontal transmission and selection. Strains with a tropism for skin express a different constellation of virulence factors than do those strains more often

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**Table 1. Estimated global burden of group A streptococcal disease.**

<table>
<thead>
<tr>
<th>Disease, population</th>
<th>Annual no. of cases</th>
<th>Annual no. of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharyngitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>616,026,000</td>
<td>...</td>
</tr>
<tr>
<td>Less-developed countries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>423,495,000</td>
<td>...</td>
</tr>
<tr>
<td>Adults</td>
<td>130,696,000</td>
<td>...</td>
</tr>
<tr>
<td>More-developed countries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>22,835,000</td>
<td>...</td>
</tr>
<tr>
<td>Adults</td>
<td>39,000,000</td>
<td>...</td>
</tr>
<tr>
<td>Impetigo</td>
<td>111,000,000</td>
<td>...</td>
</tr>
<tr>
<td>Acute poststreptococcal glomerulonephritis</td>
<td>472,000</td>
<td>5000</td>
</tr>
<tr>
<td>Acute rheumatic fever</td>
<td>470,000</td>
<td>349,000a</td>
</tr>
<tr>
<td>Invasive disease</td>
<td>663,000</td>
<td>163,000</td>
</tr>
</tbody>
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**Note.** All data were personally communicated to the authors by Dr. Jonathan Carapetis.

a Number of deaths per year attributed to acute rheumatic fever includes estimate of deaths from rheumatic heart disease, rheumatic heart disease–related stroke, and rheumatic heart disease–related infective endocarditis.
Table 2. Group A streptococcal vaccine candidates.

<table>
<thead>
<tr>
<th>Vaccine candidate</th>
<th>Protection in animals (type)</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M type specific</td>
<td>Lethal challenge (active)</td>
<td>[12, 13, 23]</td>
</tr>
<tr>
<td>Conserved region of M protein</td>
<td>Colonization and protection following intranasal challenge (active)</td>
<td>[11, 43–45]</td>
</tr>
<tr>
<td>Combination of M type specific and conserved</td>
<td>Lethal challenge (active)</td>
<td>[15]</td>
</tr>
<tr>
<td>C5a peptidase</td>
<td>Colonization and clearance following intranasal challenge (active)</td>
<td>[14, 16, 24]</td>
</tr>
<tr>
<td>Cysteine proteasea</td>
<td>Lethal IP challenge (passive and active)</td>
<td>[17]</td>
</tr>
<tr>
<td>Fibronectin binding protiensb</td>
<td>Lethal IP challenge (passive and active)</td>
<td>[18, 19]</td>
</tr>
<tr>
<td>Group A carbohydrate</td>
<td>Lethal IP challenge (passive and active)</td>
<td>[20]</td>
</tr>
<tr>
<td>Streptococcal protective antigen</td>
<td>Lethal IP challenge (passive and active)</td>
<td>[21]</td>
</tr>
<tr>
<td>Lipoproteins</td>
<td>Not determined</td>
<td>[22]</td>
</tr>
</tbody>
</table>

* Streptococcal pyrogenic exotoxin B.

** Sfb/PrtF and FBP54.

responsible for pharyngitis and rheumatic fever [10]. Independent of tissue tropism, however, all GAS strains must be efficiently transmitted from human to human, avoid innate defenses, and diseminate to a niche that supplies nutrients and shields them from chemical and physical threats. Table 2 is a partial list of proteins and polysaccharides that have been demonstrated to alter the outcome of infection in various animal models; a few were proven to induce protective immunity [11–23]. Although data demonstrate the association of opsonic antibodies with decreased rates of symptomatic infection and the association of mucosal antibodies with decreased pharyngeal acquisition of GAS and symptomatic illness, additional studies on mucosal and opsonic antibodies elicited by vaccine constructs are needed to optimize vaccine formulations.

GAS skilfully manipulate innate immune defenses at several levels. Virulent streptococci go to great lengths to initially down-regulate inflammation and restrict activation of the alternative complement system, which is critical to the phagocytosis and killing of GAS by the noninnocent host. Surface-associated C5a peptidase and M proteins inhibit detection and phagocytosis by polymorphonuclear leukocytes; first, by specific destruction of the early complement chemotaxin, C5a [24], and then by M protein–restricted deposition of C3b opsonin [25, 26]. Antibody directed at either protein can enhance clearance of streptococci from the nasopharynx and reduce colonization in mice. GAS strains express multiple adhesins, including lipoteichoic acid, M protein, and fibronectin binding proteins [27, 28]. Three of these adhesins—M, fibronectin binding protein Sfb1/PrtF, and fibronectin binding protein 54 (FBP54)—have been shown to promote efficient intracellular invasion of mammalian cells [26]. Two extracellular proteins—streptococcal inhibitor of complement (SIC) and membrane attack complex/IgG degrading enzyme of Streptococcus pyogenes (MAC/Ides)—were recently shown to also contribute to the phagocytic barrier. SIC both inhibits complement activation and inactivates human neutrophil antibacterial peptides [29]. MAC/Ides, a streptococcal homologue of mammalian CD11b (a receptor for C3b and an IgG protease), inhibits opsonophagocytosis and bacterial killing by polymorphonuclear leukocytes [30, 31]. Most strains have the potential to produce several extracellular superantigens that nonspecifically activate T cells and are thought to induce a cascade of cytokines associated with STSS [27, 32, 33]. Streptococcal pyrogenic exotoxin B (cysteine protease) has been associated with a variety of activities, including activation of IL1β and cleavage of surface M proteins [27]. Studies of streptococcal pyrogenic exotoxin B mutants have produced conflicting results with regard to its importance in tissue dissemination and other systemic complications modeled in mice [34]. Detailed reviews of GAS virulence factors and their genetic regulation have been recently published [27, 28].

Bacterial-host interactions that impact GAS pathogenesis are important for vaccine development. The association of particular HLA allelic types with susceptibility and resistance to certain GAS clinical presentations, including rheumatic heart disease, STSS, and necrotizing fasciitis, suggest that there may be different molecular mechanisms for each disease [35, 36]. Molecular mimicry—sharing of antigenic determinants between the host and antigens of GAS—has been implicated in ARF and rheumatic heart disease and has represented a major obstacle for vaccine development [37]. GAS antigens, including the M proteins and group A carbohydrate, have been shown to contain epitopes that mediate B and/or T cell cross-reactions with human tissue antigens [27]. Because the precise role of molecular mimicry in the pathogenesis of ARF has not been established, every effort should be made to exclude tissue–cross-reactive epitopes during vaccine development.

Immune correlations with STSS have been sought, because it is known that streptococcal pyrogenic exotoxins (also known as superantigens) stimulate pro-inflammatory cytokines that most likely play a critical role in the clinical manifestations of STSS. Studies have shown that patients with STSS have lower levels of serum antibodies that neutralize GAS superantigens, compared with healthy control subjects [32]. These observations are consistent with reports that suggest a benefit of intravenous immunoglobulin therapy in patients with severe STSS [38], but the specific mechanism of action of intravenous immunoglobulin in STSS is not known.

**VACCINE CANDIDATES**

Efforts to develop a safe and effective GAS vaccine have been ongoing for decades.
Vaccines previously tested in clinical trials were developed on the basis of Lancefield’s original observations that mice were passively protected from infection by rabbit antisera against whole GAS [39]. Many of the early vaccines contained whole bacteria, cell walls, or partially purified M protein preparations that were extracted from intact bacteria. Two early landmark studies, conducted by Fox and colleagues [40] and Beachey et al. [41], demonstrated that vaccines containing purified M proteins evoked protective immune responses in humans. Vaccine candidates currently under investigation have been selected on the basis of our knowledge of the pathogenesis of GAS infections and the known virulence determinants [27, 28]. For the sake of discussion, these vaccines can be divided into 2 broad categories: (1) those containing virulence determinants that are conserved among different serotypes of GAS and (2) those based on type-specific, opsonic epitopes of the surface M proteins.

**Vaccines based on common protective antigens of GAS.** Active and/or passive protection against GAS challenge in animal models has been demonstrated by several vaccine candidates that are expressed by many or all serotypes (table 2). For example, C5a-peptidase is an enzyme expressed by almost all GAS serotypes, as well as by groups B, C, and G streptococci. Immunization of animals with a recombinant, truncated form of this highly immunogenic protein with mutations in the catalytic triad has been shown to significantly reduce nasopharyngeal colonization after challenge infections with virulent GAS [14, 16, 42]. Antibody directed against C5a-peptidase inhibits cleavage of C5a, a chemotactic complement component that redirects phagocytes to the bacteria. Moreover, intranasal or subcutaneous immunization with recombinant C5a-peptidase prevents pharyngeal- and nasal-associated lymphoid tissue colonization when mice are challenged with 1 of several serotypes of GAS [14, 16]. Two extracellular products, streptococcal pyrogenic exotoxin A and the cysteine protease (streptococcal pyrogenic exotoxin B), are considered to be vaccine candidates, because they are produced by most strains of GAS and because immunization with them has been shown to be protective against lethal challenge in animal models [17, 33]. Patients with invasive GAS disease have lower serum levels of neutralizing antibodies against GAS superantigens than do healthy control subjects [32]. Although it is unclear how vaccination with these or any streptococcal superantigen would prevent pharyngitis, such immunization might prevent more serious complications.

Other surface structures that are common among many or all serotypes of GAS and that evoke protective antibodies in animals include fibronectin binding proteins [18, 19], group A carbohydrate [20], and streptococcal protective antigen [21]. The fibronectin binding proteins Sfb1/PrtF1 and FBP54 have been shown to induce protective immune responses in laboratory animals. FBP54 would be expected to produce broader protection, because it is more widely distributed than Sfb1/PrtF1 among the many serotypes of GAS [18]. Previous studies have demonstrated that group A carbohydrate antibodies are opsonic and protect mice against lethal challenge by GAS [20]. Additional conserved antigens that are potential vaccine candidates, such as lipoproteins [22], are being identified by analysis of genome sequences.

The C-terminal region of M protein contains the so-called “C-Repeats” and is highly conserved among GAS (figure 1). C-repeat peptides evoke mucosal antibodies that prevent bacterial colonization and subsequent death in mice challenged intranasally [43, 44] or intraperitonally [45] with heterologous serotypes of GAS. The C-repeat M protein epitopes have been
expressed on the surface of the commensal organism \textit{Streptococcus gordonii}, which is being developed as a vaccine delivery vehicle for clinical studies [46]. In addition, other investigators have shown that epitopes within the C-repeat region of M proteins evoke antibodies that cross-opsonize many serotypes of streptococci [15].

**Multivalent vaccines based on type-specific N-terminal regions of M protein.** Molecular characterization of streptococcal M proteins has shown that the type-specific amino-terminal region elicits antibodies with the greatest bactericidal activity and can be separated from the potentially harmful cross-reactive epitopes [47]. One vaccine approach has been to engineer recombinant fusion proteins containing N-terminal peptides linked in a tandem array to include multiple serotypes in a single vaccine construct. A prototype hexavalent vaccine was evaluated in adults in a phase 1 trial and was found to be well tolerated, did not induce cross-reactive antibodies, and stimulated vigorous immune responses with bactericidal activity [48].

A potential obstacle to the use of multivalent type-specific M protein vaccines is the fact that >120 M protein genotypes have thus far been identified by \textit{emm} genetic sequence analysis. Many M types can circulate in a community simultaneously, and both temporal and geographic variation have been observed. A 26-valent vaccine has been constructed that includes 80\%–90\% of serotypes that caused invasive infections or pharyngitis, as demonstrated by recent surveillance in North America [9, 49]. This vaccine is currently undergoing clinical evaluation in adults, with evidence to date indicating that it is safe and induces immune responses to all component antigens [50]. In contrast to data from North America, epidemiologic studies indicate that vaccine coverage may be less complete in Asia [51], and there is little information regarding the distribution of M types in developing countries. Although previous studies have suggested that, in some cases, naturally acquired bactericidal antibodies may be strain specific [52, 53], more-recent results indicate that vaccine-induced antibodies are bactericidal against almost all subtypes within an \textit{emm} type [54]. Implementation of vaccine programs may face other issues, such as emergence of new \textit{emm} types and the possibility that nonvaccine serotypes or genotypes of clinical importance may replace those contained in the vaccine.

**Implementation in the United States and at the global level.** Ensuring that a vaccine is available and introduced requires as much effort and considerably more money than developing the science behind the vaccine. Before undertaking the decision to develop a vaccine, commercial sponsors must consider the medical need, scientific and developmental feasibility, commercial value, and strategic fit of the product with the core competencies and other programs of the company. Medical needs include the nature of the disease, its incidence and severity, and the relevant populations (understood in terms of the target age group and the market countries [developing or developed]). Scientific feasibility includes knowledge of the immunity or protection associated with natural disease and with the vaccine composition, knowledge of immune correlates of protection, and the availability of animal models for the disease entity under study. Developmental feasibility includes the time-to-market, research and development expenses, intellectual property and regulatory issues, manufacturing complexity, clinical study complexity, and product complexity and compatibility with other vaccines.

Industry, donors, and governments depend on sufficient information to reduce their risk and to encourage them to make the large financial investments needed to commercialize the new vaccine product and purchase it. In the United States, the likelihood of a recommendation for universal immunization may be critical for moving forward with vaccine development. In some less-developed countries (e.g., India), there is the potential for local manufacture. The World Health Organization has a prequalification process for countries to establish vaccine manufacturing facilities.

One perceived barrier to the approval of a GAS vaccine in the United States stems from an interpretation of 21 CFR 610.19, a regulation in response to the findings of a US Food and Drug Administration panel review. The panel concluded, on the basis of safety concerns, that the uncontrolled use of the GAS antigens in bacterial vaccines with no U.S. standard of potency represented unacceptable risks, and licenses for these products were revoked in 1978. The basis of these concerns was that GAS, as a constituent of this particular group of licensed vaccines under review, might stimulate host immune responses that could trigger ARF or other adverse sequelae. Also, there was no evidence of their effectiveness for their labeled indications, which were largely for therapeutic use for diverse clinical conditions. On the basis of advances in molecular biological techniques, the opportunity now exists to better understand the potency and cross-reactivity of GAS vaccine candidates. Additional product testing for potential molecular mimicry between vaccine antigens and host tissues might include a range of studies, such as homology searches using GenBank, in vivo testing in animal models (such as clinical observations, serum chemistry, hematological analyses, and histopathological examination of animal tissues such as brain, heart, and kidney), and in vitro testing (e.g., immunological studies to rule out—to the extent possible—antibodies cross-reacting with human tissue). The US Food and Drug Administration has been working to revoke 21CFR 610.19, which will remove this perceived barrier.

**WHERE DO WE GO FROM HERE?**

There was extensive discussion of future directions in the development of GAS vaccines that go beyond the scope of this report. The basic scientific and develop-
mental issues requiring more-detailed exploration have been alluded to above. Presuming that safe and effective GAS vaccines can be developed, there remain many issues to be addressed.

The socio-economic burden, public demand, and public health needs for a GAS vaccine are different in different countries. In industrialized countries, the disruption of family life and the necessity for physician visits associated with GAS pharyngitis, as well as the concerns about rare but devastating presentations, such as necrotizing fasciitis and STSS, may be driving forces for vaccine development. A major societal benefit would likely accrue from a marked reduction in the number of antimicrobial prescriptions for sore throat symptoms.

In the developing world, there is a tremendous burden of rheumatic heart disease-related health care, including cardiac surgeries, on the limited health care budgets. Although pharyngitis is not often a cause for doctor’s visits in these countries, there is awareness by physicians that pharyngitis can lead to ARF and rheumatic heart disease. Thus, the ability to prevent ARF and rheumatic heart disease is a sine qua non for a successful vaccine in the developing world. It is hoped that such a vaccine would also prevent cutaneous GAS infections, including pyoderma and its sequel, pyoderma-associated acute glomerulonephritis.

Considerable financial resources will be needed from industry and from governments and/or private donors, and one needs to provide an incentive for their participation by reducing the scientific and financial risks. Thus, research that increases the likelihood of licensure by guiding formulation and identifying appropriate target populations is important. The development of field sites where burden of disease has been documented and that are representative of the locales where vaccine will be used will facilitate and speed the licensure process. Increasing public awareness of the morbidity and mortality associated with GAS diseases, as well as their economic impact, will help to increase acceptance and provide for a known level of demand and usage of the vaccine. Future progress requires initiating, continuing, and expanding collaborative efforts between academia, industry, the World Health Organization, and US agencies (e.g., the National Institutes of Health, the Centers for Disease Control and Prevention, and the Food and Drug Administration) to promote activities to accelerate GAS vaccine development and implementation. The discussions and recommendations from this meeting provide platforms for progress and present an optimistic outlook for GAS vaccines on the horizon.

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