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Cumulative incidence of rheumatic fever in an endemic region: a guide to the susceptibility of the population?

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SUMMARY

Aboriginal Australians in northern Australia are subject to endemic infection with group A streptococci, with correspondingly high rates of acute rheumatic fever and rheumatic heart disease. For 12 communities with good ascertainment, the estimated lifetime cumulative incidence of acute rheumatic fever was approximately 5·7%, whereas over the whole population, with less adequate ascertainment, the cumulative incidence was only 2·7%. The corresponding prevalences of established rheumatic heart disease were substantially less than the cumulative incidences of acute rheumatic fever, at least in part because of poor ascertainment. The cumulative incidence of acute rheumatic fever estimates the proportion of susceptible individuals in endemically exposed populations. Our figures of 2·7–5·7% susceptible are consistent with others in the literature. Such comparisons suggest that the major part of the variation in rheumatic fever incidence between populations is due to differences in streptococcal exposure and treatment, rather than to any difference in (genetic) susceptibility.

INTRODUCTION

Very few group A streptococcal infections actually lead to rheumatic fever, arguably because some strains or sites of infection are not rheumatogenic [1, 2]. However, host factors may also play a role. Genetic susceptibility to acute rheumatic fever was suggested by its familial aggregation and by a greater concordance in monozygotic than in dizygotic twins [3, 4]. More recently, markers of genetic susceptibility have been sought [5].

Rheumatic fever occurs at high rates in some countries, but in others it is now rare [6]. Although the dramatic decline of rheumatic fever in developed countries during the 20th century is almost certainly due to lower rates of group A streptococcal infection and to improved medical care [6–8], it is also possible that susceptible hosts may be more frequent in some populations than others. Rural Aboriginal people experience very high exposure to group A streptococci, and our epidemiological study in the Aboriginal population of northern Australia revealed rheumatic fever at the highest rates ever documented [9, 10]. We wondered whether the cumulative incidence of acute rheumatic fever in this population may offer insights into the population susceptibility to rheumatic fever. This paper also presents updated incidence and prevalence figures.

METHODS

Beginning in February 1994, clinical records and contacts were reviewed to compile a database of all known or suspected cases of acute rheumatic fever

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Table 1. *Incidence of acute rheumatic fever and prevalence of rheumatic heart disease*

Region	Acute rheumatic fever, 1987–96			Rheumatic heart disease, March 1997		
	Cases 5–14 years	Population at risk*	Incidence per 10^5 per year	Cases all ages	Population at risk†	Prevalence per 1000
Top End total	167	22441	74	422‡	134710	3·1
Aboriginal	165	7355	224	384	32474	11·8
Non-Aboriginal	2	15086	1·3	37	102236	0·4
12 Aboriginal communities	102	2007	508	185	8262	22·4

* Average 5- to 14-year-old population for the 10-year period.
† All ages; data from mid-1996 Census estimates.
‡ Ethnicity unknown for one person.

and rheumatic heart disease in the Top End of the Northern Territory of Australia: 31 March 1997 was the final date of data collection for research purposes, although the database was subsequently adapted as a register to improve ongoing clinical care. This report uses the final data set.

Previous reports have summarized the methods of data collection [9, 10]. Briefly, people with known or suspected past histories of acute rheumatic fever or rheumatic heart disease in the Top End were identified from hospital discharge and community health records from 1976 to 1996. Additional clinical information was collected by chart-review and clinical examination as appropriate. Because of the incomplete ascertainment of cases of acute rheumatic fever in earlier years, incidence was calculated only for the 10-year period 1 January 1986 – 31 December 1996. The most complete information was collected by reviewing charts, interviewing health staff and examining patients at 12 rural communities, selected to represent different geographic regions and because of their size; all had Aboriginal populations greater than 100, and the seven largest Aboriginal communities were included.

Statistical methods

Incidence and prevalence rates were calculated using denominator data adjusted for undercounting in the Census, as previously described [9]. To estimate the notional lifetime probability of acute rheumatic fever, the estimated cumulative incidence of first episodes was calculated as follows. The average annual incidence of first episodes of acute rheumatic fever was first estimated for each 5-year age group for the 14-year period 1983–96 when the number of cases ascertained each year was stable. This incidence was multiplied by five to give estimated cumulative incidences for each 5-year age group, and these were summed to estimate lifetime cumulative incidence. Estimates were made both for all Top End Aboriginal cases and for the 12 selected communities where ascertainment was most complete. As adjusted Census data were not available prior to 1986, the denominators used were the mid-period populations: average of adjusted 1989 and 1990 estimates for the Top End; and unadjusted 1991 Census estimates for the 12 communities.

RESULTS

Incidence and prevalence

From 1936 to 31 March 1997 there were records of 555 cases of confirmed acute rheumatic fever in 367 people (355 Aboriginal), of which 303 cases occurred in 232 people from 1987 through 1996. The average annual incidence of acute rheumatic fever in 5-14-year-old Aboriginal children over this period is shown in Table 1. The annual incidence in the 12 selected communities (508 per 100000) is likely to be close to the incidence rate that would have been found in most rural communities in the Top End had ascertainment been complete.

As of 31 March 1997 there were 422 people with confirmed rheumatic heart disease in the Top End (384 Aboriginal). The prevalence of rheumatic heart disease is shown in Table 1. Table 2 shows that the prevalence peaked in the 30–34 years age group. At the same time, there were 324 Aboriginal people with a history of at least one confirmed episode of acute rheumatic fever (Table 2), of whom 194 (60%) were also diagnosed at some time with rheumatic heart disease. Seventy-eight Aboriginal people aged > 30

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Table 2. *Age-stratified prevalence of rheumatic heart disease and history of acute rheumatic fever in Top End Aboriginal people at 31 March 1997*

Age group (years)*	At-risk population†	Number with RHD	Prevalence RHD‡	Number with history ARF	Prevalence history ARF‡
0–4	4596	0	0	0	0
5–9	4347	13	3·0	17	3·9
10–14	3901	25	6·4	43	11·0
15–19	3147	40	12·7	62	19·7
20–24	3170	58	18·3	67	21·1
25–29	3210	57	17·8	57	17·8
30–34	2620	72	27·5	36	13·7
35–39	2173	36	16·6	16	7·4
40–44	1567	30	19·1	11	7·0
45–49	1125	21	18·7	8	7·1
50–54	860	14	16·3	3	3·5
55–59	646	6	9·3	2	3·1
60+	1109	12	10·8	2	1·8

RHD, rheumatic heart disease; ARF, acute rheumatic fever.
* Age groups are inclusive (e.g. 10–14 means 10·0–14·9).
† Data from mid-1996 Census estimates.
‡ per 1000.

Table 3. *Average annual incidence in Top End Aboriginal people of first episodes of acute rheumatic fever 1983–96 by age group, and estimated cumulative incidence*

Age group (years)	Cases	Population*	Average incidence†	Cumulative inc. (per 5-year group)‡	Cumulative incidence‡
0–4	11	4134	19·0	95·0	95·0
5–9	76	3776	143·8	718·8	813·8
10–14	77	3127	175·9	879·4	1693·2
15–19	38	3299	82·3	411·4	2104·6
20–24	23	3134	52·4	262·1	2366·7
25–29	11	2556	30·7	153·7	2520·4
30–34	1	2012	3·6	18·0	2538·4
35–39	2	1633	8·7	43·5	2581·9
40–44	2	1096	13·0	65·2	2647·1
45–49	2	913	15·6	78·2	2725·3
50+	1	2203	3·2	16·2	2741·5

* Average 1989–90 population.
† Cases per 100000 population per year.
‡ Cases per 100000 population.
§ 1991 population.

years had a documented history of acute rheumatic fever, of whom 63 (81%) also were diagnosed at some time with rheumatic heart disease.

Cumulative incidence

Based on 1983–96 incidence rates, the estimated lifetime cumulative incidence of first episodes of acute rheumatic fever for Aboriginal people in the Top End was 2·7% (Table 3); this estimate assumes that ascertainment of cases was complete over these years, that the incidence rate of acute rheumatic fever was stable, and that the effects of mortality were negligible. One hundred and forty-four first episodes of acute rheumatic fever occurred over the same period in the 12 Aboriginal communities where ascertainment was most complete, suggesting a lifetime cumulative incidence in those communities of 5·7% (complete data not shown).

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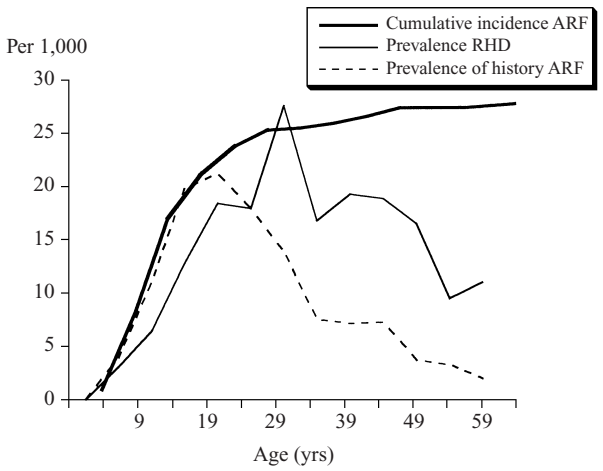

Fig. 1. Estimated cumulative incidence of first episodes of acute rheumatic fever, prevalence of rheumatic heart disease at 31 March 1997 and prevalence of a history of acute rheumatic fever at 31 March 1997. ARF, acute rheumatic fever; RHD, rheumatic heart disease. Data from Tables 2 and 3. Cumulative incidence plotted at end of 5-year intervals, prevalence of rheumatic heart disease and history of acute rheumatic fever plotted at midpoints of 5-year intervals.

Figure 1 shows that the estimated cumulative incidence of first episodes of acute rheumatic fever in the Top End closely approximated the point prevalence at 31 March 1997 of having a known history of acute rheumatic fever for each age group up to 24 years, at which age the prevalence of a history of acute rheumatic fever fell sharply. Figure 1 also shows that the point prevalence of rheumatic heart disease at 31 March 1997 paralleled the estimated cumulative incidence of acute rheumatic fever until age 34, at which age it also fell sharply.

DISCUSSION

The incidence and prevalence data presented here confirm our previous reports that acute rheumatic fever and rheumatic heart disease occur at among the highest rates in the world in the Aboriginal population of northern Australia [9, 10]. These data also suggest that 2·7% of Aboriginal people in the Top End have had an episode of acute rheumatic fever during their lifetime; in the 12 communities with somewhat larger populations and better ascertainment, lifetime risk could be as high as 5·7%.

The higher cumulative incidence in the 12 communities may represent a truly increased risk of developing rheumatic fever, i.e. the difference may not be explained entirely by better ascertainment. This could be due to their larger populations; more crowded living conditions are associated with higher rates of acute rheumatic fever, probably because of increased transmission of group A streptococci [11, 12]. Improved access to medical services is associated with a reduced incidence of rheumatic fever [7], but is unlikely to explain differing risks between the 12 communities and the whole Top End. The better access to medical services of the 30% of the Aboriginal population that lives in urban centres (not included in the 12 communities) is balanced by the fact that larger rural Aboriginal communities (included in the 12 communities) are more likely to have permanent or more frequently visiting medical staff than the smaller communities. Nor is the difference likely to be due to more virulent strains of group A streptococci circulating in the 12 communities; genotyping studies have documented that strains circulate within and between even the most geographically distant communities in the region [13]. Other possibilities include variations in antibiotic use, levels of poverty or genetic susceptibility. We have no reason to suspect that the 12 communities differ from the rest of the Top End in any of these features. Alternatively, more intensive ascertainment may have led to overdiagnosis of cases in the 12 communities; although the Jones criteria were strictly applied [14], this is a possibility in a retrospective study.

If all cases of acute rheumatic fever resulted in rheumatic heart disease, mortality was negligible, and the incidence of acute rheumatic fever was stable, the cumulative incidence of acute rheumatic fever would approximately equal the prevalence of rheumatic heart disease at a somewhat greater age (the lag period between the onset of rheumatic fever and the diagnosis of rheumatic heart disease). The overall prevalence of rheumatic heart disease in the Top End Aboriginal population was 1·2%, and the age-specific prevalence were generally lower than the estimated cumulative incidences of first episodes of acute rheumatic fever, particularly at older ages (Fig. 1). This reflects in part the reality that all acute rheumatic fever does not progress to rheumatic heart disease.

Poor ascertainment of rheumatic heart disease and premature mortality from rheumatic heart disease also were likely to contribute to the discrepancy, although we could not accurately assess the relative contribution of each factor. Incomplete ascertainment of rheumatic heart disease was especially likely for older people whose earlier episodes of acute rheumatic fever, providing a trigger for follow-up, could not

have been ascertained because of the poor quality of records in earlier years. The low proportion of older cases with a history of documented acute rheumatic fever also suggests poor medical documentation in past years. It is of interest that rheumatic heart disease was present in 21% of autopsies for otherwise unexplained sudden death in Northern Territory Aboriginal people aged 15–64 years, but in only 1% of autopsies for deaths due to suicide, homicide or accidents [15]. This suggests excess mortality from rheumatic heart disease.

It is also possible that the lower prevalence of rheumatic heart disease and of a history of acute rheumatic fever in older age cohorts (Fig. 1) reflect a real increase in the incidence of acute rheumatic fever in recent years. The incidence could have increased most in those communities where larger populations would be expected to facilitate streptococcal transmission. On the other hand, the apparent increase in rheumatic fever incidence may be due in part to better ascertainment following improvements in medical care in the 1970s. Despite improvements in primary health care, Aboriginal people in the Northern Territory still live in overcrowded and unhygienic circumstances with high rates of streptococcal skin infection [16–18], group A streptococcal bacteraemia [19], and post-streptococcal glomerulonephritis [20] as well as rheumatic fever. With such high rates of streptococcal acquisition it is possible that most susceptible people will eventually develop rheumatic fever. This would imply that the cumulative incidence of 2·7–5·7% corresponds to the proportion of the Aboriginal population of the Northern Territory that is susceptible to rheumatic fever.

The maximum prevalence of rheumatic heart disease in other populations heavily exposed to group A streptococci is 1–2%, although there are isolated reports of $> 5\%$ prevalence in sub-populations of schoolchildren in Brazil and Vietnam [21, 22]. If heavy exposure to group A streptococci in these populations leads to rheumatic fever in all susceptible people, and if 50–75% of acute rheumatic fever patients eventually develop rheumatic heart disease, then 2–4% of these populations would be judged susceptible. This approximates to the estimated cumulative incidence in the Aboriginal population.

Incidence rates of acute rheumatic fever and prevalence rates of rheumatic heart disease early this century in industrialized countries were similar to the corresponding rates in developing countries in recent years [6]. Of patients with group A streptococcal pharyngitis in US military camp outbreaks during the 1950s, 2–3% developed rheumatic fever [23]. Thus the proportion susceptible to acute rheumatic fever and rheumatic heart disease may not differ substantially from one population to another.

The basis for any genetic susceptibility is not known. Previous studies found no consistent HLA associations, although recent work suggests an association of rheumatic heart disease with certain HLA class II alleles [24]. Acute rheumatic fever patients and their family members from the United States and the Caribbean expressed a B-cell alloantigen (D8/17) in a high percentage of B cells, whereas D8/17 was found at elevated levels in only 15–20% of controls [5]. However, this D8/17 finding was not replicated in an Indian population with acute rheumatic fever and rheumatic heart disease, where a different B cell alloantigen marker (PGI/MNII) was found [25]. Further work in the Indian population identified three B cell alloantigens (PG-12A, PG-13A and PG-20A) at elevated levels in 80–92% of rheumatic fever/rheumatic heart disease patients but only 4–12% of controls [26]. It is not yet clear whether these putative markers are genetic or induced by streptococcal infection as part of the pathogenesis of acute rheumatic fever.

In conclusion, the epidemiological evidence suggests that less than 5–6% of people can develop acute rheumatic fever after relevant streptococcal exposure. Furthermore, this proportion does not appear to vary substantially between populations. Rheumatic fever is the result of interplay between host susceptibility, group A streptococcal virulence, levels of bacterial exposure, and the use of antibiotics for primary group A streptococcal infections [27]. In the absence of evidence of a more susceptible population, and where there do not appear to be highly virulent group A streptococcal strains circulating (such as in the Top End [28]), the large differences in incidence of acute rheumatic fever and prevalence of rheumatic heart disease between populations are almost certainly due to differences in exposure to group A streptococci (reflecting socio-economic disadvantage) and differences in access to and quality of primary health care.

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