Streptococcal skin infection and rheumatic heart disease

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Purpose of review
In resource-limited tropical settings, both impetigo and rheumatic disease are endemic. The major cause of impetigo in these regions is the group A streptococcus and there is a growing body of opinion implicating impetigo in the pathogenesis of rheumatic fever and rheumatic heart disease (RHD). This potentially has major implications for control of these neglected diseases, which account for at least 350 000 deaths worldwide, annually. In this review, we summarize recent advances in the epidemiology of group A streptococcal skin disease and examine evidence for the relationship between group A streptococcal skin disease and rheumatic fever.

Recent findings
Detailed epidemiologic studies of impetigo, particularly among indigenous communities in the Pacific among whom rheumatic fever is endemic, find the disease remarkably prevalent. In contrast, group A streptococcal pharyngitis occurs no more frequently than in regions wherein rheumatic fever is now rare. Studies of molecular epidemiology reveal that overall there is a greater diversity of group A streptococcal strains in tropical regions, and skin-associated strains appear predominant. These skin strains may move between skin and throat, and there is increasing evidence of skin-associated strains being linked to cases of rheumatic fever.

Summary
The available data support the hypothesis that group A streptococcal impetigo plays a role in the pathogenesis of RHD. There is considerable scope to investigate this question through studies of pathogenesis, employing advances in both human and bacterial genetics, molecular immunology, and carefully designed trials aimed at control of impetigo.

Keywords
acute rheumatic fever, rheumatic heart disease, group A streptococcus, *Streptococcus pyogenes*, impetigo

INTRODUCTION

The Lancefield group A (β-haemolytic) streptococcus (GAS, *Streptococcus pyogenes*) is a bacterial pathogen that is the major cause of impetigo in tropical settings [1]. Impetigo is the most common skin infection in children throughout the world [2].

Despite the numbers of cases worldwide (an estimated 111 million children living in less developed countries have GAS impetigo at any one time [3]), it is a widely held belief that that these diseases are a benign nuisance rather than a public health priority [1]. There is evidence to suggest that this is not the case. In developing countries, these diseases are associated with considerable suffering, particularly among children, place a sizeable economic and workforce burden on primary healthcare resources and are also a financial burden to the patient, their family and their community [4,5]. Further, a proportion of patients with impetigo suffer life-threatening consequences. In tropical settings, impetigo is the predominant source for invasive GAS disease [6], and in communities wherein impetigo is endemic, skin sores and scabies are also the major risk factor for invasive *Staphylococcus aureus* infection [7]. Group A streptococcal impetigo is responsible for endemic and

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Curr Opin Infect Dis 2012, 25:145–153
DOI:10.1097/QCO.0b013e3283511d27

KEY POINTS

- The group A streptococcus is the major cause of impetigo in the developing world, but due to a lack of high quality epidemiologic data the burden of disease is probably underestimated.
- The closely linked epidemiology of group A streptococcal skin infections and rheumatic heart disease (RHD) in tropical settings suggests that group A streptococcal skin infection may play a central role in the pathogenesis of RHD, particularly among indigenous peoples.
- Investing public health efforts in control of group A streptococcal skin infections and scabies, the major risk factor, a valid objective in itself, may be the most cost-effective approach to control RHD, a disease responsible for 350 000 deaths, annually.

epidemic acute poststreptococcal glomerulonephritis (APSGN) [8]. In addition, there is a growing body of opinion implicating impetigo in the pathogenesis of acute rheumatic fever (ARF) and rheumatic heart disease (RHD) [9]. If a link between impetigo and ARF/RHD was established, it would have important implications for control of these diseases which account for at least 350 000 deaths annually worldwide [3].

In this review, we first summarize recent advances in the epidemiology of GAS skin infections; second, evaluate the epidemiologic relationship between GAS skin infections and ARF (both 'classical' and 'alternative' views); and third, explore the scientific methods and study designs that might enable a firmer link to be drawn between GAS skin infections and RHD.

EPIDEMIOLOGY OF GROUP A STREPTOCOCCAL SKIN INFECTION

In 2005, the WHO Department of Child and Adolescent Health and Development reviewed the epidemiology of common skin diseases in children in developing countries [1]. The three prevalence surveys considered by the authors representative of a wider geographic area set in Brazil [10], Ghana [11] and Mali [5] found impetigo in 9.6–12.3% of the population, whereas estimates from other studies ranged from 0.2 to 35% [1]. Few studies quoted incidence estimates. Overall, however, the authors concluded that impetigo is endemic among children in the developing world. The foremost risk factor for impetigo is scabies, an ectoparasitic infestation by *Sarcoptes scabiei* var. *hominis*, and the epidemiologies of the two conditions are closely linked [12].

Studies investigating the bacteriology of impetigo in developing countries with a tropical climate are scarce and those that are available often provide only limited detail on case definitions and bacteriological techniques [1]. The view that GAS is the major causative agent is supported by studies set in Brazil [13] and Africa [14–16] between 1972 and 1992 which isolated GAS from 72 to 95% of impetiginous lesions. This is consistent with studies of impetigo in the USA in the 1960s among indigenous children [17] and among socially deprived children of European or African ancestry [18] where GAS was the predominant organism. The role of *S. aureus*, however, is less clear. Observers finding GAS as the predominant organism also frequently isolated *S. aureus* in the same impetigenous lesions, culturing it with GAS from 36% of cases in Brazil [13], 45% in Uganda [15], and 47–57% among the two USA populations [17,18]. Other observers working in Tanzania in 1975 [19], Nigeria in 1987 [20] and Trinidad and Tobago in 1990 [21] isolated *S. aureus* more frequently than GAS, finding 65–72% of lesions grew *S. aureus,* whereas only 8–48% grew β-haemolytic streptococci. Multiple issues underlie this discrepancy. First, bacteriologic techniques differed between the studies. The African studies that found GAS as the predominant organism plated swabs immediately [14,15] or within 2 h [16], whereas the studies finding *S. aureus* predominant either did not describe plating techniques [20,21] or stated that plating was performed within 3 days [19]. A marked bias towards the isolation of *S. aureus* has been described if plating of swabs is delayed [22]. Second, the definition of impetigo varied or was not stated, often incorporating patients with and without scabies as well as other skin conditions such as eczema, and the populations studied included community surveys, specialist dermatology clinics or a mixture. These factors are important because, for example, observations among indigenous children in the USA indicated the bacteriology of bullous and nonbullous lesions differed, the former being more closely related to *S. aureus* [18]. Further serial observations of nonbullous lesions found the same GAS serotype isolated repeatedly over time with *S. aureus* strains of changing phage-type occurring only once a lesion was established [23,24]. Finally, living conditions rather than the climate may determine the importance of *S. aureus*; for example, a study in Singapore, a developed nation with a tropical climate, isolated *S. aureus* from 72% of lesions in children and *Streptococcus* species from 6.5% [25]. Overall, GAS is the major causative agent of impetigo in developing countries with a tropical climate, although the role of *S. aureus* is not yet

fully understood, and bacteria isolated may differ from population to population.

Worldwide, the highest prevalence of impetigo is found among indigenous peoples of Australia and in populations of Pacific Island nations [3]. Extensive studies have been conducted in Australia where up to 70% of indigenous children have skin lesions, from which GAS is isolated in 80% of cases [22]. More recently, large epidemiologic studies of impetigo have been conducted in Fiji, a nation in the Western Pacific comprising two major ethnic groups, indigenous Fijians (57%) and Indo-Fijians (37.6%). Overall, the prevalence of active impetigo across 3500 primary school children was 26%, and GAS was recovered from 80% of bacterial swabs taken [26]. Remarkably, the GAS impetigo incidence rate in a 10-month prospective study of 219 children free from active impetigo at the outset was as high as 80 per 100 childyears and four-fold higher among indigenous children than others [26]. This would suggest that, on average, the majority of children experience at least one episode of GAS impetigo each year.

GROUP A STREPTOCOCCAL SKIN INFECTION AND THE CAUSE OF RHEUMATIC HEART DISEASE

RHD is a chronic, autoimmune valvular heart disease which results from infection with GAS, and is the consequence of episodes of ARF, an acute febrile illness manifesting principally as carditis (primarily valvulitis), polyarthritis, fever, and occasionally choreiform movements [27]. For many years it has been an accepted teaching that ARF only follows GAS pharyngitis, in contrast to APSGN, which may follow infection of throat or skin [28]. Today, however, the highest incidence of ARF and the greatest prevalence of RHD in the world are found among indigenous people of Australia and the Pacific Island nations [29], where, as discussed, the burden of GAS impetigo is considerable (Table 1) [12,22,26,30–36]. Crucially, in indigenous populations of Australia GAS pharyngitis is rare compared to GAS impetigo, leading to the hypothesis that GAS impetigo is at least a cofactor, if not the determinant, of ARF and RHD in these settings [9]. This viewpoint, however, continues to be debated [28].

The classical view

The observation that episodes of ARF are preceded by an episode of acute pharyngitis dates from at least the early 19th century [37]. By the 1930s, there was both epidemiologic and microbiologic evidence to support the theory that ARF was a direct

Table 1. Epidemiology of acute rheumatic fever/rheumatic heart disease, group A streptococcus impetigo and group A streptococcus pharyngeal carriage in indigenous populations in the Pacific

	ARF/RHD			Impetigo prevalence			GAS pharyngeal carriage	
Indigenous population	Study period	Parameter	Estimate	Study period	Impetigo prevalence estimate	Proportion impetigo with GAS	Study period	GAS pharyngeal carriage estimate
Indigenous Fijians in Fiji	2005–2007	ARF incidence; RHD prevalence	16.4 per 100 000[a] [30]; 8.4 per 1000 [31]	2006	33% [26]	79.8% [26]	2006	4.6% [32]
Indigenous Samoans in Samoa	1999	RHD prevalence	77.8 per 1000 [33]	1999	43.6% [33]	51.3% [33]	1999	2.4% [33]
Indigenous Australians in Australia	1989–1993	ARF incidence; RHD prevalence	254 per 100 000 [34]; 9.6 per 1000 [34]	2001–2005	69% [12]	80% GAS [22]	2003–2005	3.7% [35]

ARF, acute rheumatic fever; GAS, group A streptococcus; RHD, rheumatic heart disease.
[a]Probable significant under-diagnosis [36].

consequence of acute pharyngitis due to a haemolytic streptococcus [38]. This was supported by the observations that episodes of ARF followed epidemics of streptococcal pharyngitis in the general population [39]; teenagers institutionalized in boarding schools and cadets in military barracks suffered episodes of ARF within days of streptococcal pharyngitis [40]; children with established RHD admitted for convalescence suffered a relapse of ARF in association with recurrence of streptococcal pharyngitis [41,42]; and throat cultures obtained weekly from people living in communities where ARF was endemic were 10-fold more likely to grow 'haemolytic streptococcus' than cultures obtained from people living in nonendemic communities [43]. During the Second World War, ARF was a major problem for the allied forces, and the effectiveness of prevention by mass administration of penicillin provided further evidence for the role of β-haemolytic streptococcus [44]. This led to a series of randomized and quasi-randomized trials of penicillin treatment of GAS pharyngitis to prevent ARF conducted in military barracks in the 1950s [45]. When these studies were pooled in a meta-analysis, the risk of ARF was reduced by nearly 70% in the intervention group (relative risk 0.32, 95% confidence interval 0.21–0.48) [45]. These data provide the most convincing evidence for the role of GAS pharyngitis in causing ARF.

No mention of impetigo is made in early descriptions of ARF [46]. Even in a detailed account of 655 cases published in the 1880s, in which all concurrent skin disease is described, not a single patient is reported to have had impetigo before, during, or after an attack [47]. Interest in GAS impetigo increased in the 1960s largely because of its role in APSGN [48,49]. Notably, apparently distinct seasonal epidemiology of ARF and APSGN was described in Tennessee, USA [50]. With the recognition that GAS triggered both ARF and APSGN, efforts were made to explain why GAS infections triggered two such different postinfective pathologies [48,49,51]. For example, a study among indigenous Americans, in whom impetigo, APSGN [17], and ARF [52] were common, investigated antibody responses to skin and pharyngeal infection, finding antistreptolysin O titres were elevated after both pharyngeal infection and ARF, but were infrequently elevated following impetigo [53]. By 1972, it was widely accepted that GAS infection of the 'upper respiratory tract' was a '*sine qua non* for ARF' [54].

Typing of GAS strains has also contributed to the classical view of GAS pharyngitis and ARF. A number of methods exist to type GAS [55,56]. The current gold standard method relies on the sequence of the 5′ extremity of the *emm* gene (*emm* typing) [57]. This gene encodes for the M protein, a heterogeneous surface-exposed virulence factor protein [58,59▪▪]. In temperate regions in the industrialized world, some associations were noted between specific M-protein types and disease. Indeed, the strains classically isolated from the throat associated with pharyngitis differed considerably from those isolated from the skin [48,49,60]. Later, on the basis of the antigenicity of the 3′ terminal repeat region of *emm*, M-protein types were divided into two categories, class I and II, with only the former associated with ARF [61]. Further, five patterns (A–E) of *emm* chromosomal arrangement, accounting for nearly all known isolates, correlated well with site of isolation and clinical picture: pattern A–C (class I), pharyngitis; pattern D (class I), impetigo; pattern E (class II), both pharyngitis and impetigo [62]. Importantly, for nearly all GAS strains examined, a given *emm* type is restricted to a single *emm* pattern grouping [63▪▪]. In temperate regions, only pattern A has been associated with ARF. In the 1980s, ARF became resurgent in parts of the USA, facilitating further investigation [64]. In Utah, during the peak years of resurgent ARF activity, specific M types including an unusual clonal mucoid M18 strain became the most abundant type among isolates causing pharyngitis [64–66]; then during years of decreased ARF activity, this strain disappeared [67]. The M18 strain was further implicated in the outbreak with the finding that sera from 35 patients were reactive to the class I peptide associated with M18, but sera from cases of pharyngitis and controls were nonreactive to this peptide [61]. The classical view of ARF being caused by pharyngitis-associated isolates alone comes mostly from North American data obtained during the 20th century. There are very few data regarding its applicability to different epidemiological settings elsewhere in the world.

The alternate view

Although there has been a marked decline in the incidence of ARF and RHD in industrially developed regions of the world, the disease is endemic in the developing world and among indigenous peoples [3]. Investigation into the role of GAS impetigo in the pathogenesis of ARF in tropical developing regions was proposed by the WHO in the 1960s [68]. However, it has been the extensive studies of GAS disease in central and northern Australia that have provided the most compelling epidemiologic evidence that GAS impetigo may be the driving force behind ARF in impetigo endemic regions [9]. In such settings, the epidemiology of disease is very

different; among indigenous Australians, for example, cases of GAS impetigo outnumber throat carriage or infection nine fold and only 16% of all isolates carry a pattern A–C genotype, characteristic of the throat [69]. This discrepancy has been independently noted elsewhere in Uganda [15], in Trinidad [70] and in New Zealand [71]. Recent studies in Fiji add further weight to this conjecture; although there is very little difference between the incidence of GAS pharyngitis in industrialized nations today and that reported in prospective surveillance of sore throats among school children in Fiji [32], there is at least a 50-fold difference between the incidence rate of impetigo in Europe [2] and indigenous peoples in Fiji [26]. At least in the UK, impetigo, having been endemic in groups at highest risk of RHD such as soldiers and urban dwelling children, appears to have declined in parallel with RHD [39,72–75]. Thus, the closely linked epidemiology of GAS impetigo would support the hypothesis that impetigo plays a role in the pathogenesis of RHD.

The proportion of ARF patients with a preceding sore throat may be less than previously thought. Of the 274 confirmed cases included in the Utah outbreak through 1992, only 17% sought medical attention for a sore throat and only two patients had positive throat cultures for GAS [76]. In a large study of school-based diagnosis and treatment of sore throat to prevent ARF in New Zealand, 14 of 26 patients with ARF were known to have had sore throat prior to the onset of ARF and only five patients had swabs that were GAS positive; despite involving over 85 000 personsyears, the trial was negative (incidence risk ratio 0.79, 95% confidence intervals 0.41–1.52, $P = 0.47$) [77]. Finally, during recent prospective surveillance of ARF in Fiji, only 14 of 33 patients reported a preceding sore throat [30].

Recent systematic reviews of M-protein typing data have revealed that overall there seems to be far greater diversity of *emm* types of GAS in developing countries where RHD is endemic, particularly in Africa and the Pacific [78,79]. Three particular studies in Fiji [80], Hawaii [81] and Brazil [82] have observed a high level of diversity among *emm* types, most likely reflecting many circulating impetigo-associated GAS strains. The difference between the diversity of GAS strains in temperate and tropical climates is remarkable and it is possible this diversity precipitates autoimmunity. Interestingly, the diversity of the M proteins of Brazilian isolates, the majority being skin associated and pattern D and E, was limited to the *emm*-type defining region, whereas the remaining sequence of the M protein was far more conserved; in contrast, the sequences of the M protein of pattern A–C isolates were highly divergent [83▪▪,84]. However, these pattern D strains were more frequently recovered from the throat of children than the classical A–C pattern isolates [82], raising the possibility that passage of typical skin isolates into the pharynx might also potentially explain their involvement in ARF and RHD in specific settings. Temporal linking of GAS strains to ARF is problematic because of the delay between the infection and the onset of autoimmunity [85]; a bacteria isolated at the point ARF is diagnosed may be incidental. Nevertheless, the results of three recent studies are noteworthy. In a study of ARF in Ethiopia, pattern D genotype strains were isolated from the throats of four of seven patients. In the accompanying population-based survey, pattern D–E accounted for the majority of isolates from both skin and throat and were the predominant cause of impetigo [86]. In a study in Hawaii, eight out of 63 patients with ARF had GAS isolated on throat swab at presentation [87]. These isolates were *emm* typed (types 65/69, 71, 92, 93, 98, 103 and 122); none of these *emm* types is known to be classically associated with ARF, five of seven *emm*-types (types 65/69, 71, 93, 98 and 122) belong to the skin-associated pattern D, the remaining two being pattern E. Indeed, these *emm* types are uncommon among pharyngitis isolates in Hawaii, accounting for less than 5% of 1258 pharyngitis isolates [87]. Unfortunately, there were no descriptions of the *emm* types associated with impetigo. In a study in North India, seven *emm* types were found among 11 pharyngeal GAS isolates temporally associated with ARF (D pattern *emm* 33, 43, 74, 80 and 93; E pattern *emm* 49 and 112) [88]. Pharyngeal and impetigo isolates were collected in surrounding communities in the same time period; four of the seven ARF *emm* types were found in both skin and pharynx [88,89].

REACHING AN EXPLANATION

If the alternate view as outlined above were to be true, there would be considerable implications for the prevention and control of ARF/RHD. Currently, primary prophylaxis for ARF focuses on the timely treatment of GAS pharyngitis [90]. Further investigation of this potential link between GAS impetigo and ARF/RHD is therefore important from a clinical and public health perspective, and also for GAS vaccine development as the current approach focuses upon prevention of GAS pharyngitis [91]. We outline below some of the potential methods by which this link could be tested.

Molecular epidemiology

Although representing a high proportion (40%) of the 200 *emm*-types described so far, D pattern

associated *emm*-types have not been as extensively studied as A–C and E pattern associated *emm* types [59▪▪]. For example, most structural and biological studies on M protein pertain to types 1, 3, 5, 6 and 12 belonging to the A–C pattern. Similarly, no strain belonging to D pattern has yet been completely sequenced.

However, different studies have tried to characterize molecular markers associated with skin infections. Many *emm*-pattern D strains are able to bind plasminogen via the PAM region of the M protein (plasminogen-binding GAS M protein). This binding has been shown to play a role in the pathogenesis of skin infection in a mouse model [92]. PAM binds to plasminogen and is converted into an active form by the Ska streptokinase virulence factor [93], which subsequently leads to fibrinolysis [93].

Previous studies have also shown that *emm* pattern D strains have a higher level of *emm*-type and multilocus sequence type diversity among the different *emm* patterns [94]. Recombination events appear to be the most frequent in *emm* pattern D strains and include replacement of the *emm*-type locus [94]. Similarly, multilocus sequence typing identified substantial genetic recombination between the so-called skin and throat strains as well as various new combinations of *emm* and housekeeping genes in a small community with high rates of ARF and GAS impetigo [95]. Some *emm* pattern D strains might have evolved to acquire the capacity to colonize and/or infect both cutaneous and pharyngeal environment, and therefore cause ARF. A recent study used pangenome microarrays on a set of 97 different GAS strains to highlight that the transition between pharynx and skin is associated with changes in the fibrinogen-binding gene content, suggesting that this gene is a potential marker of tissue tropism [96▪].

Although there appears to be evidence of exchange of GAS between skin and throat, this process is not fully understood but may be important in pathogenesis. Investigation into this issue will require detailed molecular analyses of GAS isolates from skin and throat, probably by whole genome sequencing, collected from a relatively isolated community over time.

Immunopathogenesis

Advances have been made in our understanding of the pathogenesis of ARF in the past decade with application of increasingly sophisticated immunologic experimental techniques [97]. Current theories suggest cross-reactive antibodies appear to initiate inflammation at the endothelial surface of the cardiac valve and facilitate entry of primed CD4+ T cells through the upregulation of inflammatory mediators such as vascular cell adhesion molecule-1 and P-selectin on the endothelial surface of the valve [98–100]. Subsequent inflammation within cardiac valves is mediated predominantly by Th1 and Th17 cytokines, leading to chronic valvular disease [101,102▪]. The immune response to GAS at the skin and the role of GAS skin infection in the immunopathogenesis of rheumatic fever has not been well studied. One intriguing possibility is that 'priming' of CD4+ cells occurs at the skin, but it is the immune response at the pharynx to GAS that drives the autoimmune process of ARF [9]. The immune response to GAS is different in the pharynx compared with the skin, with a dominant Th17 response seen at the pharynx but not the skin which may be a key factor in dysregulation of the immune response [103▪]. One possible method to determine the site at which T cells are primed or activated would be to characterize homing receptors on T cells extracted from rheumatic valvular tissue. Homing receptors are specialized adhesion molecules expressed on the surface of immune cells that vary according to the site of initial activation [104]. Overall, however, a more detailed understanding of ARF/RHD pathogenesis is needed, that takes advantage of the latest technologies [105].

Host susceptibility

One approach to understanding pathogenesis is the study of host genetic susceptibility, which has in the last 5 years proved a powerful tool in the study of a number of autoimmune diseases, most notably Crohn's disease [106▪]. This was successful through international collaboration, sufficient sample size (providing adequate statistical power), standardized disease definitions and prudent application of the latest technology [107]. There is evidence that ARF is both heritable [108▪] and dependent on environmental factors [109]. Large RHD registries are becoming established in the Pacific and elsewhere where the disease is most endemic, and echocardiographic diagnostic criteria have been standardized by an international consensus group (A Steer, personal communication). With these advances it is very possible that the application of tools such as genome-wide association analyses and sequencing to RHD and the study of host susceptibility will provide further insight into pathogenesis.

Epidemiologic studies and treatment trials

Indirect epidemiologic evidence linking GAS skin infection and ARF/RHD already exists as outlined above [110]. There is a need for prospective

epidemiologic studies and even treatment trials to further investigate the link. These studies will be limited by at least two factors: first, the sample size for studies wherein ARF is the outcome measure will need to be very large, given the incidence of ARF; and second, direct comparisons of antibiotic treatment of skin infection with antibiotic treatment of pharyngeal infection will be confounded by the fact that treatment of one will treat the other. Given these challenges, a novel approach would be to focus on RHD as the outcome measure and to randomize an intervention that treats scabies, the main predisposing factor for GAS impetigo. Evidence-based criteria for the echocardiographic diagnosis of RHD, developed by an international consensus group, provide a standardized outcome measure. An appropriate intervention may be community mass treatment in a scabies endemic population using ivermectin, an oral scabicide that has been widely used for the control of onchocerciasis and lymphatic filariasis [111]. The hypothesis to be tested would be that community treatment with ivermectin will reduce the occurrence of GAS skin infection in the intervention group, which over time will lead to a reduction in the prevalence of RHD. Preliminary evidence for this approach is encouraging; a study of mass drug administration of ivermectin for scabies in the Solomon Islands led to a reduction in the prevalence of scabies from 25% to less than 1% at 3 years, with a concomitant reduction in impetigo prevalence (40–21%), GAS contamination of fingers, GAS serology titres and haematuria (a potential marker of APSGN) [112]. The effect of this approach on ARF/RHD is yet to be tested.

CONCLUSION

There is good evidence that early investigators were correct to conclude that ARF was frequently triggered by GAS infections in Europe and USA prior to the decline of RHD. Although pharyngitis was a clear precedent to ARF, it is remarkable that GAS impetigo is rarely referred to in this body of literature. However, the majority of early observations were made in white populations living in industrialized societies in Europe and the USA. Given the striking epidemiologic association between streptococcal skin infections and RHD observed today [9], we think that it is timely to reassess previous dogma as it is applied to tropical developing countries where ARF and RHD are common.

Acknowledgements

T.P. is supported by a UK National Institute for Health Research Academic Clinical Fellowship. The funders had no role in the preparation of the manuscript. P.R.S. is 'chargé de recherche' FNRS (Fond National de Recherche Scientifique). The funders had no role in preparation of the manuscript. A.C.S. is supported by a combined Australian National Health and Medical Research Foundation/Australian National Heart Foundation Training Fellowship. The funders had no role in preparation of the manuscript.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 230).

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