# Clinical and epidemiological aspects of streptococcus pyogenes pharyngitis and carriage in Africa

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## ABSTRACT

**Infection with Group A β-haemolytic Streptococcus, also known as Streptococcus pyogenes, results in various mucosal and skin diseases including pharyngitis. An exaggerated immune response to a single or repeated group A streptococcal (GAS) infection subsequently results in acute rheumatic fever (ARF) and, in the absence of intervention, repeated bouts of ARF may in turn result in progression to RHD, particularly in those ARF patients with cardiac involvement. Addressing GAS pharyngitis through appropriate primary prevention measures and treating all symptomatic GAS sore throats with a course of oral or parenteral penicillin presents an opportunity for the primary intervention of RHD. Failure to eradicate streptococci from the pharynx occurs in about one third of non-treated cases, giving rise to carrier status in those individuals harbouring intracellular GAS and thus representing a potential source of the acquisition of infections for other children and adults.**

**Improved living conditions and access to healthcare during the last century are credited for the considerable decline in the prevalence of ARF and RHD in developed countries. However, a few studies have been reported from within Africa, and in these GAS carriage ranged around 9.0%. In South African studies GAS carriage isolation rates, which range from 1.62% to16.8%, were reported. As regards the prevalence of GAS pharyngitis, it is generally higher in developing countries and impoverished communities within industrialised nations. The most-up-to-date data from South Africa was collected more than 30 years ago with rates then ranging from 23.2% to 45.5%. There are no incidence data on GAS pharyngitis in Africa.**

**This review found that there is a need to document the epidemiology of GAS carriage and GAS pharyngitis in school children of all ages within Africa. Molecular characterisation of strains harboured in the pharynx of carriers and of those isolated during bouts of pharyngitis, will help to identify risk factors associated with carriage in school-aged children and influence the planning and evaluation of management programmes in the screening of pharyngeal carriers and treatment of GAS pharyngitis.** SAHeart 2013;10:434-439

## INTRODUCTION

Infection with Group A β-haemolytic Streptococcus, a gram-positive bacterium also known as Streptococcus pyogenes, results in mucosal and skin diseases such as pharyngitis and pyoderma.[1] While most cases of sore throat are due to viral infections such as influenza and require symptomatic treatment before eventually self-resolving, group A streptococcal pharyngitis specifically refers to a sore throat resulting from an infection with group A streptococcus (GAS). Following the initial infection, or after repeated GAS pharyngeal and skin infections, more serious GAS-related illnesses may result (Table 1) such as acute post-streptococcal glomerulonephritis, acute rheumatic fever (ARF) and rheumatic heart disease (RHD).[2-5] RHD is associated with significant morbidity and mortality in children and young adults living in developing countries.

In South Africa, guidelines for the management of pharyngitis (including bacterial tonsillitis) are provided in various Department of Health publications.[6,7] Clinical features suggestive of β-haemolytic streptococci group A are sore throat, inflamed tonsils with exudate, tender and enlarged cervical lymph nodes and often, a sudden onset of fever as illustrated in Table 2. The current standard of care targets children aged 3 - 15 years for primary prevention, i.e. patients presenting with a sore throat are treated with penicillin if there are no signs of viral infection. Addressing GAS pharyngitis through appropriate primary prevention measures and treating all symptomatic GAS sore throats with a course of oral or parenteral penicillin[8] presents the opportunity for primary intervention of RHD,[9] thereby reducing the economic and major public health consequences associated with disease burden.[10,11]

**TABLE 1:** Group A streptococcal-related diseases[2,5,19]

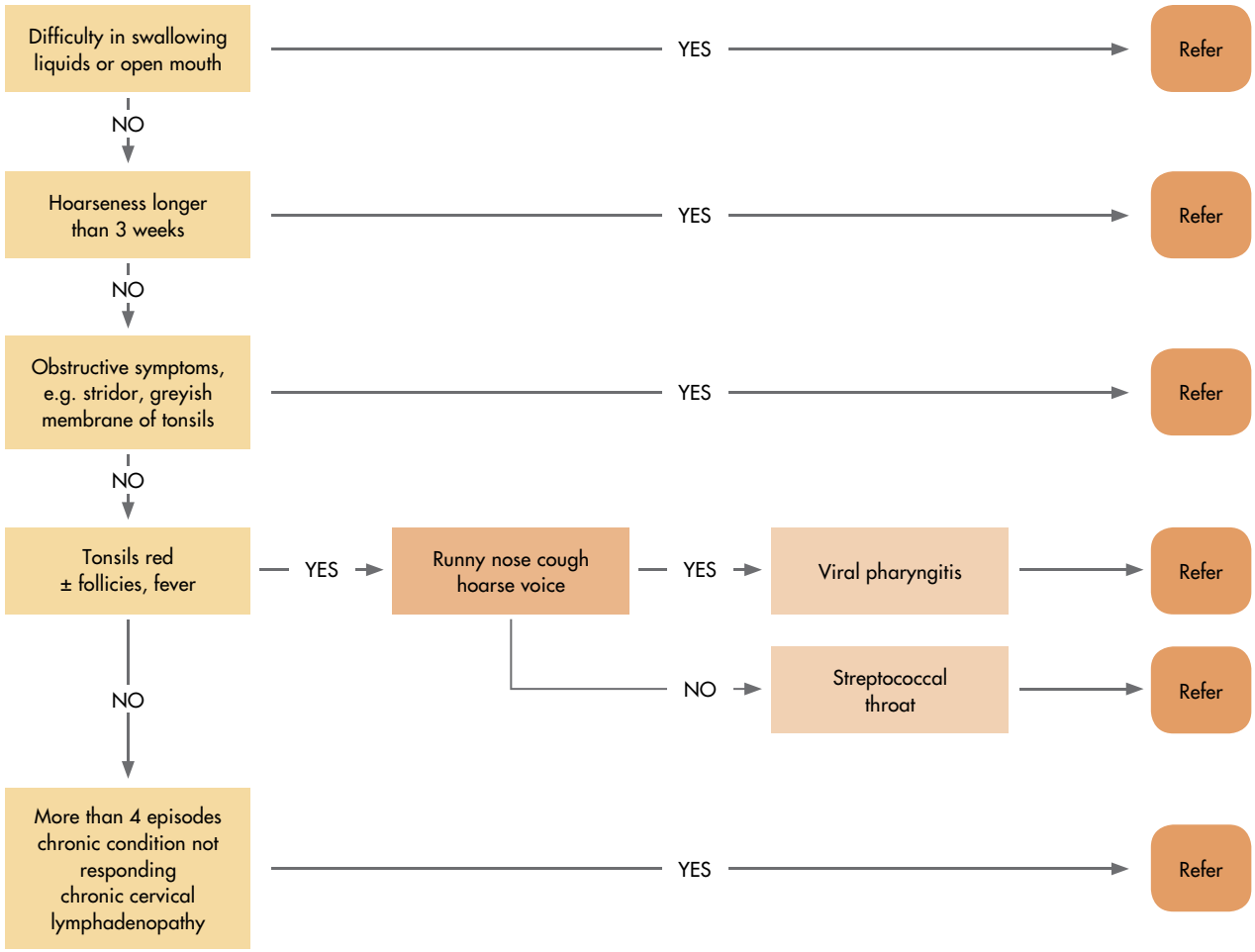
| |
|---|
| Pharyngitis and Scarlet Fever |
| Pyoderma and Streptococcal Skin Infections |
| **Invasive Streptococcal Disease:** |
| Streptococcal Toxic Shock Syndrome |
| Necrotizing Fasciitis |
| Septicaemia |
| Post-Infectious Sequelae |
| Rheumatic fever |
| Acute post-streptococcal glomerulonephritis |
| Reactive arthritis |
| PANDAS |

*PANDAS = Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections.*

Failure to eradicate streptococci from the pharynx occurs in about one third of non-treated cases, giving rise to the carrier status in those individuals harbouring intracellular GAS.[12] Carriers of GAS may represent a potential source for the acquisition of infections for other children and adults. A longitudinal study over 44 months demonstrated the persistence of carrier strains during repeated episodes of GAS infection in 50% of participants.[13] Thus, GAS carriage reflects the reservoir of circulating strains, which are relevant to disease, such as pharyngitis.

In culture, Streptococcus pyogenes can be differentiated from normal throat flora by their distinct appearance as β-haemolytic colonies on 5% sheep agar incubated under anaerobic conditions (Figure 1). β-haemolytic streptococci can further be differentiated into serotypes using the Lancefield grouping system including, for example, GAS which is distinguished by its group A carbohydrate.[2,14] Earlier work by Rebecca Lancefield established a type-specific surface antigen on GAS, the M-protein which is encoded by

**TABLE 2:** South African Essential Drug List: Diagnosis and Treatment of streptococcal infection in children aged 3 - 15 years.[6]



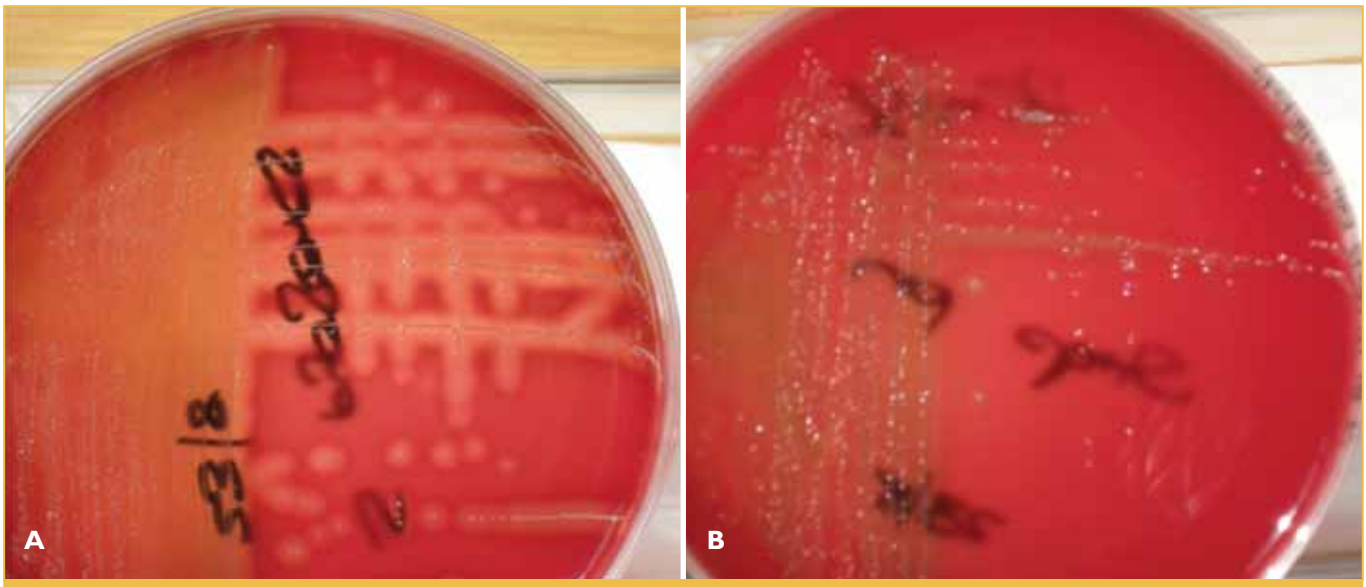



**FIGURE 1: Pattern of haemolysis around streptococcal colonies** distinguishing beta (A) with large zones of complete haemolysis around colonies from alpha (B) with its incomplete haemolysis and dark green agar under the colonies. Photo: M Engel, 2012

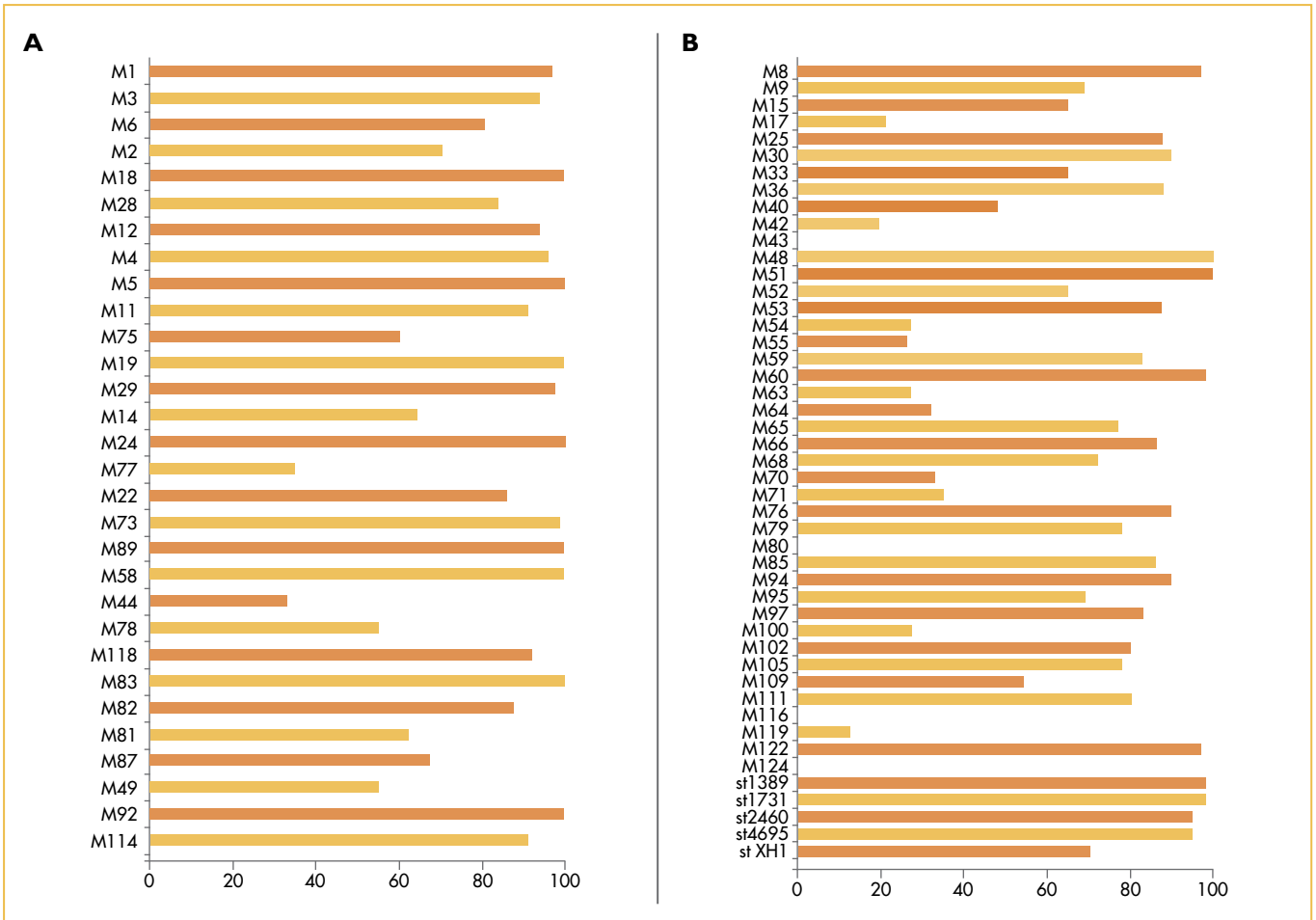



**FIGURE 2: In vitro percentage killing in human whole blood**
Percentage killing by bactericidal antibodies evoked by the 30-valent vaccine. A. Vaccine serotypes. B. Non-vaccine serotypes. Courtesy of J. Dale.

the emm gene and is the major target for the immune system.[15] Recent advances in molecular biology have made it possible to differentiate the more than 200 variations in the emm sequence by so-called emm typing.[16,17] The N-terminal region of the M-protein is the target for vaccine development, having been shown to evoke antibodies with the greatest bactericidal activity, while showing no cross-reaction with human tissues.[18] Amino acid sequences of M proteins of 30 emm types have been included in the latest vaccine initiative and preliminary results indicate bactericidal killing of >40% in over 90% of the vaccine serotypes and additional cross-opsonic activity against 60% of 40 non-vaccine serotypes of GAS evaluated (Figure 2).

## EPIDEMIOLOGY OF ASYMPTOMATIC PHARYNGEAL CARRIAGE

Asymptomatic children can be a major reservoir of pharyngeal GAS. A pooled GAS carriage prevalence of 12% (95% CI: 9% - 14%) in healthy children aged 5 - 17 years was reported in a recent review of 18 clinic- and school-based studies on streptococcal carriage in both industrialised and developing countries.[20] Amongst the 7 studies on school-aged children included in the review, the prevalence of asymptomatic carriage ranged from 10% in Sweden to 21% in Iran. In another 16 month follow-up study conducted in community-based family medicine practices in Australia, seasonal carriage rates ranged from 8% - 16% amongst 160 randomly selected families,[21] while in a prospective surveillance study conducted over 9 months in Fiji, a GAS carriage of 6.0% was observed amongst 685 healthy children.[22]

Results from India show contrasting figures; in Chennai, 8.4% of 1 102 school children from overcrowded government or charity-aided schools in slum-like conditions harboured GAS[23] while in a rural community in Northern India, a prevalence rate of only 1.3 % was observed in 3 385 children aged 5 - 15 years.[24] Still within the region, a cross-sectional study across 4 schools in Nepal, isolated GAS from 10.9% of 350 students 5 - 15 years of age.[25] Elsewhere, in Grenada, a study conducted in randomly selected schools observed a GAS prevalence of 5.2% among 1 388 children aged 5 - 15 years.[26]

Data on GAS carriage from countries in Africa remain scarce with only a few studies reporting on carriage. In Ethiopia, Abdissa reported a 9.7% carriage rate in pharyngeal isolates from 937 healthy participants aged 6 - 14 years (mean age, 11 years).[27] An earlier study in Tunisia documented a rate of 9.0% from throat swabs taken from 155 controls.[28] More recently, Sadoh reported a prevalence of almost 10% among asymptomatic school children in Nigeria.[29]

In South Africa there is a dearth of recent studies on GAS carriage rates in school-aged children, with only 4 studies conducted more than 25 years ago. In a study of 12 050 school children from largely lower-socio economic households in Soweto, isolation rates of 5.2% were reported with a significantly higher rate of GAS isolation during the winter months and a peak incidence in fifth and sixth school grades.[30] In another study from the northern part of South Africa, contrasting carriage rates of 1.62% and 16.8% were reported in asymptomatic Black participants from a remote traditional community and an urban setting respectively.[31] In the same study, urban Whites had a carriage prevalence of only 3.4%. A study conducted in the late 1970s in the densely overcrowded Hout Bay community of Cape Town reported an overall prevalence of 3.6% amongst 1 150 children aged 6 - 17 years.[32] The 2 schools surveyed had respective prevalence rates of 2.4% and 12%, the latter speculated to be reflective of the 10km distance from the nearest primary health care polyclinic. Finally, a study involving mostly grade 3 school children of either mixed or Indian ancestry reported GAS carriage rates >20% in summer and <5% in spring.[33]

Few studies report on the distribution of emm types amongst asymptomatic GAS carriers.

In Fiji, while not reporting specific emm types, Steer et al. observed that 32% of GAS emm sequence types were shared between carriage and sore throat isolates.[22] To date, only 1 study reports on the distribution of emm types amongst asymptomatic GAS carriers in Africa, indicating diversity in M strains.[34]

## EPIDEMIOLOGY OF GAS PHARYNGITIS

GAS-positive pharyngitis is common among school-aged learners, with the peak age of incidence for GAS infections being between 5 and 15 years.[35] Generally, developing countries have higher prevalence rates of GAS isolated from patients with pharyngitis compared to industrialised nations, except for impoverished populations within industrialised countries.[19] A recent review of 17 studies of GAS prevalence calculated a pooled prevalence estimate of 37% among children presenting with sore throat from both industrialised and developing countries.[20] Of the studies included in the review, the prevalence rates ranged from 23% in the United States to 58% in a study from the Netherlands; although on closer inspection of the Netherlands study, the isolation of GAS was actually only 32%.[36] In the same review, 2 studies from developing countries reported rates of 45% (Sri Lanka) and 33% (Egypt/Croatia/Brazil) respectively.

In a hospital-based study from Kolkata, GAS was isolated from 42 out of 100 throat swabs from patients of all ages presenting with pharyngitis, with a peak incidence observed in the 5 - 15 years age group.[37] Elsewhere in India, a cross-sectional study comprising 4 249 children aged 5 - 15 years from 25 randomly selected villages in the Panchkula district of Haryana in northern India, reported respective prevalence rates for βHS and GAS of 25.7% and 2.8% from children with pharyngitis with rates of isolation being significantly higher in the winter months.[24] In the same study, the investigators observed pharyngeal βHS and GAS carriage rates of 15.4% and 1.3% respectively.

The incidence of GAS positive pharyngitis is estimated to be 616 million cases per year amongst all ages across the world based on a systematic review of population-based data using United Nations population data as the denominator. In more developed countries approximately 15% of school-aged children will suffer an episode of GAS pharyngitis each year, whereas in less-resourced countries, the incidence may be more than 5 times greater.[3] A few studies have documented incidence of GAS pharyngitis. Respective incidence rates of acute sore throat and GAS swab-positive pharyngitis include, in former Czechoslovakia, 8.3 and 3.9 cases per 100 child-years,[38] Northern India, 705 and 95 cases per 100 child-years[39] and Melbourne, Australia, 33 and 13 cases per 100 child-years[21] as well as 162 and 14.7 cases per 100 child-years.[22]

Prevalence and incidence data on GAS pharyngitis from developing countries are largely lacking when compared to industrialised nations,[40] especially in South Africa. A study conducted in Pretoria over 30 years ago on 232 unselected patients who presented with a complaint of sore throat reported an overall prevalence of 33.2% with a significant difference between rates for Blacks (45.5%) and Whites (23.2%).[41] No variation in rates was observed by season and the overall background carriage rate of 165 controls was 12.1% (Blacks, 16.8%; Whites, 3.4%). In another study of 112 participants aged 2 to 19 years of age conducted during the summer months at a hospital serving the Black community in Bloemfontein, 42% of throat swabs cultured returned a positive GAS result.[42]

## DISCUSSION

Contemporary data on GAS carriage rates among asymptomatic school children in Africa and South Africa remain scarce, with no school-based studies undertaken across the complete spectrum of age groups. There is a need to document GAS carriage in school children of all ages which, together with molecular characterisation of strains harboured in the pharynx of carriers, will help to identify risk factors associated with carriage in school-aged children and influence the planning and evaluation of management programmes in the screening of pharyngeal carriers.[23] Also, knowledge of the pre-test probability influences assessment of the post-test probability of GAS pharyngitis, so as to minimise unnecessary diagnostic testing in children.[20]

There is considerable heterogeneity amongst epidemiological studies on GAS pharyngitis in terms of participant selection, study setting and duration of enrolment. Few studies employed a passive surveillance approach where participants are enrolled only at the time of presenting to the clinic or health facility, thereby reducing the risk of selection bias. Furthermore, few studies extend much beyond a year in duration, thus making it difficult to make conclusive judgements on seasonality. An understanding of the incidence of GAS pharyngitis in children within a local context is an important component of any ARF and RHD control programme.[43] Given that no data exist on the incidence of GAS pharyngitis among children with pharyngitis attending primary health care clinics in South Africa, a prospective surveillance study of sufficient duration (>3 years) is required.

Given the advancement in molecular methods to enable the characterisation of GAS strains through M-typing of the emm gene, there is a need to conduct emm strain typing on GAS isolates from patients presenting with pharyngitis at primary health care facilities in order to compare strains with those isolated from carriers. In the light of recent progress towards a streptococcal vaccine[18] and given that asymptomatic carriers have been shown to maintain the carrier streptococcal strain when progressing to active disease,[13] identification of the DNA sequencing pattern of the 5' hypervariable region of the cell-surface M-protein (so called emm typing)[44] may inform vaccine development and later help in assessing the impact of vaccination, the monitoring of serotype changes and its efficacy within the population.

**Conflict of interest: none declared.**

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