Changing Epidemiology of Acute Rheumatic Fever in the United States

Grace M. Lee1,2 and Michael R. Wessels2

1Department of Ambulatory Care and Prevention, Harvard Medical School and Harvard Pilgrim Health Care, and 2Division of Infectious Diseases, Children’s Hospital Boston, Boston, Massachusetts

(See the article by Shulman et al. on pages 441–7)

Group A streptococci (GAS) infection results in a wide spectrum of clinical presentations, ranging from mild infection (such as pharyngitis or pyoderma) to severe infections due to invasive disease or nonsuppurative sequelae (such as acute rheumatic fever [ARF]). Historical reviews suggest that clinical presentations of GAS infection have changed considerably over the past century. Up until the early 1900s, scarlet fever epidemics were common, and the mortality rate for scarlet fever was estimated to be as high as 30% [1–3]. Over the past 50 years, the incidence and severity of disease due to scarlet fever have decreased precipitously, such that it is now considered to be a mild illness associated with GAS infection. ARF also caused significant morbidity and mortality prior to the 1950s, occurring frequently enough to justify the existence of rheumatic fever registries [4]. However, the overall incidence of ARF decreased significantly over the past 50 decades, despite the occurrence of a few localized outbreaks in civilian and military populations in the 1980s [5–9]. Conversely, invasive disease syndromes may have become more common. For example, streptococcal toxic shock was not generally recognized as a distinct clinical syndrome before the 1980s [10]. Now, the specter of invasive disease is of much greater concern in the United States than is that of ARF.

Factors that have contributed to the evolution of GAS disease—in particular, the decrease in the incidence of ARF—in the United States over the past 5 decades may include changes in the host, the environment, or the pathogen. Although host immune responses to GAS infection and environmental factors, such as degree of crowding and access to health care, likely play a role in disease manifestation, pathogen-associated factors—in particular, differences found among GAS M types—have been highlighted as an important determinant of the changing patterns of GAS disease and its sequelae [11, 12]. The M protein is a major virulence factor for GAS and is the target of opsonic, type-specific antibodies that confer protective immunity [13]. Genetic variation in the *emm* gene, which encodes the M protein, has been correlated with varying disease manifestations [14–18]. Certain M types common in cases of pharyngitis appear to be responsible for invasive disease and/or ARF, whereas other M types are associated with pyoderma and poststreptococcal glomerulonephritis, but not with ARF [19, 20].

The link between pharyngitis strains of particular M types and subsequent ARF has been mostly circumstantial, because it is usually not possible to culture GAS from individuals with ARF at the time that the diagnosis is suspected. However, data in support of this concept include the association of several outbreaks of ARF with the circulation of mucoid GAS strains of putative rheumatogenic serotypes in the community [21, 22]. Older studies of primary prevention programs for ARF in the United States also lend credence to this concept, because prompt treatment of epidemic pharyngitis was found to reduce rates of subsequent ARF [22, 23]. Ideally, a prospective study could demonstrate causality through prospective identification of pharyngeal isolates in a population and follow-up studies to identify individuals who develop ARF. However, the low incidence of ARF in the United States makes such a study design unrealistic.

The study by Shulman et al. [24] in this issue of *Clinical Infectious Diseases* examines the possibility that changes in the prevalence of particular M serotypes account for the significant decrease in the incidence of ARF. The authors compare the M type distribution of GAS recovered from pharyngeal isolates from Chicago...
schoolchildren in the 1960s and from US children in the 2000s and place it in the context of the changing epidemiology of ARF in the United States. They demonstrate a significant decrease in the incidence of rheumatogenic GAS strains and a simultaneous increase in the circulating prevalence of nonrheumatogenic strains. Although these observations are suggestive, the magnitude of change may be overestimated because of the exclusion of M type 1 strains from the group analysis. This serotype was the single most common M type both in the 1960s and in the 2000s, and it includes rheumatogenic strains. As the authors point out, many recent M1 isolates appear to be clonal, but whether the contemporary clone has rheumatogenic potential is not clear. Depending on whether the M1 strains are included, the change in prevalence of rheumatogenic M types is approximately 2- to 5-fold, whereas the reduction in incidence of ARF over the same period has been ≥20-fold. Thus, it seems unlikely that the shift in prevalence of rheumatogenic M types is solely responsible for the decrease in the ARF incidence. Nevertheless, the temporal association is compelling and supports prior studies that suggest that particular GAS strains are responsible for ARF. Although a causal link cannot be definitively established from this study, the authors provide a landscape for furthering our understanding of the shifting epidemiology of GAS strains in the United States.

The results of this study are particularly timely given 2 recently published articles on GAS vaccine trials. These phase I trials of M protein–based GAS vaccine candidates are promising and demonstrate that both 6-valent and 26-valent vaccine candidates are reasonably well tolerated and immunogenic [25, 26]. More importantly, these M protein–based vaccines did not appear to induce antibodies that cross-react with human tissue, which had halted the development of GAS vaccines over the past 40 years. The serotypes found in the 26-valent vaccine, which is most likely to go forward in clinical trials, were chosen on the basis of the most prevalent types to cause significant invasive disease and uncomplicated pharyngitis [19, 27]. Of the known rheumatogenic M types, 90% would be included in this vaccine. The promise of such a vaccine in the United States is considerable, but the potential to use a similar vaccine in the developing world, where the incidence of rheumatic fever is much higher, is even more exciting.

Unfortunately, vaccine development is complicated by the fact that the epidemiologic characteristics and serotype distribution of GAS elsewhere in the world are quite different from what they are in the United States. In particular, the experience with ARF in the Australian Aboriginal community challenges our traditional concept of rheumatogenic strains [28, 29]. GAS pyoderma is hyperendemic in this population, and the distinction between “skin” and “throat” strains is blurred. Furthermore, in areas where ARF is endemic, both GAS infection and ARF may be associated with different M types from those targeted by the vaccine. A potentially interesting use of the 26-valent M protein–based GAS vaccine may be to estimate the burden of disease due to putative “rheumatogenic” strains, compared with “nonrheumatogenic” strains [30]. For example, a vaccine trial in a country with high rates of endemic ARF could be used to deduce the proportion of ARF cases due to vaccine serotype strains, further reinforcing the concept of rheumatogenic strains if the vaccine is found to be efficacious.

As the 26-valent vaccine moves forward in clinical trials, concern over the prospect of “serotype replacement” will also be an issue, whether the result of unmasking or true replacement [31]. In addition, although particular M types are thought to be rheumatogenic, recombination events may allow for the transfer of virulence factors and other genetic material to nonvaccine serotypes. Given the genetic and phenotypic evolution of GAS to date, we must continue to explore potential prevention strategies that will be critical for reducing the burden of ARF in both developed and developing countries in the future.

**Acknowledgments**

**Financial support.** Agency for Healthcare Research and Quality, US Department of Health and Human Services (K-08 HS01980-01 A1 to G.M.L.).

**Potential conflicts of interest.** G.M.L. and M.R.W.: no conflicts.

**References**


**Potential conflicts of interest.** G.M.L. and M.R.W.: no conflicts.