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Systematic Review: Estimation of global burden of non-suppurative sequelae of upper respiratory tract infection: rheumatic fever and post-streptococcal glomerulonephritis

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Summary

OBJECTIVES To establish the incidence of post-streptococcal glomerulonephritis (PSGN) and acute rheumatic fever, the prevalence of rheumatic heart disease (RHD), and to estimate morbidity and mortality caused by these diseases globally.

METHODS Systematic literature review and review of World Health Organisation (WHO) vital registration data (VRD).

RESULTS Incidence and prevalence of rheumatic fever and RHD show very significant global variation. The greatest burden was found in sub-Saharan Africa, the lowest in North America. The highest mortality rates from these two diseases were reported in the indigenous populations of Australia (23.8 per 100 000). Among countries with VRD, the highest mortality was found in Mauritius (4.32 per 100 000). A few studies reported mortality from PSGN and these reported low mortality rates (mean 0.028 per 100 000 in developing countries).

CONCLUSION Lack of data from key parts of the world limits our ability to make precise statements of disease burden. Further research and surveillance is required to generate more primary data to inform future estimates.

keywords rheumatic fever, rheumatic heart disease, streptococcal infection, glomerulonephritis, infection, upper respiratory tract

Introduction

Upper respiratory tract infections (URTI) are the commonest childhood illnesses (Denny 1987) and are associated with numerous well-established sequelae (Rodriguez-Noriega *et al.* 1988). Group A streptococcal (GAS) infection of the upper respiratory tract is estimated to be responsible for approximately 26% of URTI, with the majority of URTI caused by viral infection (Smith *et al.* 1989). GAS pharyngitis is generally self-limiting but can lead to a number of suppurative complications including quinsy and retropharyngeal abscess, as well as non-suppurative complications such as acute rheumatic fever (ARF) and post-streptococcal glomerulonephritis (PSGN). ARF is a multisystem autoimmune inflammatory disorder. Severe carditis in the first episode or in recurrent attacks of ARF can lead to rheumatic heart disease (RHD) which is a chronic valvulopathy (Carton *et al.* 2006). Importantly, these diseases may lead to further complications including cardiac failure, stroke, chronic renal failure and death.

Like PSGN, ARF has become considerably less common in the developed world over the last half-century (Land & Bisno 1983; Gordis 1985; Miyake *et al.* 2007). However, studies in developing countries have revealed that it still occurs frequently, and the resultant RHD is the source of substantial mortality (Markowitz 1981). Indeed, in some developing countries ARF has caused nearly half of all admissions for heart disease in children (Lennon 2004), making it the most common cause of acquired heart disease in children (Carapetis *et al.* 2005).

While it is known that the incidence of PSGN has recently decreased considerably in the developed world, the global burden of the disease has been less well quantified. Studies have shown that PSGN incidence has fallen substantially in Europe (Simon *et al.* 1994), South America (Rodriguez-Irturbe *et al.* 1985; Berrios *et al.* 2004), Asia (Yap *et al.* 1990; Zhang *et al.* 1994) and the USA (Roy &

Stapleton 1990). However, the disease may still cause a substantial burden in indigenous communities and in poor, rural parts of developing countries (Currie & Brewster 2001; Orta & Moriyon 2001; Pakash *et al.* 2001). It is thought that the main underlying GAS infection in these regions is likely to be impetigo (Lawrence *et al.* 2005).

To update current estimates of mortality from ARF, RHD and PSGN, we conducted a literature review on incidence, prevalence and mortality from ARF, RHD and PSGN from 1980 up to March 2010.

Methods

A systematic literature review and analysis of World Health Organization (WHO) vital registration data (VRD) were carried out as described below.

Search strategy for literature search

Medline, Medcarib, WHOLIS, Indmed, Global Health and Embase were searched using the search strategies detailed in Appendix S1. Searches were limited to the articles published between 1980 and March 2010 to conform with the WHO global burden of diseases project dates. Reference lists of relevant articles were also searched, in addition to reports published by the WHO.

Study selection and assessment

After the literature search, studies that matched the study were extrapolated independently by two individuals according to the following criteria: (i) *Study type:* All population-based studies with a defined study population were included. Studies searching hospital or government records were also reviewed. Cohort studies were incorporated if they had a minimum of 100 cases. (ii) *Disease definitions:* Studies of RHD were only included if they used echocardiography in establishing the diagnosis since this has been shown to significantly increase sensitivity by detecting sub-clinical RHD (Jaffe *et al.* 1988; Folger *et al.* 1992; Marijon *et al.* 2007; Vijayalakshmi *et al.* 2008; Carapetis *et al.* 2008). It also allows accurate differentiation between congenital heart disease and RHD (Bahadur *et al.* 2003).

Studies that used government or hospital records were only included if the appropriate WHO International Classification of Diseases (ICD) codes were used. Glomerulonephritis can occur following numerous infections (Boon *et al.* 2006; Naicker *et al.* 2007). Consequently, to be included in the literature review, PSGN studies had to display evidence of preceding streptococcal infection.

Search strategy for WHO VRD.

Vital registration data were obtained from the WHO website (WHO 2010), and files that contained data reporting the number of deaths from ARF in ICD-10 were searched (Appendix S2). Countries were only included in the study if the completeness of death reporting was more then 90% of the total deaths occurring in the country. Mortality rates were calculated using the most recent population data available in the WHO database. Countries were then classified according to the Global Burden of Diseases Study (GBD) global regions (Appendix S3).

Statistical analysis

Unless otherwise stated, all mortality, incidence and prevalence rates are expressed per 100 000 population. Many studies investigating the prevalence of RHD were carried out in schoolchildren. Several studies reported the proportion of people in each age group of the population with RHD (Myo *et al.* 1992; Agarwal *et al.* 1995; Carapetis *et al.* 2000; Central Australian RHD steering committee 2002). The WHO (2005) identified two studies in schoolchildren on which extrapolations were based. First, an Australian study reported that there are 7.2 times the number of people with RHD aged over 15 years than those aged 5–14 years (Carapetis *et al.* 2000; Central Australian RHD Steering Committee 2002). Secondly, a study from India reported this number to be 5.5 (Agarwal *et al.* 1995). Using the mean of these values, 6.35, estimations of the total number of people with RHD could be generated [total population with RHD estimate = number of children with RHD + (number of children aged 5–14 with RHD $\times$ 6.35)]. Where one country reported more than one prevalence rate in schoolchildren, the mean of the two rates was used. Population data for the relevant county were obtained from the Population Reference Bureau (2010), which allowed calculation of the total number of people with RHD per 100 000 population.

Reports of case fatality ratios from case series and cohort studies were used to estimate mortality rates by multiplying the case fatality ratio by appropriate incidence rates reported for episodes of similar disease severity for that country. Incidence rates were taken from estimates calculated in the WHO Report (2005).

Results

This review identified 13 studies investigating the incidence of PSGN and six studies examining the mortality of the disease. Forty-nine studies reported data on ARF/RHD

incidence, and 12 studies demonstrated the associated mortality with the diseases. The incidence and mortality associated with both diseases showed significant global heterogeneity. Figure 1 gives a schematic overview of the search strategy results.

Post-streptococcal glomerulonephritis incidence

Thirteen studies reported data on incidence of PSGN (Table 1). These demonstrated significant global variation, with the highest incidence of 239 per 100 000 in Australian Aborigines and the lowest incidence of 0.04 per 100 000 in an Italian study of people under the age of 60.

Post-streptococcal glomerulonephritis mortality

Six cohort studies reported case fatality rates from PSGN and, although three revealed a case fatality rate of zero, two studies in India revealed case fatality rates of 1.4% and 2%, (Table S1). The WHO (2005) estimated that the incidence rate for PSGN in developing countries is 24.3 per 100 000. Applying the mean case fatality ratio from the two India studies (1.7%) found in this study, the mortality of PSGN in India can be estimated at 0.4 per 100 000. Using the same principle, the mortality from PSGN in Turkey (case fatality rate 0.08%) can be estimated as 0.02 per 100 000.

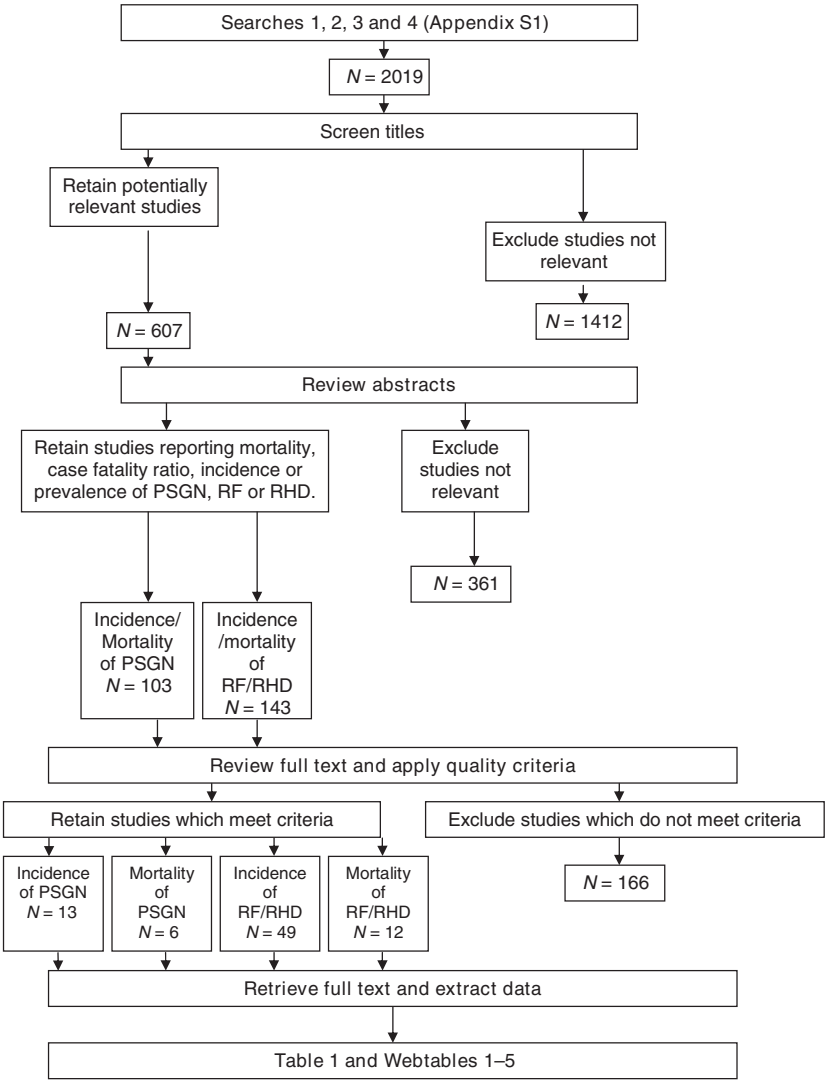

Figure 1 Search strategy results for the mortality, incidence and prevalence of PSGN, RF or RHD.

Table 1 Incidence of post-streptococcal glomerulonephritis

References	Country	Date	Population	Incidence (per 100 000 per year)
Baker *et al.* (2000)	New Zealand	1988–1997	5- to 14-year-olds	8.1 (all) Approximately 48 (Maori) Approximately 80 (Pacific Islander)
Berrios *et al.* (1986)	Chile	1980–1989	<15-year-olds	18.1
Carapetis (1998)	Australia	1993–1995	<15-year-olds	239 (Aboriginal) 6 (non-Aboriginal)
Coppo *et al.* (1998)	Italy	1998	>60 <60	0.09 0.04
Eke and Eke (1994)	Nigeria	1986–1991	<15-year-olds	24.3
Herrera and Rodriguez-Iturbe (2003)	India	1991–1998	Goajiro Indians	2.9 ± 1.3
Khuffash *et al.* (1986)	Kuwait	1980–1984	Children	19.5
Lennon *et al.* (1988)	New Zealand	1981–1984	Children	50.5 (Maori) 46.5 (Pacific Islander) 5.9 (Other)
Majeed *et al.* (1992)	Kuwait	1980–1983	Children	17.8
Muscatello *et al.* (2001)	Australia	1989/1990–1997/1998	<20-year-olds	2.2
Simon *et al.* (1994, 1995)	France	1986–1990	All ages	0.15
A. C. Steer, personal communication	Fiji	2005–2007	≤14-year-olds	6.3 (95% CI 3.5–10.6)
Yap *et al.* (1990)	Singapore	1985	<12-year-olds	10.8

Several of the studies reporting the mortality from PSGN documented associated long-term morbidity. However, these data were limited and inconsistent. While one study revealed no long-term complications of PSGN (Rajajee 1990), the majority of studies revealed considerable morbidity. Chugh *et al.* (1987) demonstrated hypertension in 8% of subjects at follow-up. D'Cruz *et al.* (1990) revealed hypertension in 43.6% of subjects and hypertensive encephalopathy in 11.3% of subjects. Oner and Demircin (1995) demonstrated that 0.8% of subjects developed hypertensive encephalopathy. Haematuria was found in 13.7% of patients (D'Cruz *et al.* 1990), while proteinuria was found in 0.8% (Oner & Demircin 1995). Importantly, Shiva *et al.* (1994) described the development of rapidly progressive glomerulonephritis after PSGN in 2% of patients, while Oner & Demircin 1995 demonstrated rapidly progressive glomerulonephritis in 4% of subjects. Khuffash *et al.* (1986) revealed that 0.5% of patients required peritoneal dialysis, while Shiva *et al.* (1994) showed that 2% of subjects needed haemodialysis. D'Cruz *et al.* (1990) also described the development of pulmonary oedema (36.3% of subjects) and uraemia (16.5% of subjects).

Rheumatic fever and RHD incidence and prevalence

A total of 49 studies met the quality criteria (Incidence of ARF – Table S2, and prevalence of RHD – Table S3). The studies reported incidence of ARF per year ranging from 0.1 per 100 000 in Greece to 826 per 100 000 in Sudan. The highest prevalence of RHD was found in Tonga (3320 per 100 000) (Carapetis *et al.* 2008), the lowest in India (68 per 100 000).

Most of these studies were carried out in schoolchildren because children are the highest risk age group for ARF. Prevalence rates for RHD in schoolchildren were extrapolated to the whole population as described previously (Table 2).

Rheumatic fever and RHD mortality

Two studies investigating the mortality of ARF/RHD were excluded from the study as they were not conducted in English (Appendix S4). Twelve studies reporting mortality rates for ARF/RHD met the quality criteria (Tables S4 and S5). No studies fitting the study criteria were found from North Africa/Middle East, Oceania or sub-Saharan Africa.

Mortality rates for RHD ranged from 1.2 to 23.8 per 100 000. The highest mortality rates from RHD or RF were found in the indigenous populations of northern Australia (23.8 per 100 000) while developed world mortality rates were generally lower, as in the USA (1.65 per 100 000).

Mortality rates were estimated (Table 3) from reported case fatality ratios and incidence rates by GBD region reported by the WHO (2005). This analysis shows that Pakistan has the highest estimated mortality from RHD.

Table 2 Prevalence estimates of RHD extrapolated from studies in schoolchildren to the whole populations

Country	Mean RHD prevalence (per 100 000) in 5–14 age group	Population of 5–14 age group	Estimated number of people younger than 14 with RHD	Estimated number of people older than 14 with RHD (using 6.35 multiple)	Total population of country (millions)	Overall national prevalence estimate (all ages) (per 100 000)
Cambodia	3677	5 298 000	194 807	1 237 024	14.7	9740
Mozambique	3040	8 685 000	264 024	1 676 552	20.4	9513
Tonga	1910	36 000	688	4369	0.2	2529
Ethiopia	550	33 849 000	186 170	1 182 180	79.1	1730
Egypt	620	24 957 000	154 733	982 555	74.9	1518
Fiji	410	245 000	1004	6375	0.8	922
Kenya	240	15 941 000	38 258	242 938	37.954	741
Turkey	317	21 234 000	67 312	427 431	74.8	661
Saudi Arabia	240	10 274 000	24 658	156 578	28.1	645
India	268	362 140 000	970 535	6 162 897	1149.3	621
Nepal	120	10 113 000	12 136	77 064	27	330
Oman	80.8	829 000	670	4255	2.7	182

Brazil and Japan had the lowest estimated mortality rates from RHD.

Rheumatic fever mortality rates obtained from VRD

Vital registration data from 23 countries were excluded as they did not meet the criterion of >90% completeness of death reporting. The countries that satisfied this inclusion criteria and reported ARF deaths with appropriate ICD codes are shown in Table S6, and a detailed breakdown of mortality rates can be found in Table S7.

These VRD data show that Mauritius had the highest mortality rates from ARF (4.32 per 100 000) (Figure S1). However, these data also demonstrate that mortality rates all over the world are falling, from a mean global mortality rate of 0.96 per 100 000 in 1995–1999, to 0.65 per 100 000 in 2005–2007. The data also demonstrate the lack of information regarding the possible disease burden in Africa.

Table 3 Estimates of national mortality rates from RHD [based on reported incidence and case fatality ratio data (see Table S5)]

Country	Case fatality ratio (%)	Mean incidence in GBD zone (per 100 000)	Estimated national mortality (per 100 000)
Pakistan	6.8	54	3.7
Thailand	5.7	54	3.1
Japan	16.7	10	1.7
Brazil	0.03	19.6	0.006

RHD, rheumatic heart disease.

Discussion

This review attempts to provide an estimate of the morbidity and mortality burden posed by two of the main sequelae of upper respiratory tract infection, based on available published data and WHO VRD.

Study limitations

There are several limitations in the methods of many of the studies included in this review, which may limit the validity of our findings. First, ARF and PSGN have been linked with lower socio-economic classes and poor living conditions. Studies carried out in schools are likely to underestimate the disease burden because lower socio-economic classes may not be fairly represented. In addition, although school-based surveys detect asymptomatic children with RHD, children with ARF or those with symptomatic RHD are unlikely to attend school because of ill-health, which may further underestimate the burden of the disease. Similarly, hospital-based surveys will underestimate the disease frequency as patients with subclinical disease will not be recorded. With only some exceptions, studies have shown ARF, RHD and PSGN to be more common in rural areas than urban areas (al Sekait *et al.* 1990; Myo *et al.* 1992; Haque *et al.* 1992; Thakur *et al.* 1996; Carapetis 1998; Longo-Mbenza *et al.* 1998). Consequently, studies in poor rural areas that are extrapolated to the whole country may overestimate the disease burden (and studies from urban areas may underestimate the burden).

The major limitation of the PSGN aspect of the study is the uncertainty as to the nature of preceding site of GAS infection. The majority of acute PSGN in tropical regions

occurs in outbreaks, predominantly as a result of skin infections (Streeton *et al.* 1995). Therefore, the burden of PSGN attributable to URTI is probably lower than we have estimated. In addition, as PSGN occurs with substantial seasonal variation (Ilyas & Tolaymat 2008), investigations carried out over short periods of time may reflect the incidence of the disease in that season only. ARF also displays significant seasonal variation in temperate regions, although less so in tropical regions (Rammelkamp *et al.* 1952; Saksena *et al.* 1969). In temperate regions, cold weather results in more time spent indoors, more crowding and consequently increased transmission of GAS.

Studies performed using government database searches used ICD codes 8, 9 and 10. However, ICD definitions have changed from ICD 8 to ICD 10 and as a result, some of the changes in reported mortality rates may partly reflect this change in the definitions. ICD-8 and ICD-9 in the VRD were not analysed for ARF deaths. PSGN is not listed in ICD as a separate disease code, and thus it was not possible to extract the deaths specific to this disease.

Another limitation is related to estimation of ARF disease burden. There was a predominance of RHD data, because studies investigating the prevalence of RHD are more common than those investigating the incidence of ARF. In addition, although likely to be small, no studies were found that investigated the mortality from ARF after 1980. It is also worth noting that colour echocardiography was introduced in 1986; this date would perhaps have been a more appropriate start date for our search.

In some instances, the countries in the VRD were not truly representative of the GBD regions used in this report. For example, Japan and Korea are both high-income countries and it is therefore unlikely that the mortality rates obtained from these countries can be applied to other low-income countries in Asia. In addition, although the most recent population data were used, the population denominator data were often several years ahead of the VRD data.

Finally, we did not attempt to estimate the burden caused by more distal sequelae of RHD/ARF, most notably cardiac failure, infective endocarditis and stroke. These also need to be estimated to present a complete picture of the burden of RF, because, for example, RHD is an important cause of stroke. A study in Japan reported that 33% of strokes were associated with underlying RHD (Yasaka *et al.* 1998).

Post-streptococcal glomerulonephritis incidence and mortality

While only 13 studies establishing the incidence of PSGN met our quality criteria, our data demonstrate significant global variation. Although the incidence of PSGN is as high as 239 per 100 000 among Australian Aborigines, the overall mortality from PSGN is low (0.02–0.4 per 100 000). This generally supports, but is somewhat higher than, the estimate by the WHO (2005) of 0.005 per 100 000. This is perhaps attributable to the conservative approach taken by the WHO, which was partly because of the poorly documented mortality and long-term sequelae of PSGN. Although we agree with this approach, evidence for the association between PSGN and chronic renal failure is building (Chugh *et al.* 1987; Richmond & Doak 1990; Bohle *et al.* 1992; Hoy *et al.* 1998 White *et al.* 2001), and thus this approach may underestimate the disease burden. Overall, although the studies found in our review suggest that the mortality from PSGN is low, much of the world was not represented by these studies and many estimates were based on extrapolations from specific age groups.

Rheumatic fever and RHD incidence and prevalence

Data on RHD prevalence and ARF incidence show considerable global variation, consistent with previous reports (WHO 1988, Tibazarwa *et al.* 2008). Data from consecutive studies in some countries in the developing world revealed that the prevalence of RHD is falling. In India, for example, the prevalence of RHD has dropped from 646 per 100 000 in 1991 (Agarwal *et al.* 1995) to 68 per 100 000 in 2001–2002 (Jose & Gomathi 2003). However, differing methods of disease detection in differing geographical locations within countries make comparisons over time unreliable. The WHO (2005) previously reported a similar pattern of RHD prevalence globally using an approach comparable to our study. Although our study provides a more up-to-date search of the current burden, we required use of echocardiography in order for studies to be included in the review, and we used VRD.

We estimate that the highest prevalence of RHD is found in sub-Saharan Africa, South Central Asia and the Pacific. Data published after our analysis were complete and indicate that high rates of RHD may also be present in Central and South America, as a large RHD prevalence study in Nicaragua found a prevalence of 48 per 1000 children (Paar *et al.* 2010). The prevalence estimates reported by Carapetis (WHO 2005) are, however, lower than those in our study. Because of the increased sensitivity, we only included studies using echocardiography in case ascertainment. This may explains the discrepancy with Carapetis' (WHO 2005) findings. The introduction of echocardiography as a first-line screening tool, as performed in landmark studies in Mozambique and Cambodia (Marijon *et al.* 2007), is currently the subject of interna-

tional debate (Steer & Carapetis 2009). There is potential for over-diagnosis of RHD using echocardiography of asymptomatic subjects, particularly of mild mitral regurgitation. On the other hand, it is possible that application of the current WHO echocardiogram criteria for the diagnosis of RHD may have lead to an underestimate of the true prevalence of subclinical RHD by missing up to three-quarters of these cases (Marijon *et al.* 2009). Echocardiographic studies in non-RHD-endemic regions may soon provide clarity to this issue. While echocardiograms improve the accuracy of RHD recognition, its role in the diagnosis of ARF (which may be less obvious as symptoms are often initially vague) is not clear (Padmavati 2001). The true incidence of ARF may therefore be harder to estimate. Furthermore, unlike Carapetis (WHO 2005), we also included studies reporting data on children younger and older than 5–14. The approach taken to estimate the prevalence of RHD is thus far from accurate and does not replace the need for prevalence studies in all ages.

Rheumatic fever and RHD mortality

This review supports previous studies in demonstrating that the highest reported mortality rates from ARF and RHD are found in the indigenous populations of Australia (Davidson *et al.* 1993; WHO 2005). However, mortality data from developing countries were very limited with the only developing country data identified by this review from Pakistan and Thailand. Low mortality rates were found in developed countries, such as, the USA (0.1 per million), Canada (2.34 per 100 000 for ARF alone) and New Zealand (2 per 100 000 in non-Maoris). Conversely, mortality rates based on case fatality rates in developing countries revealed higher mortality rates (for example, the case fatality rate from RHD in Pakistan was 3.7 per 100 000). The difference in mortality rates between developed and developing countries is likely to be partly attributed to differences in access to care, particularly access to regular penicillin prophylaxis and cardiac surgery. Our review again highlights the lack of data from large areas of the world with the largest burden of these diseases.

The poor representation of the developing world was also found in the VRD, with no VRD data meeting our quality criteria available from areas of high disease burden such as sub-Saharan Africa. Nevertheless, the VRD do illustrate that the burden of ARF and RHD is highest in the developing world. Given that studies have shown the incidence of ARF to have declined significantly in developed countries (Land & Bisno 1983; Gordis 1985; Miyake *et al.* 2007), it is surprising that the mortality rates recorded in the VRD from North America (1.57 per 100 000) and Latin America (1.03 per 100 000) were so high. This may be attributable to the high mortality in indigenous sub-populations of these countries. It may also be explained by the enhanced diagnostic ability in these continents as opposed to developing countries.

Overall, ARF and RHD mortality data were available from a few countries – in particular, there were a few good-quality studies from developing countries where the disease burden is highest. There were also no data available that allowed assessment of trends in mortality over time.

Future directions

It is still not possible to make accurate estimates of incidence and mortality from RF and PSGN because of the lack of data from large parts of the world. The current systems for reporting RHD in developing countries have been shown to be insufficient (Robertson *et al.* 2005; Nkgudi *et al.* 2006). Nevertheless, the available data on incidence and mortality from RHD and PSGN, especially in children and young adults, support the conclusion that these diseases are an important cause of premature mortality. One possible strategy to improve data on disease burden and temporal trends may be to establish sentinel sites where good-quality prospective surveillance data (such as RHD prevalence survey data using echocardiography) can be collected; the disadvantage to this strategy would be its potential high cost. Another approach would be to use routine hospital information system data to report disease correlates that can be tracked over time. An example might be the number of admissions of pregnant women with RHD. We noted that there were several studies reporting mortality from ARF and RHD in pregnancy. One report from Taiwan noted that strokes occurred in 46.2 of 100 000 pregnancies, and 44% of cases had underlying RHD (Jeng *et al.* 2004). Another study in Egypt revealed that rheumatic mitral valve disease accounted for 89.5% of cardiac disease associated with pregnancy and over a third of maternal deaths (Nkomo 2007). Because this may account for substantial mortality and morbidity, it warrants further investigation to better estimate the magnitude of this problem and also provides a relatively easily identifiable marker of disease prevalence. This could greatly expand the number of countries from which some relevant data are available.

Establishing the true burden of the GAS sequelae of ARF and PSGN is particularly important at this time when there is the potential to invest in the development of a vaccine to control GAS disease. Good-quality global disease burden

data would help assign appropriate priority to these efforts and identify settings in which vaccine trials could be conducted.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Search strategy.

Appendix S2. ICD-10 codes used for the classification of acute rheumatic fever.

Appendix S3. Country classification for the global burden of disease.

Appendix S4. Studies in languages other than English with mortality rates quoted in abstract.

Figure S1. Diagrammatic representation of the mean ARF mortality rates for the period 1995–2007 (all ages; both sexes).

Table S1. Mortality from PSGN.

Table S2. Incidence of ARF.

Table S3. Prevalence of RHD.

Table S4. Studies using ICD coded vital registration data to report the number of deaths from RF/RHD.

Table S5. Cohort studies investigating case fatality ratios for RHD that confirmed RHD presence with echocardiography.

Table S6. Countries from which VRD was available.

Table S7. ARF mortality (1995–2007) by sex and region based on vital registration reports (in WHO VRD).

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