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The Current Evidence for the Burden of Group A Streptococcal Diseases

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List of abbreviations

ACTH	Adreno-corticotrophic hormone
APSGN	Acute post-streptococcal glomerulonephritis
ARF	Acute rheumatic fever
CMR	Crude mortality rate
GAS	Group A streptococcus
IE	Infective endocarditis
RHD	Rheumatic heart disease
SES	Socio-economic status
SMR	Standardised mortality rate
UN	United Nations
WHO	World Health Organization

Executive summary

Group A streptococcus (GAS) causes a broad spectrum of disease, from severe invasive infections and the post-streptococcal complications of acute rheumatic fever (ARF) and acute post-streptococcal glomerulonephritis (APSGN) to mild superficial infections of the throat or skin. These diseases may lead to further complications (e.g. ARF may cause rheumatic heart disease, which in turn may be further complicated by endocarditis or strokes).

The only GAS disease for which global disease burden estimates have previously been made is rheumatic heart disease (RHD). Systematic reviews were conducted to ind all published and unpublished data relating to the burden of each manifestation of GAS disease. We aimed to include only recent data, and population-based data where possible, and applied incidence and prevalence estimates to population denominator data from the UN Population website. We defined the following regions according to presumed homogeneity of GAS disease rates: Sub-Saharan Africa, South-Central Asia, People's Republic of China, other countries in Asia (excluding Japan), Latin America, Middle East and North Africa, Eastern Europe, Pacific Island countries and indigenous Australian and New Zealand, and Established Market Economies.

RESULTS

Burden of Disease

We conclude that approximately 18.1 million people currently suffer from a serious GAS disease, another 1.78 million new cases occur each year, and these diseases are responsible for over 500,000 deaths each year (See table below). Added to this are over 111 million prevalent cases of streptococcal pyoderma, and 616 million new cases of GAS pharyngitis each year.

Summary of estimated global burden of group A streptococcal diseases

Disease	Number of existing cases	Number of new cases each year	Number of deaths each year
Rheumatic heart disease	15.6 million	282,000*	233,000**
History of acute rheumatic fever without carditis, requiring secondary prophylaxis	1.88 million	188,000*	
RHD-related infective endocarditis		34,000	8,000
RHD-related stroke	640,000	144,000	108,000
Acute post-streptococcal glomerulonephritis	-	472,000	5,000
Invasive group A streptococcal diseases		663,000	163,000
Total severe cases	**18.1 million**	**1.78 million**	**517,000**
Pyoderma	111 million		
Pharyngitis		616 million	

All estimates rounded off. Note that these estimates assume constancy of incidence and prevalence over time.

* New RHD cases were calculated based on the proportion of incident ARF cases expected to develop RHD. The remainder of incident ARF cases are included in the "History of ARF without carditis" row. Therefore, the total number of new ARF cases each year is 282,000 + 188,000 = 470,000.

** Includes ARF deaths. RHD deaths are based on proportion of existing RHD cases expected to die each year.

\- No attempt has been made to quantify the prevalence of APSGN-induced chronic renal impairment or end-stage renal failure

The vast majority of all of these cases came from less developed countries (79% of RHD cases, 95% of ARF cases, 97% of APSGN cases, 97% of invasive GAS cases). We have used relatively conservative assumptions at each step, so these are minimum summary estimates of the burden of GAS diseases.

Quality of data

There were many areas where the data were deficient, particularly from less developed countries. We found sufficient data to be confident of the estimates for prevalence of RHD, and for incidence of invasive GAS diseases in more developed countries. All of the remaining estimates (ARF incidence, APSGN incidence, ARF/RHD mortality, invasive GAS disease incidence in less developed countries, RHD-related IE and stroke, pyoderma prevalence, GAS pharyngitis incidence) are based on relatively poor-quality data, particularly in some regions. Therefore, there is considerable uncertainty surrounding the estimates presented here. However, at each step we have attempted to make assumptions that tend to under-estimate rather than over-estimate the burden of disease. The estimates presented here relate to numbers of cases and deaths. GAS causes disease predominantly in children and young adults, so the burden to communities in terms of years of potential life lost is even higher than reflected purely in terms of numbers of cases and deaths.

CONCLUSIONS

Even given the limitations of the data on which they are based, these estimates suggest that GAS causes a substantial burden of disease and death on a global scale, mainly in children and young adults and in less developed countries (although they also remain relatively important diseases in more developed countries).

The data presented here also indicate that GAS diseases are highly prevalent in some regions, but may be less so in others. For example, RHD is very common in Sub-Saharan Africa and the Pacific, common in South-Central Asia and the Middle East / North Africa, but apparently less common in many Asian countries and Latin America. The ARF incidence data do not always match the RHD prevalence data. In some cases, this may be due to reducing incidence of ARF, which precedes by some years a reduction in RHD prevalence. However, a more likely explanation is the poor quality of data from some regions, particularly Sub-Saharan Africa, Asia and South-Central Asia. The pyoderma data also suggest regional differences in prevalence, which cannot be solely attributed to climate or socio-economic conditions. For example the highest pyoderma prevalences were documented in the Pacific region, whereas poorer, tropical African countries had substantially lower prevalences. The data were inadequate to draw any conclusions regarding regional differences regarding ARF/RHD mortality, APSGN, invasive GAS disease, or pharyngitis. Better data from a number of key regional sites in less developed countries would allow a more detailed analysis of regional differences and perhaps reveal markers that might enable local authorities to determine if they should be investing resources into efforts to control GAS diseases. Such data may also improve our understanding of the individual diseases and how to prevent them.

PRIORITY ISSUES

The burden of GAS diseases and the association of these diseases with poverty cannot be ignored. It is now critical to develop mechanisms for data collection to provide disease burden estimates with greater confidence. Regional variations in disease burden and the paucity of data relating to particular diseases and outcomes make it critical to improve data collection in less developed countries.

Field sites are needed for intensive population based GAS disease burden studies (including bacteraemia surveillance) in less developed countries. Ideally, at least one site would be established in each of Sub-Saharan

Africa, Pacific Island nations, East or South-east Asia, and South-Central Asia. In many regions there are already instutions with the necessary infrastructure, and even some with baseline GAS epidemiological data (e.g. the Wellcome/KEMRI Clinical Research Unit in Kenya, where bacteraemia data are being collected), which would simplify the process of establishing GAS field sites. There are a number of research institutes in South-Central Asia that collect GAS epidemiological data; it should not be difficult for one site to expand its program to collect information on all GAS diseases, or perhaps for a collaborative project to be established across institutes.

In addition to collecting complete epidemiological data, these sites could attempt to develop simpler tools for making some GAS disease burden estimates in other less developed countries. These field sites would also likely be ideal locations for future clinical trials of GAS vaccines, with the aim of evaluating their efficacy against the GAS diseases of greatest importance to less developed countries.

Introduction

Group A streptococcus (GAS) causes a broad spectrum of disease, from mild superficial infections of the throat or skin, to infections such as cellulitis and erysipelas, severe invasive infections including bacteraemia and necrotising fasciitis (often complicated by the streptococcal toxic shock syndrome), and the post-streptococcal complications of acute rheumatic fever (ARF) and acute post-streptococcal glomerulonephritis (APSGN). These diseases may lead to further complications (e.g. ARF may cause rheumatic heart disease, which in turn may be further complicated by endocarditis or strokes).

All group A streptococcal diseases are most common in settings of poverty, where living conditions promote transmission of the organism, and prevention and treatment programs are less likely to be present or effective. These settings also rarely have efficient systems for collecting disease burden data.

Therefore, any attempt to measure the global burden of GAS diseases will be hindered by the breadth of information that is needed and the paucity of reliable information from countries where these diseases are most important. To our knowledge, there has been no attempt to pull such information together. The only GAS disease for which global disease burden estimates have been made is rheumatic heart disease (RHD). (1, 2)

We aimed to use existing data sources to estimate the global burden of GAS diseases, and to identify the most critical deficiencies in GAS disease burden data.

Methods

We conducted systematic reviews to find all published data relating to the burden of each GAS disease. We aimed to include only recent data, and population-based data where possible. For severe GAS diseases, we searched for publications after January 1 1985 in order to provide only the most recent data, while including many of the relevant studies that took place during the 1980s. We also aimed to include as many unpublished sources of GAS disease burden data from 1985 through 2002 as possible, by reviewing the proceedings of the 3-yearly meetings of the Lancefield International Symposia on Streptococci and Streptococcal Diseases, and contacting key opinion leaders in the field of GAS diseases to try to locate data from theses or other unpublished research projects. In addition, the World Health Organization library database was searched for all articles containing the same search terms as used in the Medline searches.

For streptococcal skin and upper respiratory infections, we extended the literature search back to January 1, 1980, in order to be able to include more studies.

SEARCH STRATEGIES

MEDLINE was searched via the PubMed search engine. The following searches were conducted. Aside from the date limits outlined above, no other limits were set.

- All fields: (rheumatic fever OR rheumatic heart disease) AND (incidence OR prevalence)
- All fields: (rheumatic fever OR rheumatic heart disease) AND (mortality OR cause of death OR burden of disease)
- All fields: glomerulonephritis AND (streptococcus OR streptococcal OR post-streptococcal OR poststreptococcal OR group A streptococcus) AND (incidence OR prevalence)
- All fields: (invasive OR bacteremia OR bacteraemia OR toxic shock syndrome OR necrotising fasciitis OR necrotizing fasciitis) AND (incidence OR prevalence) AND (group A streptococcus OR group A streptococcal OR streptococcus pyogenes)
- All fields: stroke AND (rheumatic fever OR rheumatic heart disease)
- All fields: endocarditis AND (rheumatic fever OR rheumatic heart disease)
- All fields: (impetigo OR pyoderma OR scabies) AND (incidence OR prevalence)
- All fields: (pharyngitis OR sore throat) AND (group A streptococcus) AND incidence
- All fields: developing country AND (mortality OR cause of death)
- All fields: (bacteremia OR bacteraemia) AND developing country

Abstracts were reviewed by 2 investigators, and those that seemed likely to offer population-based prevalence data were selected for review of the full article. Specific assumptions are outlined in the results section for each disease category.

REGIONS

Studies were categorised by geographical region. Regions were pre-determined according to presumed homogeneity of GAS disease rates (based on similarities in socio-economic status and/or ethnicity). The following regions were defined: Sub-Saharan Africa, Indian Subcontinent, People's Republic of China, other countries in Asia (excluding Japan), Latin America, Middle East and North Africa, Eastern Europe, Pacific Island countries and indigenous Australian and New Zealand, and Established Market Economies. The makeup of regions, and the WHO regions that they correspond to, is shown in Table 1.

Table 1. Makeup of regions as defined for this study

Region as defined for this study	Regions from UN Population Division included*	Corresponding WHO region
Subsaharan Africa	Eastern Africa, Middle Africa, Central Africa, Southern Africa	AFRO, EMRO
South-Central Asia	South-central Asia	SEARO, EMRO
Asia other	Eastern Asia, South-eastern Asia, excluding China and Japan	SEARO, WPRO
Latin America	Caribbean, Central America, South America	PAHO
ME and Nth Africa	Northern Africa, Western Asia	EMRO
Eastern Europe	Eastern Europe	EURO
Pacific and indigenous Australia/NZ	Melanesia, Micronesia, Polynesia plus indigenous Australians and Maori/Pacific Islanders in New Zealand	WPRO
Established market economies	Japan, non-indigenous Australia and New Zealand, Northern Europe, Southern Europe, Western Europe, Northern America	PAHO, EURO, WPRO
China	(China)	WPRO

* The countries making up each region are detailed on the UN Population Division website (http://esa.un.org/unpp/definition.html)

DENOMINATORS

Denominator population data were obtained from the United Nations Population Division 2002 projections (available on the internet at http://esa.un.org/unpp/).

SPECIFIC METHODS FOR RHD REVIEW

During the review, it became clear that the vast majority of RHD surveys have taken place in school-age children, so this age group became the reference point for further calculations. To extrapolate data from school-age children to other age groups, we also identified the few studies that described the prevalence of RHD in all ages.

Rheumatic heart disease inclusion criteria

For the calculation of RHD prevalence, we included only articles and reports that documented population-based data. These were mainly surveys – usually school-based – but also included data based on population-based registers. We gave preference to studies that reported the methods used, the denominator (population base for

registers, or number surveyed), and the numerator (number of RHD cases present or detected). In general, we did not include reports that cited prevalence rates without giving details about the method of data collection or the numbers in the numerator and denominator. However, where no other data were available for a region, such summary prevalence rates were used.

Extraction of data

The key data compiled for this study included the date and location of each study, the age group studied, the denominator (number of people surveyed, or population covered by registers), the numerator (number of cases of RHD found, or number of RHD cases registered), whether or not echocardiography was used to confirm RHD diagnoses, and the type of study (survey, or register-based).

Compilation of data

Overall prevalence rates for school-aged children were determined for each region by dividing the total denominator for all studies by the total number of RHD cases included or detected. A separate calculation was made, including only those studies that used echocardiography to confirm RHD cases. It has been demonstrated that clinical diagnosis of RHD is inaccurate, even in the most experienced hands, and may lead to two- or three-fold over-diagnosis of RHD. The calculated regional prevalence rate used for final calculations was that based on echo-confirmed studies only, except for those regions where there were no, or very few, studies in which echo was used. For those regions, the combined (echo and non-echo) prevalence rate was used.

The regional prevalence rate was then assumed to apply to the 5 to 14-year age group (the age group used in most of the studies). Therefore, the regional prevalence rate was multiplied by the population aged 5-14 years in that region to estimate the number of RHD cases.

Extrapolation to other age groups

Once the number of cases in the 5-14 year age group was calculated, we attempted to determine the fraction of total RHD cases (in all age groups) that this represented. To do this, we identified four studies that determined the prevalence of RHD in different age groups. Two of these studies listed the prevalence in Aboriginal Australians of all ages by age group in two regions; northern Australia and central Australia. (3, 4) The total number of cases in people aged ≥5 years from this study was divided by the total number of cases in people aged 5-14 years. This gave a fraction by which the estimated number of RHD cases in the 5-14 year age group from other studies could be multiplied to estimate the number of cases in people aged ≥5 years.

The third study listed RHD prevalences in an Indian population in the age groups <15, 15-24, and 25-34 years. (5) The prevalence of RHD in each age group was multiplied by the age-group specific population of India (from the United Nations Population Division website, above) to obtain an extrapolated total number of RHD cases in the Indian population aged 5-34 (assuming that the prevalence in those aged <5 was zero, and thus the <15 year prevalence applied to those aged 5-14). To estimate the number of cases aged >34 years, we applied an assumption from the Top End Australian Aboriginal study (which was the only study to document prevalences in all age groups). (3) We calculated the ratio of number of cases aged 15-34 to the number aged >34 from the Australian study, and applied that ratio to the Indian data. This allowed us to determine a final multiplication factor to be applied to the number of cases in 5-14 year age group, resulting in an estimate of the number of cases aged >14 years.

The fourth study surveyed a population of all ages >15 years in Myanmar. (6) Although this study did not include children 5-14 years as a reference point, we assumed that the prevalence in the 5-14 year age group was the same as in those aged 15-24 years (a conservative assumption, given that both the Australian and Indian studies, above, found higher prevalences in young adults than in children and adolescents). We then performed the same calculations as for the Indian study, using United Nations Population Division estimates of the Myanmar population in different age groups, to determine a multiplication factor to be applied to the number of cases in the 5-14 year age group in order to estimate the total number of RHD cases in the population.

Results

RHEUMATIC HEART DISEASE AND ACUTE RHEUMATIC FEVER

Prevalence of rheumatic heart disease

We found 57 studies that met our inclusion criteria. The summary data for each of these studies are listed in Appendix 1. Most regions had 7 or more studies included, but there was only one population-based study for each of Eastern Europe, China and Established Market Economies. Sufficient data were available to include only studies using echocardiographic confirmation of RHD lesions from all regions except Eastern Europe, Asia Other and China.

The highest calculated regional prevalences were found in Sub-Saharan Africa (5.7 per 1,000), the Pacific and Indigenous Australia and New Zealand (3.5 per 1,000) and South-Central Asia (2.2 per 1,000). Based on the regional prevalence data, we estimate that over 2.4 million children aged 5-14 years are affected with RHD (Table 2).

Extrapolation to all ages

Data from three studies that documented age-specific RHD prevalence rates confirm that the prevalence increases beyond the adolescent years, peaking in the third and fourth decades of life. This finding accords with the natural history of ARF and RHD. Although the peak incidence of first episodes of ARF occurs at approximately age 12 years, RHD is increasingly likely to develop after subsequent ARF recurrences. Moreover, RHD is a chronic disease. Survivors may retain heart lesions for many years, while new cases accumulate as a result of recurrent ARF episodes in older adolescents and young adults.

Data from northern Australian Aboriginals show that the prevalence rate in people aged 5-14 years (4.6 per 1,000) increased to 15.5 in those aged 15-24 years, 22.1 in those aged 25-34 years, and remained between 10 and 20 per 1,000 in all age groups over 34 years. (3) The overall prevalence in people aged >14 years was 17.6 per 1,000. The total number of cases aged 5-14 years was 38 whereas the total number of cases ≥5 years was 346. These data suggest that, in the Aboriginal population, there are 9.1 times the number of RHD cases in people aged ≥5 years as those aged <15 years. Similar data from Central Australian Aboriginals suggest that there are 7.2 times the number of RHD cases in people aged >15 years as there are in people aged 5-14 years (37 compared to 230 cases). (4)

This multiplication factor is supported by the Myanmar data, which included adults of all ages, including 470 aged ³56 yrs. (6) Although this study did not include children aged <15 years, it did find that the prevalence rates of RHD increased from 5.6 per 1,000 in those aged 15-24 yrs, to 26.4 in those aged 26-35 yrs, and 12.0 for those aged 36 yrs. Assuming that the prevalence rate in those aged 15-24 yrs also applied to those aged 5-14 yrs, and applying these prevalence rates to the overall Myanmar population, the conclusion is that there are 7.5 times as many people with RHD aged ³15 years as there are aged 5-14 years.

The Indian study only documented prevalence rates to the age of 35 years. In that study, the prevalence rates (per 1,000) were 5.2 (0-14 yrs), 16.6 (15-24 yrs), and 7.0 (25-35 yrs). Applying these prevalence rates to the age-

Table 2. Estimated number of Rheumatic Heart Disease cases in children aged 5-14 years

Region	No. of studies (no. using echo)	Median (IQR) RHD prevalence (per thousand)	Types of studies used for calculations*	No. in denominator (screened)	No. of RHD cases found	Calculated regional RHD prevalence (per thousand)	Population 5-14 yrs (thousands)	Estimated RHD cases aged 5-14 yrs
Subsaharan Africa	14 (10)	3.0 (2.7-6.4)	E	92823	528	5.7	177244000	1008207
South-Central Asia	14 (12)	1.6 (1.3-2.4)	E	129300	279	2.2	340530000	734786
Asia other	6 (0)	1.1 (0.8-1.3)	A	243668	199	0.8	124677000	101822
Latin America	7 (4)	3.0 (2.0-4.1)	E	45850	58	1.3	108278000	136971
ME and Nth Africa	7 (4)	1.9 (0.8-2.4)	E	28408	52	1.8	83956000	153679
Eastern Europe **	1 (0)	1.0	A	228958	225	1.0	41076000	40366
Pacific and indig Aust/NZ	7 (6)	7.6 (2.7-13.5)	E	32742	116	3.5	2185798	7744
Established market economies	1 (1)	0.3	E	385000	116	0.3	110621202	33330
China	1 (0)	0.8	A	31180	25	0.8	220226000	176576
Total				**1217929**	**1598**	**1.3**	**1208794000**	**2393482**

IQR, interquartile range

* E, only included studies using echocardiographic confirmation of RHD lesions; A, all studies included.

** For Eastern Europe, 1998 data from Romania were used, based on prevalence cited in regions where RHD registers not operating. Numerators and denominators not available. 1994 government statistics from Russia cite a prevalence of 5 per 1,000 in schoolchildren, but the more conservative Romanian estimate was used. See text for details and references

group specific population of India, there are 3.6 times as many RHD cases in people aged 15-34 years as in those aged 5-14 years (42576 cases compared to 11767 cases, respectively). The Australian study concluded that the number of cases in those aged >34 years was 0.52 times the number of cases in those aged 15-34 years. Applying this assumption to the Indian data, the number of cases in people aged >14 years is 5.5 times the number of cases aged 5-14 years.

We therefore present two estimates of the total number of cases of RHD globally. The first is a conservative estimate using the 5.5 multiplication factor derived from the Indian data. The second is a higher estimate, based on the 7.2 multiplication factor from Central Australia, which also approximates that from the Myanmar data. We have not calculated the upper-end estimate using the 9.1 multiplication factor from northern Australia. Using the 5.5 multiplication rate, we estimate that there are more than 15.5 million people alive with RHD (Table 3). The upper-range estimate based on a 7.2 multiplication rate is 19.8 million cases.

Table 3. Estimated global number of rheumatic heart disease cases – and inferred RHD prevalence - in all age groups

Age group and assumption	Estimated global number of RHD cases	Inferred all-age prevalence of RHD in Less Developed countries*
5-14 years (from Table 2)	2393482	
All ages, assuming 5.5 times the number of 5-14 yo cases in older age groups	15557632	2.5
All ages, assuming 7.2 times the number of 5-14 yo cases in older age groups	19626551	3.2

* Assumes 79% of all RHD cases in Less Developed Countries (see text for details) and total population in Less Developed Countries is 4,876 million (from UN Population Division website).

Seventy-nine percent (1247 of 1588) of all RHD cases in the studies in Table 2 came from countries defined by the United Nations Population Division as "Less Developed" (all countries except the Established Market Economies plus Eastern Europe, by our definition). The total population of the Less Developed Countries is 4.876 billion (80% of the world's population). Therefore, our estimates of the total number of RHD cases correspond to all age prevalence rates in Less Developed Countries ranging from 2.5 to 3.2 per 1,000 (Table 3). This seems reasonable, based on 4 studies that documented all-age prevalences of RHD ranging from 0.3 to 6.4 in Indian populations (5, 7) to 11.8 and 12.5 in Aboriginal Australians. (3, 4)

Quality of RHD prevalence data

The data relating to the prevalence of RHD were the most comprehensive of all GAS diseases on a global scale. The number of studies and diversity of populations studied was sufficient for us to be confident about the regional prevalence estimates for Sub-Saharan Africa, the Pacific and Indigenous Australia and New Zealand, and South-Central Asia. Although fewer studies were found from Latin America and the Middle East and North Africa, the prevalence estimates from these regions accord with the anecdotal impressions of clinicians and public health physicians in those regions. Similarly, although only one study was found from an Established Market Economy, the prevalence of 0.3 per 1,000 accords with earlier data from more developed countries (8).

We are less confident about the estimates from Asia, China and Eastern Europe. Five of the six Asian studies came from the Philippines, and one came from Thailand. We suspect that these data underestimate the rate of RHD likely to be present in the less economically developed countries in Asia. In Myanmar, for example, a population-based survey of adults during the early 1990s (using echocardiographic confirmation) found an overall prevalence rate of RHD in those aged >15 years of 13.2 per 1,000, peaking at 52.9 per 1,000 in rural women aged 26-35 years. (6) These data are comparable to the rates found in Aboriginal Australians, where the prevalence of RHD in those aged e"15 years was 17.6 per 1,000 and the peak prevalence (27.5 per 1,000) occurred in people aged 30-34 years. (3) The prevalence of RHD in people aged 15-24 in the Myanmar study was 5.6 per 1,000 (9.7 per 1,000 in rural areas), suggesting that the prevalence in 5-14 year olds is likely to be substantially higher than the regional prevalence of 0.8 per 1,000 cited in Table 2. The only other Asian data we could find came from Indonesian Government statistics during 1986, which cited the overall prevalence of RHD at all ages as 0.12 per 1,000; the reliability of these data must be questioned. (9)

There was only one study from China, conducted as a pilot survey for the Global Programme for the Prevention of RF and RHD. (10) In a population of over 1 billion people, covering a wide geographic region and range of living and economic conditions, it is impossible to know how representative this survey was of the national prevalence of RHD. The only population-based data from Eastern Europe came from a report from Romania to the World Health Organization in 1999. (11) This report documented the success of register-based control programs in reducing rheumatic heart disease prevalence in selected parts of the country. Therefore, we used the prevalence rate from the earliest year of data collection in this report (1993), under the presumption that most countries in Eastern Europe do not operate coordinated RHD control programs so the rate at the commencement of the Romanian program may be most representative of the situation in the rest of Eastern Europe. However, 1994 Government statistics from Russia cited a prevalence rate of RHD in "children" as 5 per 1,000 (without specifying the data on which the rate was based), suggesting that the Romanian prevalence rate may be an underestimate for the region.

As an example of the effect of these underestimates, if the regional prevalence rates for Asia Other and China were double the rate cited in Table 2, and the prevalence rate from Russian Government statistics were used instead of that from Romania, the total number of RHD cases in children aged 5-14 years would increase by over 400,000 to 2.85 million, and the estimated number of RHD cases in all ages would range from 9.4 million (instead of 7.9 million) to 28.8 million (instead of 24.2 million).

The level of selection bias in each study was difficult to determine. Most studies used school-based screening; this would likely bias in favour of lower RHD prevalence, as the main risk factors for ARF (overcrowding, poverty) may also be associated with lower school attendance. Most surveys also took place in urban settings, which also would bias in favour of lower RHD prevalence, given the apparent higher risk to residents of rural areas. However, it is not possible to determine whether studies deliberately took place in regions with a presumed high prevalence of RHD. This may be the case, although some studies were based on population registers, others were community rather than school surveys, and others were of a large size, suggesting that this form of selection bias may not have dominated all studies.

Rheumatic heart disease prevalence in urban compared to rural areas

With some exceptions, most studies have found that residents of rural areas are at higher risk of RHD than urban residents, with the exception of slum dwellers who appear to have the highest risk of all (Table 4).

Table 4. Studies comparing risk of rheumatic heart disease in rural compared to urban residents, or in different socio-economic strata

Year and reference	Country	Age group	Risk ratio for RHD rural compared to urban	Other findings related to socio-economic status
Early 1990s (6)	Myanmar	>15	3.25 rural vs urban	
1997 (12)	Australia	All	2.1 rural vs urban	
1997 (13)	Samoa	5-17	1.9 rural vs urban	
Late 1980s (14)	Saudi Arabia	6-15	1.5 rural vs urban	
Mid 1990s (15, 16)	India	5-16	1.8 rural vs urban Government schools	RR 1.6 Urban Government schools vs private schools
Early 1990s (17)	Bangladesh	5-15	0.3 rural vs urban	
1989-90 (18)	Algeria	6-19	0.3 rural vs urban	
1989-90 (19)	India	5-15		6.8 slums vs other urban
1996 (20)	Zaire	5-16		RR 0.2 rural vs slums RR 3.6 low SES vs upper SES
Early 1990s (21)	India	6-16		Prevalence RHD: Poor SES: 3.6 Average SES: 2.4 Good SES: 0.4 V good SES: 0.0

Incidence of acute rheumatic fever

Appendix 2 lists the studies that were found since 1980 that documented the incidence of ARF in children and adolescents (aged <20 years). The median incidences were calculated by region (Table 5). As noted below (under *Quality of ARF incidence data*) the resulting estimate of the annual number of ARF cases – over 336,000 – must be considered a very crude estimate, particularly for Sub-Saharan Africa, China, Asia other and South-Central Asia, where no or only one study was available. Ninety-five percent of ARF cases came from less developed countries (i.e. excluding Established Market Economies and Eastern Europe).

Not all first episodes of ARF occur in children aged 5-14 years. In the Aboriginal Australian population of the Northern Territory, 33% of all first episodes and 40% of all episodes occurred in people aged ³15 years. (3) In the 1940s, Schwentker found that 39% of all first episodes and 54% of all episodes occurred in people aged ³15 years. (22) Taking the more conservative Aboriginal estimates of the proportion of all episodes occurring in those aged ³15 years, the estimated annual number of ARF cases increases to 471,107.

It is also possible to estimate the number of new RHD cases occurring each year. The long-term USA/UK follow-up study of acute rheumatic fever patients found that 42% of all children with ARF had cardiac murmurs after 5 years of follow-up. (23) In the Aboriginal Australian population, 60% of those with a history of ARF subsequently developed RHD. (3) The 40% to 58% of people with ARF who will not develop RHD will still require secondary prophylaxis until age 21 years, according to American Heart Association guidelines. (24) The median age at diagnosis of first episodes of ARF is approximately 11 years, (25, 26) so it is reasonable to assume that cases of ARF without carditis will require an average of 10 years of secondary prophylaxis. Therefore, the number of cases

Table 5. Estimated annual number of acute rheumatic fever cases in children aged 5-14 years, and extrapolation to all ages

Region	Number of studies	Median incidence ARF (per 100,000)	Population aged 5-14 yrs	Annual number of cases of ARF
Subsaharan Africa*	0	13.4	177244000	23662
South-Central Asia	1	54.0	340530000	183886
Asia other	1	21.2	124677000	26432
Latin America	10	19.6	108278000	21222
ME and Nth Africa	10	13.4	83956000	11208
Eastern Europe	6	10.2	41076000	4169
Pacific and indig Aust/NZ	7	374.0	2185798	8175
Established market economies	3	10.0	110621202	11062
China*	0	21.2	220226000	46688
Total aged 5-14 yrs	38		1208794000	336505
Total all ages**				**471107**

Studies documented in Appendix 2. Where one publication detailed rates for different ethnic groups, geographic regions, or time period, these were included as separate studies.

* No studies available. For Sub-Saharan Africa, median incidence from Middle East and North Africa used. For China, incidence for Asia other used.

** Assumes 40% of all ARF cases occur >14 years of age (see text for details).

of ARF without carditis presently requiring secondary prophylaxis is approximately ten times the number of new ARF cases each year that will not develop RHD (the remainder of ARF cases will develop RHD and are accounted for in the RHD prevalences, above).

Therefore, of the 471,107 new cases of ARF each year, we estimate that 60% will develop RHD; i.e. that there will be approximately 282,000 new cases of RHD each year. We also estimate that there are an additional 1.88 million people with a history of ARF but no carditis presently requiring secondary prophylaxis.

Quality of ARF incidence data

Because ARF is a relatively short-lived illness, and not all cases progress to RHD, determining ARF incidence requires an active surveillance system. Therefore, ARF incidence data are less available and less reliable than those for RHD prevalence. We found no studies of ARF incidence from China or Subsaharan Africa, and only one study from each of Indian Subcontinent and Asia Other. The incidence data from the remaining regions are more reliable. The incidence in the Pacific and Indigenous Australia and New Zealand region rely entirely on studies in Aboriginal Australians, Maori and Pacific Islander New Zealanders, and Samoans living in Hawaii. The lack of studies in other Pacific Islands raises questions about the generalisability of these results throughout the Pacific, but the high ARF incidence accords with the high RHD prevalence found in this region.

Overall, there is a paucity of high quality prospective studies of ARF incidence from less developed countries.

Prevalence of a history of acute rheumatic fever without rheumatic heart disease

People who have had ARF but not developed RHD should have no ongoing health problems related to their previous ARF, as carditis is the only potential permanent sequel of ARF (with the exception of occasional cases of chorea that may last up to two or three years). (27) However, this history has implications for their health care and lifestyle, because of the need for them to take secondary prophylaxis for many years in order to prevent ARF recurrences and the associated development of RHD. This is mentioned above.

Mortality from Acute Rheumatic Fever and Rheumatic Heart Disease

Mortality from these diseases is difficult to quantify. In the regions where ARF and RHD are most common, cause-specific mortality data collection is usually non-existent or unreliable. To verify this, crude mortality rates (CMR) were calculated from a number of selected countries using death data registered with the World Health Organization Mortality Database (Table 6). The only sub-Saharan African country reporting to this database is South Africa. Very few of the world's poorest countries report data. Although the highest ARF/RHD CMRs came from Kazakhstan and Romania, the next highest rates came from the United Kingdom and Japan. These countries had higher CMRs for ARF/RHD than any Latin American country. Although ARF and RHD rates have fallen in recent years in Latin American countries, it is hard to envisage that the mortality from these diseases is likely to be several-fold lower in Latin America than in countries that have had low rates of ARF and RHD for several decades. These data attest to the unreliability of Government mortality reporting in measuring death rates due to ARF and RHD. The other main method of mortality data collection in less developed countries, verbal autopsy, does not help, as it is unable to separate out causes of deaths due to specific cardiac diseases.

Table 6. Calculated all age crude mortality rates from acute rheumatic fever and rheumatic heart disease (combined causes) in selected countries

Country	Year	Deaths due to ARF or RHD*	Population** (thousands)	ARF / RHD Crude mortality rate
Brazil	1995	1665	171,796	1.0
Dominican Republic	1998	37	8,353	0.4
Japan	1999	2576	127,034	2.0
Kazakhstan	1999	786	15,640	5.0
Mexico	2000	1301	98,933	1.3
Nicaragua	2000	41	5,073	0.8
Panama	2000	24	2,950	0.8
Romania	2000	737	22,480	3.3
South Africa	1996	537	44,000	1.2
UK	1999	1857	58,689	3.2
USA	1999	3676	285,003	1.3
Uruguay	2000	30	3,342	0.9
Venezuela	2000	194	24,277	0.8

* Cause specific deaths from World Health Organization Mortality Database (http://www3.who.int/whosis/) accessed March 31, 2003

** Population estimates from United Nations Population Division Website (http://esa.un.org/unpp/).

Therefore, there are two reasonable approaches to measuring ARF and RHD mortality. One could rely on natural history studies of ARF and RHD outcome, applying the expected death rates to the number of existing cases to estimate the total number of deaths each year. Alternatively, one could extrapolate cause-specific mortality rates from the few studies in less developed countries that have measured this with some rigor.

There are few long-term follow up studies of patients with RHD, on which to base estimates of expected death rates. Most occurred in the United States or United Kingdom in the early to mid 1960s. In a study from Boston, 40% of 653 cases of RHD diagnosed between 1921 and 1931 had died after 20 years of follow-up (an average of 2% per year), the vast majority from ARF or RHD-related causes. (28) A separate study from New York followed 1042 children diagnosed with RHD prior to the age of 15 years, and found, after a total of over 15,000 person-years of follow-up, an average of 1.47% died per year, 1.26% of cardiac causes. (29) A subsequent follow-up of 757 of these same children who survived until age 20 years demonstrated that after over 9,300 person-years of observation, an average of 0.83% died each year. (30) Seventy-eight percent of all deaths were due to cardiac causes. A later collaborative USA / UK report was published of a cohort of 497 children who were treated either with ACTH, cortisone or aspirin in the initial phase of their ARF. (31) After 10 years, 84.5% of the initial cohort were able to be followed-up, and 19 (3.8% of the initial cohort, 4.5% of those whose status was known) had died of RF or RHD. Fourteen of the 19 (74%) RHD deaths occurred in the first 5 years of follow-up.

The first two studies took place in the first half of the 20th Century, at a time when most patients did not have access to modern prevention or therapy, and suggest that between 1% and 2% of patients with RHD can be expected to die each year. The third study, which suggests a lower mortality rate of approximately 0.5% per year, occurred later, when secondary prophylaxis was already available and medical interventions had improved somewhat.

It is difficult to know how comparable these results are to the prognosis in less developed countries currently. Although the impact of medical interventions may be similar in the two settings (in that these interventions were not widely available in the USA or UK in the early to mid-1900s, and they are still not widely available in less developed countries today), the general standards of living, frequency of ARF recurrences, and access to other forms of medical care (which is clearly associated with ARF incidence (32)) are likely to be very different, and favour a worse prognosis currently in less developed countries. This is supported by a small follow up study in Aboriginal Australians, in which 24% of 33 Aboriginal children with RHD had died after approximately 12 years of follow-up (an average of approximately 2% per year).

Data from four Asian countries (Japan, Thailand, Indonesia and Taiwan) from patients studied between the 1940s and 1970s found that the mortality rates during the 1970s of those who did not receive secondary prophylaxis varied from 0.5% per year (Thailand) to 3.4% per year (Taiwan) up to an astonishing 8.4% per year in Indonesia. (33) In the few cases that did receive secondary prophylaxis, the mortality was 0% in Japan, and 0.6% per year in Taiwan.

Therefore, it is conservative to estimate that, in less developed countries where secondary prophylaxis is usually not delivered and medical and surgical therapy of RHD is usually not available, an average of 1.5% of patients with RHD will die each year. Based on this assumption, the number of RHD deaths each year ranges from over 230,000 to almost 300,000 (Table 7).

Table 7. Estimated global deaths due to rheumatic heart disease each year, based on estimates of mortality rates of existing RHD patients

Estimate of RHD cases (from Table 3)	Estimated global number of RHD cases	Number of RHD deaths each year (assuming 1.5% per year)
Low-range estimate	15557632	233364
High-range estimate	19626551	294398

We found no reliable, population-based studies of cause-specific ARF/RHD mortality from less developed countries (Table 8). Most data come from more developed countries, or rely on Government statistics, which are likely to be unreliable in less developed countries.

In order to gain a reasonable estimate of numbers of deaths due to ARF/RHD, we found three studies that compared the RHD age-standardised mortality rates (SMR) of indigenous, high RHD prevalence populations living in the same geographical region as non-indigenous, low RHD prevalence populations. This technique adjusts for the different age structure of the two types of population (one with high birth and mortality rates and thus a younger population, the other with low birth and mortality rates and thus an ageing population). These studies came from New Zealand, Alaska and Australia. (34-36) The SMRs for the indigenous populations ranged from 8.5 to 30.2, and those for the non-indigenous populations ranged from 1.1 to 4.2. We chose to use the SMRs from New Zealand – 2.0 and 9.6 for non-indigenous and indigenous, respectively – to represent reasonable middle-range estimates for RHD mortality in more developed and less developed countries. Note that the prevalence of RHD in the New Zealand Maori population is moderate to high, but that mortality rates may be expected to be modified by good access to secondary prophylaxis and medical and surgical care. Therefore, the RHD SMR in New Zealand Maori may underestimate the overall less developed country RHD mortality rates.

Applying the New Zealand SMR estimates to denominator data from the UN World Population web site for more developed countries (population 1.194 billion, calculated RHD deaths per year 23,877) and for less developed countries (population 4.877 billion, calculated RHD deaths per year 468,164), we estimate a total of 492,042 deaths per year due to RHD, which is slightly more than the higher-range estimates from Table 7. These estimates are also consistent with the 385,000 deaths due to RHD projected to occur in 2000, from the Global Burden of Disease exercise,(1) and the 338,000 deaths from RHD estimated to occur during 2001 in the World Health Report 2002. (2)

In considering ARF and RHD mortality, it should also be kept in mind that most deaths due to these causes occur in childhood or early adulthood. In the Aboriginal Australian population, the mean age of death due to ARF or RHD was 35.7 years, compared to 67.3 years for non-Aboriginal ARF/RHD deaths. (36) It has been projected that ARF/RHD caused 6.1 million years of potential life lost before age 70 during 1990, 5.5 million of which occurred in less developed countries. (36) The 2002 World Health Report estimated that RHD accounted for 6.1 million disability-adjusted life years lost during 2001. (2)

Quality of ARF/RHD mortality data

Reliable cause-specific mortality data relating to ARF and RHD are only available from indigenous populations living in relative poverty in wealthy countries. We could find no reliable ARF/RHD mortality data from any less developed country. Therefore, the mortality estimates presented here are open to question. The fact that mid-

Table 8. Published crude or age-standardised mortality rates from rheumatic heart disease with or without acute rheumatic fever

Ref	Year of mortality estimate	Place	Age	Crude mortality rate (per 100,000 per year)	Age-standardised mortality rate (per 100,000 per year)
(37)	1988	USA	All		1.7
(38)	1982-90	Valencia, Spain	All		3.2 to 4.7 in males 7.6 to 9.5 in females
(34)	1985-1987	New Zealand Maori	All		9.6
(34)	1985-1987	New Zealand Non-Maori	All		2.0
(35)	1979-1988	Alaska Native	All		8.5
(35)	1979-1988	Alaska Non-Native	All		4.2
(36)	1979-96	Australia, Aboriginal	All		30.2
(36)	1979-96	Australia, non-Aboriginal	All		1.1
(39)	mid-1980s	Spain	All	~ 3	
(40)	1991-95	Sao Paolo, Brazil	Women 15-49	1.63	
(41)	1987	Havana, Cuba	All	2.0	
(9)	1986	Indonesia	All	2.1 (principal cause) 3.1 (associated cause)	
(42)	1990	China	All	7.7 (rural) 7.9 (urban)	

range estimates from indigenous prospective studies are similar to high-range estimates from natural history studies provides some support to the mortality estimates. However, there is a clear need for better ARF / RHD mortality data.

Other data relating to rheumatic heart disease

During the search, we encountered numerous studies that presented non-population based data relating to rheumatic heart disease burden (Appendix 3). Most of these were hospital-based studies of the cause or severity of hospitalizations, or cause of death studies. Although little can be inferred from these studies in terms of overall disease burden, the number of studies and consistency of findings from less developed countries suggest that RHD remains a prominent cardiac cause of presentation and admission to hospital. These studies also highlight the young age at which RHD causes cardiac disease, and that in less developed countries RHD remains the most common acquired heart disease in children, adolescents and young adults hospitalized or seen by specialist cardiology services (and in many cases is the most common cardiac disease in childhood; more common even than congenital heart disease). They also attest to the continuing problem of RHD causing heart failure and death in pregnant women in less developed countries. These findings were particularly prominent in hospital based studies from Sub-Saharan Africa and parts of Asia (particularly Malaysia).

Other RHD-related morbidity and mortality

Infective endocarditis

Infective endocarditis (IE) occurs predominantly in previously-damaged valves, and there is good evidence that the major underlying cause in less developed countries is RHD. We found 11 studies published since 1980 that documented the proportion of IE due to RHD in less developed countries (Appendix 4). RHD was responsible for a median of 63% of all IE cases in less developed countries, and was the most common underlying cause of IE in all of these studies. There was no obvious difference in the RHD-related proportion between studies performed in children compared to those in adults. IE had a median mortality rate of 25% in the 5 less developed country studies where this was documented. By contrast, we found 3 similar studies from more developed countries; RHD underlay a median of 5% of IE cases in these studies, and mortality rates were not stated.

Unfortunately, we found only one population-based study documenting the incidence of IE. This study, from Israel, found an incidence of IE in adults of 1.2 cases per 100,000 per year. (43) Applying this incidence to less developed countries is likely to underestimate the burden of IE, as the overall standards of living and access to preventive health care in Israel are substantially better than in most less developed countries. Nevertheless, applying this assumed incidence, and the median proportion of IE cases due to RHD (65%) and IE mortality (25%) from less developed countries, we estimate that over 33,000 RHD-related IE cases occur each year in less developed countries, and that these lead to over 8,000 deaths (Table 9). A small additional number of RHD-related IE cases and deaths are likely to occur each year in more developed countries. (43) As we could find no incidence data on which to base these estimates and their overall contribution to global disease burden is likely to be very small, we have not included more developed country estimates here.

Table 9. Estimated number of rheumatic heart disease-related infective endocarditis cases and deaths in less developed countries per year

Calculation	Assumption	Estimate
Population aged >5 years		4326130000
Annual number of IE cases	Incidence 1.2 per 100,000 per yr	51914
Annual number of RHD-related IE cases	RHD underlies 65% of IE cases	33744
Annual number of RHD-related IE deaths	IE mortality 25%	8436

Stroke

Strokes may sometimes be due to underlying RHD, with thromboses occurring on affected valves or as a result of atrial fibrillation leading to emboli to the brain. The Global Burden of Disease study estimated that, during 1990, 6.08 million people suffered their first stroke, 30.9 million people were alive with a history of stroke, and 4.4 million people died from stroke. (44) Seventy nine percent of all first strokes (4.8 million) and 82% of all stroke deaths (3.6 million) were estimated to occur in less developed countries. Twenty-four percent of all strokes in the USA are due to emboli, most of which originate from the heart. (45) In Saudi Arabia, cardiac emboli were the cause of 19% of strokes, and in a separate study, 9.6% of all stroke cases had underlying RHD. (46, 47) In Argentina, over 20% of all embolic stroke cases had underlying RHD, (48) and in Serbia RHD was a risk factor in 4% of all strokes. (49) An autopsy study in India found that 25% of all strokes were embolic, and that RHD and infective endocarditis were the main precipitants. (50) A separate Indian study found that 10% of all ischaemic strokes were cardio-embolic,

and that RHD and coronary artery disease were responsible for most of these. (51) Even in Japan, 33% of cardioembolic stroke patients aged 65 to 74 years had underlying RHD. (52) A comparative study found that 23% of all ischaemic strokes in adults aged <50 years in Thailand were related to underlying RHD, compared to only 2% in the Netherlands. (53)

It is likely therefore that RHD is associated with at least 4%, and possibly 10% or more of all strokes in less developed countries. If so, this represents between 192,000 and 480,000 new strokes, and between 144,000 and 359,000 stroke deaths each year in less developed countries. There are no data to determine the proportion of these strokes that would not have occurred in the absence of RHD, although embolic strokes in patients with RHD are usually considered to be directly related to the valvular heart disease or associated atrial fibrillation. Taking a conservative estimate of 75%, we estimate that RHD causes 144,000 to 360,000 strokes and 108,000 to 269,000 stroke deaths each year in less developed countries alone. Several thousand more stroke cases and deaths each year in more developed countries are also likely to be due to RHD. If we also estimate that RHD is responsible for the same proportion of strokes in stroke survivors (75% of 4%, or 3%), then RHD was the causative factor in approximately 640,000 of the estimated 21.4 million stroke survivors in less developed countries. (44)

ARF-RHD related morbidity and mortality not included here

Other complications of RHD not included in these calculations are those due to cardiac surgery on RHD affected valves (perioperative mortality, thrombo-embolic, infective and mechanical complications), and complications of anticoagulation therapy and anti-cardiac failure therapy. These have not been included because there are very few data on which to base morbidity and mortality estimates.

Quality of other RHD-related morbidity and mortality

As noted above, the burden of RHD-related IE and stroke has been largely neglected in the past, and has not been quantified by any good population-based studies. The contribution of RHD to stroke cases and deaths in less developed countries is potentially enormous. The estimates included here are based on conservative assumption, and serve to highlight the possible size of the problem and the need for better data.

OTHER GROUP A STREPTOCOCCAL DISEASES (NOT INCLUDING ARF/RHD)

Acute post-streptococcal glomerulonephritis

We found 11 population-based studies documenting the incidence of APSGN; 3 in more developed countries, 3 in more developed countries but with separate documentation of rates in indigenous minority populations, and 5 in less developed countries (Appendix 5). Of the more developed country studies, two were based only on biopsy-proven diseases and included only or mainly adults, so are therefore substantial under-estimates of the true disease incidence. (54-56) The third came from Singapore; (57) although this country is economically more developed, the populations it contains include some with a relatively high risk for streptococcal diseases and the APSGN incidence was >10 per 100,000, so this rate was included in the less developed country studies. The best indicator of APSGN incidence in children in more developed countries came from the Australian and New Zealand studies, (58-60) in which the incidence in non-indigenous children was approximately 6 per 100,000 per year.

The median APSGN incidence in children from less developed country studies (including Singapore, NZ Maori, NZ Pacific Islander, and Aboriginal Australian studies) was 24.3 per 100,000 per year. The incidence in adults in

either less or more developed countries is not well documented. Using data from Kuwait on the incidence of APSGN in children (17.8 per 100,000) and at all ages (6.7 per 100,000) and also using UN World Population denominator data for Kuwait, we calculated an estimated incidence in people aged ³15 years in Kuwait of 3.9 per 100,000. (61) In order to be conservative in estimating the number of APSGN cases, we chose to assume that the incidence of APSGN in people aged ³15 years was half of the calculated Kuwait rate - 2 per 100,000 - in less developed countries and 0.3 per 100,000 in more developed countries (based on the Italian biopsy study).(54)

Applying these estimated incidences (24.3 per 100,000 in less developed countries and 2.0 per 100,000 in more developed countries) to the populations of those regions, we estimate that over 470,000 cases of APSGN occur annually, 97% in less developed countries (Table 10).

Table 10. Estimated number of cases of acute post-streptococcal glomerulonephritis

Region	APSGN incidence in children*	Population aged <15 y (thousands)	Annual number of APSGN cases in children	APSGN incidence in adults*	Population aged >5 y (thousands)	Annual number APSGN cases in adults	Total APSGN cases all ages
Less developed countries	24.3	1609317	391064	2	3267392	65348	456412
More developed countries	6	218859	13132	0.3	975013	2925	16057
Total		**1828176**	**404196**		**4242405**		**472468**

* See text for details of how incidences calculated

Mortality and complications from APSGN

The mortality from APSGN is said to be less than 0.5%, less than 2.0% of patients progress to end stage renal disease, and most of the deaths and cases of chronic disease occur in adults and/or after sporadic disease, whereas the majority of APSGN cases occur in children and/or epidemics. (62) Our review supported most of these statements. A number of studies found that children with APSGN may have high rates of encephalopathy, hypertension and renal failure in the short term, but that all recovered in the long-term without residual renal impairment. (63-66) Of these studies, only one reported any deaths in the acute phase; a study from India in which 1.4% of children hospitalized with APSGN died. (65) However, a number of other studies reported substantial mortality from APSGN. A Nigerian study reported that approximately 6% of APSGN cases in children progressed to acute renal failure, and that approximately 2% died of this complication. (67) A study from Iran found that 2% of APSGN cases in children progressed to chronic renal impairment. (68) Another study from India found that 6% of children with APSGN died of renal failure in the short term, but none of the survivors had long-term renal insufficiency (compared to adults with APSGN, in whom 28% died of renal causes or had end-stage renal failure after a mean of 4.8 years). (69)

Evidence to support an association of APSGN with chronic renal failure has been building in recent years. A number of other follow-up studies have documented high rates of chronic renal failure in adults with APSGN. (70,

71) More recently, childhood APSGN has been found to increase the risk of later chronic renal impairment in Aboriginal Australians, with odds ratios of 4.8 to 6.0. (72, 73) Although it is possible that the contribution of APSGN to chronic renal disease may prove to be substantial, the evidence is not yet sufficient to make definitive conclusions.

Because the mortality and long-term sequelae of APSGN have been poorly documented in most settings, we conservatively assumed that 1% of people with APSGN die each year, either in the acute phase or from long-term renal failure.

Quality of APSGN data

The overall quality of APSGN incidence data was poor, and there were very few studies from low-income countries where the incidence is likely to be higher than in middle-income countries such as Chile and Kuwait. Moreover, APSGN may occur in devastating epidemics, which may not be accounted for in surveillance studies over defined periods of time. Mortality data, and long-term follow-up studies, provide conflicting evidence about the severity of this disease. Conservative estimates of incidence, mortality and prognosis have been used here, so the burden of APSGN is likely to be greater than reflected in the above figures. There is a need for better studies of the epidemiology of APSGN and its relationship to chronic renal failure in less developed countries.

Invasive group A streptococcal disease

We found 16 published studies documenting the incidence and 13 documenting the case fatality rate of invasive GAS diseases in non-indigenous populations in more developed countries (Appendix 6). Three studies documented the incidence in indigenous populations in the USA and Australia. We found only one population-based study of invasive GAS infections in a less developed country; an unpublished study from Kenya (which has since been published).(74)Over a four-year period 1998-2002, they documented 48 cases of GAS sepsis in 16,570 admitted children aged <15 yrs. The incidence of GAS bacteraemia in neonates was 0.55 per 1,000 live births, and in children under 1 year, 2 years and 5 years was 96, 63 and 29 per 100,000, respectively. GAS was the 3rd most common cause of neonatal bacteraemia, the most common cause of bacteraemia in infants aged 7-59 days, and the 5th most common cause of community acquired bacteraemia in children aged <1 year and <5 years. The overall incidence of GAS bacteraemia in children aged <15 years was 13 per 100,000, with a 25% case fatality rate (J Berkley, personal communication).

The high incidence of invasive GAS disease in young infants in Kenya reinforces the findings of the recent WHO Young Infants Study, which found that GAS was one of the three leading causes of bacteraemia in children aged <90 days, accounting for 29% of all positive isolates in four less developed countries (Papua New Guinea, Ethiopia, The Gambia and The Philippines). (75) GAS sepsis in neonates is usually due to colonisation or infection acquired in the birth canal. These data suggest that GAS puerperal sepsis and septic abortion are likely also to remain common in less developed countries, although we could find no data to relating to this. This would accord with the overall profile of GAS diseases in less developed countries; the common manifestations of disease (ARF, APSGN, pyoderma) are those that were also common in more developed countries a century or more ago, when living conditions were similar to those in less developed countries now. (8)

Based on passive bacteraemia surveillance in Fiji, the minimum incidence of GAS bacteraemia in all age groups between 2000-2003 was 11.2 per 100,000 and 8.7 per 100,000 in children aged <15 years, with the highest rates found in children aged <5 and 84.9 in adults aged ≥65 years (23.1 and 84.9 per 100,000, respectively). (unpublished data from our group) The Fijian data and studies from other groups suggest that, although incidence of invasive

GAS infections peaks in young children and the elderly, the overall incidence in children aged <15 years approximates the incidence in all ages. (76-81)

In calculating the estimated numbers of cases and deaths due to invasive GAS infections, we used the median incidence and mortality rates from the more developed country estimates. We separately used three estimates for less developed countries; low (using the same incidence and mortality rates from more developed countries), middle (using the rates from the Kenyan study), and high (using the median incidence rates from the USA and Australian indigenous populations and the mortality rate from the Kenyan study). Assuming the middle estimate for less developed countries, we estimate that there are over 660,000 cases of invasive GAS infections each year (97% from less developed countries), and over 160,000 deaths (Table 12). These estimates do not account for premature mortality, or the considerable disability that may occur in survivors, particularly amputations, disfigurement and other complications that may follow necrotising fasciitis.

Table 12. Estimated number of cases and deaths due to invasive group A streptococcal diseases

Region	Population (thousands)	Incidence rate (per 100,000 per yr)	Annual number of cases	Mortality rate	Annual number of deaths
More developed countries	1193872	2.45*	29250	0.15*	4387
Less developed countries	4876709				
- Low estimate		2.45*	119479	0.15*	17922
- Middle estimate		13.00**	633972	0.25**	158493
- High estimate		46.00***	2243286	0.25***	560822
Total (using middle estimate)			**663222**		**162881**

* Median rates from studies in more developed populations listed in Appendix 5.
** From Kilifi, Kenya data (see text for details).
*** Median incidence from studies in indigenous populations in USA and Australia (see text for details).

Quality of invasive disease data

Overall, the incidence and mortality of invasive GAS diseases have been very well studied in more developed countries, and the resulting estimates of cases and deaths in those countries can be made confidently. There have been very few good quality population-based studies in poor settings or less developed countries. Importantly the few high quality data from surveillance studies in settings of poverty (in Native Americans, indigenous Australians, and the WHO and Kenyan studies) support the contention that invasive disease is more common and more severe in less developed countries. These data suggest that invasive GAS diseases may affect many hundreds of thousands or even millions of people in less developed countries each year, and cause several hundred thousand deaths. However, these statements cannot be made confidently until better data are available.

Superficial group A streptococcal diseases

Pyoderma

The 24 population based studies since 1980 documenting the prevalence of pyoderma are listed in Appendix 7, together with the prevalence of scabies where this was stated. These data suggest that, as with RHD, the highest prevalences of pyoderma occurred in Aboriginal Australians and Pacific Island nations. Most, but not all, populations with high pyoderma prevalence also had high prevalence rates of scabies. Although children had the highest prevalences of pyoderma and scabies, these diseases were also common in adults in many studies. On the whole, pyoderma prevalence ranged from approximately 1% to 20% in most less developed countries, but prevalences of 40% to 90% were found in Pacific regions. These studies and some additional studies documenting only scabies, suggest scabies prevalence ranging from approximately 1% to 10% in African and Asian countries, to 50% to 80% in the Pacific region. (82-87)

The median pyoderma prevalence in children in the studies listed in Appendix 6 is 58% in Pacific and Aboriginal Australian studies, and 7% in the remaining studies. Applying these prevalences to children aged <15 years in less developed countries, we estimate that over 111 million children aged <15 years have pyoderma in less developed countries at any one time. This excludes pyoderma in adults and in adults or children in more developed countries.

Pharyngitis

There were very few recent population based studies documenting the incidence of GAS pharyngitis. The most comprehensive studies came from the USA during the 1950s and 1960s, documenting incidences of serologically-proven symptomatic GAS pharyngitis ranging from 0.15 to 0.22 per person-year in children and approximately 0.06 per person-year in adults. (88-90) A further prospective study of 678 people in Egypt during 1967 to 1969 documented an incidence of serologically proven GAS pharyngitis of 0.42 per person year in children aged 2 to 4 years, 0.31 in children aged 6 to 12 years, and 0.10 in adults aged >25 years. (91) However, most of these infections were asymptomatic; the authors commented that the occurrence of typical exudative pharyngitis was rare. Other data suggest that acute pharyngitis is one of the most common illnesses for which patients seek medical advice in more developed countries, accounting for nearly 18 million office visits in 1996 and over 7 million visits to paediatricians each year in the United States. (92, 93) In Australia, 4% of all symptomatic presentations to general practitioners are for throat complaints, second only to cough at 7%, and sore throat consultations result in an antibiotic prescription in 89% of cases. (94, 95) GAS is the most common bacterial cause and is estimated to account for 15-30% of cases of pharyngitis in children and 5-10% of cases in adults. (96, 97)

Table 13. Recent population-based studies of the incidence of symptomatic group A streptococcal pharyngitis

Ref	Year	Place	Age	Number of subjects	GAS pharyngitis incidence (per person-year)	Serological confirmation
(98)	1988	Kuwait	5-14	28,920	0.03	No
(99)	1995-96	India	5-15	536	0.95	No
(100)	1998	New Zealand	School age	~24,000	0.50	No
(101)	2001-02	Australia	All	852	0.14 <18 yrs 0.04 >18 yrs	Yes

We found only four population-based studies after 1980 (Table 13). Three of these took place in populations where ARF is also common; in a predominantly Maori and Pacific Islander region of Auckland, New Zealand, in Kuwait and in northern India. (98-100) In these populations, sore throat with a positive throat swab for GAS occurred once every one to two years in each child. These infections were not confirmed using serology, so the true incidence will be somewhat lower. Only one study came from an affluent population; a study from Melbourne, Australia, which found an incidence of serologically proven symptomatic GAS pharyngitis of 0.14 per child-year. [Danchin, 2004 #1345] This suggests that the incidence has not changed dramatically in similar settings since the studies half a century earlier in the USA.

Therefore, it seems reasonable to conclude that approximately 15% of school-age children will suffer a symptomatic episode of GAS pharyngitis each year in more developed countries, and that 4-10% of adults will be similarly affected. The incidence in less developed countries may be five to ten times greater. Assuming that the incidence from the New Zealand study is representative of the incidence in school aged children in less developed countries, and also assuming that 80% of GAS culture-positive sore throats would be proven serologically (reducing the incidence from 0.5 to 0.4 per child-year), we estimate that over 600 million cases of symptomatic GAS pharyngitis occur annually, and that over 550 million of these occur in less developed countries (Table 14).

Table 14. Estimated annual number of cases of symptomatic group A streptococcal pharyngitis

Region	Incidence in children (per person-yr)	Population 5-14 years (thousands)	Annual cases in children (thousands)	Incidence in adults (per person-yr)	Population >14 years (thousands)	Annual cases in adults (thousands)	Annual cases all ages (thousands)
Less developed countries	0.4	1058738	423495	0.04	3267392	130696	554191
More developed countries	0.15	152233	22835	0.04	975013	39000	61835
Total		**1210971**	**446330**		**4242405**	**169696**	**616026**

Quality of superficial disease data

Pyoderma prevalence is affected by many climatic and other environmental factors, so rates may vary substantially between and within countries. This is exemplified by the dramatic variation in prevalence rates in Appendix 7. As a result, one cannot be confident of the generalisability of these results. This highlights the need for more prevalence surveys in different rural, urban, tropical, temperate, coastal and inland settings in less developed countries. In addition, cross-sectional surveys do not give any indication of the incidence of these infections or duration of lesions and transmissibility.

Prospective studies of GAS pharyngitis incidence are difficult to conduct. They require cohort retention, swabbing and, ideally, serological confirmation of infection. There are very few of these studies available, and none of good quality from less developed countries. A small number of high-quality studies is needed.

SUMMARY

By combining the low-range estimate for RHD prevalence, the middle-range estimate for invasive disease, and our other estimates, we conclude that approximately 18.1 million people currently suffer from a serious group A streptococcal disease, another 1.78 million new cases occur each year, and these diseases are responsible for over 500,000 deaths each year (Table 15). Added to this are over 111 million prevalent cases of streptococcal pyoderma, and 616 million new cases of GAS pharyngitis each year.

We have used relatively conservative assumptions at each step, so these are minimum summary estimates of the burden of GAS diseases. Moreover, we have not attempted to include a number of conditions whereby GAS contributes to serious disease (e.g. complications of RHD cardiac surgery, complications of medical therapy for cardiac failure due to RHD, infections with resistant bacteria as a result of antibiotic use for GAS pharyngitis and impetigo), nor do they attempt to quantify the costs of these diseases, so the true burden of disease is not completely represented in Table 15.

Table 15. Summary of estimated global burden of group A streptococcal diseases

Disease	Number of existing cases	Number of new cases each year	Number of deaths each year
Rheumatic heart disease	15.6 million	282,000*	233,000**
History of acute rheumatic fever without carditis, requiring secondary prophylaxis	1.88 million	188,000*	
RHD-related infective endocarditis		34,000	8,000
RHD-related stroke	640,000	144,000	108,000
Acute post-streptococcal glomerulonephritis	-	472,000	5,000
Invasive group A streptococcal diseases		663,000	163,000
Total severe cases	**18.1 million**	**1.78 million**	**517,000**
Pyoderma	111 million		
Pharyngitis		616 million	

All estimates rounded off. Note that these estimates assume constancy of incidence and prevalence over time.

* New RHD cases were calculated based on the proportion of incident ARF cases expected to develop RHD. The remainder of incident ARF cases are included in the "History of ARF without carditis" row. Therefore, the total number of new ARF cases each year is 282,000 + 188,000 = 470,000.

** Includes ARF deaths. RHD deaths are based on proportion of existing RHD cases expected to die each year.

\- No attempt has been made to quantify the prevalence of APSGN-induced chronic renal impairment or end-stage renal failure

Discussion

These estimates suggest that GAS causes a substantial burden of disease and death on a global scale. This is not surprising, given that all of these diseases are related to poverty, and hence are most common in less developed countries, and that GAS causes such a broad spectrum of acute and chronic disease.

We have not attempted to estimate the proportion of these cases and deaths that is potentially preventable. In a separate report on strategies for control of group A streptococcal disease, the ability to prevent the majority of RHD cases and deaths using secondary prophylaxis programs is highlighted. Such programs would also be expected to prevent most cases of RHD-related IE and stroke. That report also outlines the availability of successful strategies to control skin infections, which would also be expected to prevent many cases of APSGN and invasive GAS diseases. Primary prevention of ARF remains a vexed question, and the report on control strategies identifies a number of related critical issues, including the need to evaluate healthy-skin programs compared to management of throat-infections as potential measures to prevent ARF.

We have identified many areas where the data are deficient, particularly from less developed countries. The paucity of good-quality data relating to ARF incidence, APSGN incidence, ARF/RHD mortality, invasive GAS disease incidence in less developed countries, and RHD-related IE and stroke means that there is considerable uncertainty surrounding the estimates presented here. However, at each step we have attempted to make assumptions that tend to under-estimate rather than over-estimate the burden of disease. The estimates presented here relate to numbers of cases and deaths. GAS causes disease predominantly in children and young adults, so the burden to communities is even higher than reflected purely in terms of numbers of cases and deaths.

The absolute numbers of cases of pyoderma and pharyngitis dwarf those of the more severe diseases. Although these diseases may seem relatively unimportant because of their apparently benign nature, in themselves they cause substantial ill health, are a major drain on health services, and are costly (particularly because of use of antibiotics and symptomatic medications, and time away from school and work). Moreover, these are the primary infections that subsequently cause invasive and post-streptococcal diseases, so their importance cannot be neglected. Primary prevention of GAS diseases is aimed at controlling these superficial infections.

The data presented here also indicate that GAS diseases are highly prevalent in some regions, but may be less so in others. For example, RHD is very common in Sub-Saharan Africa and the Pacific, of moderate prevalence in South-Central Asia and the Middle East / North Africa, but apparently less common in many Asian countries and Latin America. The ARF incidence data do not always match the RHD prevalence data. In some cases, this may be due to reducing incidence of ARF, which precedes by some years a reduction in RHD prevalence. However, a more likely explanation is the poor quality of data from some regions, particularly Sub-Saharan Africa, Asia and South-Central Asia. The pyoderma data also suggest regional differences in prevalence, which cannot be solely attributed to climate or socio-economic conditions. For example the highest pyoderma prevalences were documented in the Pacific region, whereas poorer, tropical African countries had substantially lower prevalences. The data were inadequate to draw any conclusions regarding regional differences regarding ARF/RHD mortality, APSGN, invasive GAS disease, or pharyngitis. Better data from a number of key regional sites in less developed

countries would allow a more detailed analysis of regional differences and perhaps reveal markers that might enable local authorities to determine if they should be investing resources into efforts to control GAS diseases. Such data may also improve our understanding of the individual diseases and how to prevent them.

Priority issues

The number of cases and deaths due to GAS diseases, the young age of onset (and of mortality) of most of these diseases, their even greater indirect burden, and their association with poverty mean that these diseases cannot be ignored. Regional variations in disease burden and the paucity of data relating to particular diseases and outcomes make it critical to improve data collection in less developed countries.

Field sites are needed for intensive population based GAS disease burden studies (including bacteraemia surveillance) in less developed countries. Ideally, at least one site would be established in each of Sub-Saharan Africa, Pacific Island nations, East or South-east Asia, and South-Central Asia. In many regions there are already instutions with the necessary infrastructure, and even some with baseline GAS epidemiological data (e.g. the Wellcome/KEMRI Clinical Research Unit in Kenya, where bacteraemia data are being collected), which would simplify the process of establishing GAS field sites. There are a number of research institutes in South-Central Asia that collect GAS epidemiological data; it should not be difficult for one site to expand its program to collect information on all GAS diseases, or perhaps for a collaborative project to be established across institutes.

In addition to collecting complete epidemiological data, these sites could attempt to develop simpler tools for making some GAS disease burden estimates in other less developed countries. These field sites would also likely be ideal locations for future clinical trials of GAS vaccines, with the aim of evaluating their efficacy against the GAS diseases of greatest importance to less developed countries.

Studies since 1985 of rheumatic heart disease prevalence in school-age children, used to calculate regional and global rheumatic heart disease burden

Ref	Year of study	Place	Age (yrs)	RHD Prevalence (per 1,000)	Number screened	Number of cases	Echo	Type of study
Sub-Saharan Africa								
(102, 103)	1995	Ethiopia – Addis Ababa	13-15	6.4	9388	60	Yes	School survey
(104)	1984	South Africa - Indiana	4-18	1.0	4408	4	No	School survey
(105)	1988-89	Cameroon - Yaounde	6-15	2.1	3382	7	Yes	School survey
(106)	1985	Kenya - Kakamega	5-15	1.7	3631	6	No	School survey
(107)	1994	Kenya – Eldoret	5-15	2.7	1115	3	Yes	School survey
(108)	1986-89	Sudan - Sahafa Town	School-age	3	13332	40	Yes	School survey
(109)	1996	Zaire - Brazzaville	5-16	1.4	2153	3	Yes	School survey
(110)	1987	Zambia - Lusaka	5-16	12.2	11944	146	Yes in 25%	School survey
(111)	1989-90	Ethiopia - Butijara	5-19	4.6	3235	15	No	School survey
(10)	1986	Zambia - Lusaka	5-15	14.6	5200	76	? Yes in subset	School survey
(10)	1986	Mali - Bamako	5-15	2.9	14351	41	? Yes	School survey
(20)	1996	Zaire - Kinshasa	5-16	14.0	4848	68	Yes	School survey
(112)	1987-88	Guinea - Conakry	6-25	3.0	27110	81	Yes	School survey
Asia Other								
(10)	1986	Thailand - Bangkok and Nakornrajasima	5-15	0.2	55465	9	? No	School survey
(113)	1987-90	Philippines - Laguna	5-15	0.8	91694	72	? No	School survey
(113)	1996-97	Philippines - Mindanao	5-15	1.3	10635	14	? No	School survey
(113)	1996-97	Philippines - Albay	5-15	1.2	40000	48	? No	School survey
(113)	1995-97	Philippines - La Union	5-15	1.0	28554	29	? No	School survey
(10)	1986	Philippines - Laguna	5-15	1.6	17320	27	? No	School survey
China								
(10)	1986	Guangdong Province	5-15	0.8	31,180	25	? No	School screening
Established Market Economies								
(114)	1992 publ	Japan	School-age	0.3	385,000	116	? yes	School survey

Ref	Year of study	Place	Age (yrs)	RHD Prevalence (per 1,000)	Number screened	Number of cases	Echo	Type of study
Indian Subcontinent								
(15, 16)	1990s	India – north	5-16	2.9	15080	44	Yes	School survey
(5)	1991-92	India - Uttar Pradesh	0-15	6.4	3760	24	Yes	Village screening
(7)	1988-91	India - north	5-15	2.1	31200	66	Yes	Community project
(21)	1991	India - Jammu City	6-16	1.4	10263	14	Yes	School survey
(115)	1988-90	India - Rajasthan	3.5-18	3.3	10168	34	Yes	School survey
(116)	1991	Nepal (rural)	5-16	1.4	4452	6	Yes	School survey
(117)	1997	Nepal - Kathmandu	5-16	1.2	4736	6	Yes	School survey
(118)	1986	India - Anand	5-15	1.8	11,069	20	? Yes	School survey
(119)	1987	India - Ludhiana	6-16	1.3	6005	8	? Yes	School survey
(17)	1992	Bangladesh - Dhaka and Dhamrai	5-15	2.2	15798	36	Yes	School survey
(120)	1993	Bangladesh - Dhaka	5-15	2.4	10538	25	Yes	School survey
(121)	1991	Bangladesh - Dhaka	5-15	1.4	5923	8	Yes	Community survey
(122)	1992	Bangladesh - Rajbari	5-20	1.45	686	1	No	Community survey
(10)	1986	Pakistan - Islamabad	5-15	0.26	11,700	3	? No	School survey
(19)	1989-90	India - Agra	5-15	1.4	8449	12	Yes	School survey
Middle East and North Africa								
(123)	1995	Turkey - Ankara	6-17	0.7	4086	3	Yes	School survey
(10)	1986	Egypt	6-15	1.5	60022	87	? No	School survey
(124)	1997	Oman	6-18	0.8	9904	8	Yes	School survey
(125)	1992	Yemen	5-18	3.6	5000	18	Yes	School survey
(14)	1990	Saudi Arabia - Western district	6-15	2.4	9418	23	Yes	Community survey
(18)	1990	Algeria - Oran	6-19	1.94	15430	30	? No	School survey
(18)	1989-90	Algeria - Setif	6-19	2.0	11228	23	? No	School survey

Ref	Year of study	Place	Age (yrs)	RHD Prevalence (per 1,000)	Number screened	Number of cases	Echo	Type of study
Pacific and Indigenous Australia / New Zealand								
(126)	1985	Tonga	5-12	2.7	1106	3	Yes	School survey
(10)	1986	Tonga - Tongatapu	5-15	0.7	16456	11	Yes	School survey
(13)	1997	Samoa	5-17	77.8	8767	682	No	School survey
(3)	1997	Australia - Aboriginal	5-14	22.4	8248	38	Yes	Registry data
(127)	1987	Australia - Aboriginal	>5	12.3	976	12	Yes	Community survey
(4)	2001	Australia - Aboriginal	5-14	12.5	4843	37	Yes	Registry Data
(128)	1985	Australia - Aboriginal	5-18	13.5	1113	15	Yes	School survey
Latin America								
(41, 129)	1987	Havana, Cuba	5-14	1.1	6119	7	? Yes	School survey
(10)	1986	Bolivia - La Paz	5-15	7.3	1377	11	? No	School survey
(130, 131)	1986	Cuba - Santiago de Cuba and Pinar del Rio	5-14	3.0	14662	44	? Yes	School survey
(130)	1996	Cuba - Pinar del Rio	5-14	0.2	24519	5	? Yes	School survey
(10)	1985	El Salvador - San Salvador	School age	0.1	10248	1	? No	School survey
(132)	1992	Brazil - Belo Horizonte	10-20	3.6	550	2	Yes	School survey
(133)	1989	Bolivia - La Paz	4-21	4.07	5655	23	No	School survey
Eastern Europe								
(11)	1998	Romania	5-15	0.054	NA	NA	? No	Register based
(134)	1994	Russia	Children	5	NA	NA	? No	Government statistics

APPENDIX 2

Recent studies documenting the incidence of acute rheumatic fever in children and adolescents

Ref	Year of study	Place	Age	ARF incidence (per 100,000 per year)
Asia other				
(135)	1981-90	Malaysia, Kuala Lumpur	Children	21.2
Eastern Europe				
(136)	1982-87	Yugoslavia, Belgrade	0-19	9.2 (1982), 3.3 (1987)
(137)	1990-91	Slovenia	0-14	0.7
(138)	1982	Serbia	5-14	11.1
(11)	1999	Romania	5-15	16.5
(134)	1994	Russia	Children	18
Established Market Economies				
(139)	1984-88	USA, Hawaii	4-18	9.5 (All)
(100)	1982-97	New Zealand, Auckland	5-15	<10 (European descent)
(58)	1988-97	New Zealand	5-14	16.7 (All)
Indian subcontinent				
(140)	1984-95	India	5-14	54
Latin America and Caribbean				
(141)	1982-92	Martinique and Guadaloupe	<20	17.4 to 19.6 (1982)
(130)	1996	Cuba, Pinar del Rio	5-14	2.7
(142)	1986-90	Barbados	0-19	8
(41, 143)	1982	Cuba, Havana	5-14	10.5
(130, 131)	1986	Cuba, Santiago and Pinar del Rio	5-14	21.0 (Santiago) 28.4 (Pinar)
(144)	1987-91	Martinique	5-14	53
(145)	1994-99	Mexico	5-20	70
(146)	1992	Brazil, Belo Horizonte	10-20	360
Middle East and North Africa				
(18)	1997 - 2000	Algeria	4-19	11.1 (1997), 6.2 (2000)
(147)	1966-84	Israel	5-15	4.4
(148)	1988-97	Israel	5-35	5
(149)	1984-94	Qatar	4-14	11.2
(150)	1980-90	Israel, Tel Aviv	5-15	15.5
(61)	1980-83	Kuwait	Children	19.6
(151)	1984-88	Kuwait	5-14	29
(152)	1990	Tunisia	School age	30
(124)	1997	Oman	6-18	40
Pacific and Indigenous Australia / New Zealand				
(100)	1982-97	New Zealand, Auckland	5-15	80-100 (Pacific Islanders) 40-80 (Maori)
(139)	1984-88	USA, Hawaii	4-18	195 (Hawaiian Samoans)
(4)	2002	Australia, Aboriginal	5-14	374
(153)	1988-92	Australia – Aboriginal	5-14	375
(3)	1987-96	Australia, Aboriginal	5-14	508
(127)	1978-87	Australia, Aboriginal	5-14	815

Hospital-based and cause of death studies relating to rheumatic heart disease

Ref	Year of study	Place	Age (years)	Burden
Asia other				
(154)	1999 (publ)	Hong Kong	Adults	12.5% of hospitalised Chinese CCF pts had RHD
(9)	1986	Indonesia	All	RHD mortality rate 2.1 per 100k as principal cause, 3.1 per 100k associated cause
(155)	1984 (publ)	Malaysia	All	RHD 20.6% of cardiac admissions
(156)	1950-89	Malaysia	All	RHD caused 0.7% of all deaths 1975-89. Similar percentage between 1965 and 1989
(135)	1981-90	Malaysia	Children	ARF/RHD 21.2 per 100,000 paediatric admissions
(157)	1979-90	Taiwan	Pregnant women	• RHD 34.4% of organic heart disease in pregnant women (vs 53% congenital) • 38/42 cases with RHD had a complication
Subsaharan Africa				
(158)	1981-89	Cameroon	<16	RHD 3.4 per 1000 paediatric admissions. (113 RHD vs 211 congenital)
(159)	1985-88	Ethiopia	>10	RHD most common cause for cardiac admission (45.5%). Average age 33 yrs
(160)	1981-88	Ethiopia	Children	RHD most common cardiac admission (54.5% vs 35.5% congenital)
(161)	1989-92	Ethiopia	Children	RHD 59.4% of children seen in cardiology clinic (vs 35.9% congenital)
(162)	1989-90	France Burkina Faso Ivory Coast Tunisia	All	RHD as proportion of cardiology referrals in clinics: • France 0.04: 3.2% • Ivory Coast: 13.2% • Burkina Faso: 13.0% • Tunisia: 29.3%
(163)	1992-1995	Ghana	All	RHD 2nd most common cause of heart failure in large teaching hospital (20% vs 21% hypertensive) RHD cases young (mean 36.2 yr vs 56 yr hypertensive and 62 yr IHD) RHD most common acquired heart disease in children 24% (vs congenital 48.7%)
(164)	1989-90	Ivory Coast	All	RHD 14.5% of all cardiology admissions, vs 39% hypertension and 12.4% congenital
(165)	1988	Kenya	Children	One-third of paediatric cardiac referrals for RHD (10/31), vs 12/31 for congenital
(166)	1999 (publ)	Kenya	Adults	Heart failure caused 3.3% of admissions to hospital, and RHD most common cause (32%)
(167)	1991-92	Kenya	>60	RHD responsible for only 0.5% of CVD admissions in elderly
(168)	1994	Mozambique	All	RHD registered cause of death for 0.05% of 8114 deaths. CVD altogether responsible for 8.1%. Of 1523 medicolegal autopsies, 15 deaths due to RHD (1%)
(169)	1982-90	Nigeria	All	79% of hospitalised RHD patients aged 11-30 yrs. 48% presented in heart failure
(170, 171)	1961-91	Senegal	All	RHD responsible for 26.5% of all cardiac admissions (50% <20y)
(172)	1985-89	Senegal	12-18	• RHD and ARF responsible for 46% of all adolescent hospital admissions (next most common was anaemia at 10.5%) • RHD caused 22/39 deaths (56.4%) in this age group • 12.7% of RHD admissions died

Ref	Year of study	Place	Age (years)	Burden
(173)	1998	South Africa	Mothers	RHD the major cause of maternal mortality due to preexisting disease in Sth Africa. • 565 maternal deaths, of which 59 (10%) due to preexisting disease, and RHD in 18/59
(174)	1992-1995	Sth Africa	All	Risk of death due to ARF in 1990s 2.6 times that for France in 1951
(175, 176)	1997 (publ)	Sth Africa	Mothers	Cardiac disease complicated 0.65% of pregnancies, most commonly due to RHD. Maternal mortality rate 9.5%
(177)	1980s-1990s	Sudan	Children	RHD cause of 39% of cardiac clinic presentations (vs 56% congenital)
China				
(178)	1980s-1990s	China	All	Rising trend in mortality from RHD
(179)	1948-89	China	Adults	RHD constant as cause of cardiac admissions to 2 adult teaching hospitals between 1950s and 1980s
Eastern Europe				
(180)	1955-94	Croatia	Children	Dramatic reduction in number and severity of hospitalised RF and RHD (from 472 in 1955-64 to 19 in 85-94)
(181)	1979-93	Hungary	Children	Steady decrease in RHD referrals to a tertiary cardiology centre
Indian Subcontinent				
(182)	1960-89	India	All	RHD admissions steady at ~40% all cardiac admissions over 30yrs, whereas ARF admissions reduced dramatically
(183)	1995-96	India	Adults	RHD caused 53% of 125 consecutive pts admitted with cardiac failure
(184)	1960-89	India	Adults	RHD responsible for 40% cardiac admissions (most common cause) even in 1980s
(185)	1989	Sri Lanka	All	In 1988, 7500 and in 1989, 6500 admissions with ARF/RHD, with 284 deaths. Similar to hypertensive heart disease, but less than IHD and stroke
Latin America				
(186)	1999 (publ)	Antigua	Adults	293 pts hospitalised with heart failure. RHD not one of the two main causes.
(187)	1995	Brazil	Adults	Valvular heart disease responsible for 22% of cardiac failure admissions, which in turn were responsible for 9.4% of all medical admissions.
(188)	1991	Brazil		RF responsible for 0.62% - 0.35% of hospital admissions, with a 4-7% hospital mortality rate.

Ref	Year of study	Place	Age (years)	Burden
Middle East and North Africa				
(189)	1981-98	Iran	All	Steady increase in RF/RHD hospitalisations during early 1990s, but decrease since 1994
(190)	1977-89	Israel	Children	No decline in hospitalisations due to ARF over this time
(191)	1987-97	Tunisia	Children	ARF 18.25 per 1000 hospitalisations
(192)	1993-98	Turkey	Children	ARF cause of 3.4% of paediatric cardiology admissions
Pacific and Indigenous Australia / New Zealand				
(193)	1979-91	NT, Australia	15-64	RHD caused 7% of excess deaths in Aboriginal women. Major cause of premature mortality
(194)	1998-2000	Goroka, PNG	0-12y	RHD not a cause of death in 41 consecutive deaths in children aged 5-12 years
Established Market Economies				
(195)	1994	England	Adults	RHD associated with 6.7% of atrial fibrillation admissions
(196)	1960s-90s	Italy		Progressive reduction in ARF incidence in hospitalisations in 2 hospitals in Italy
(197)	1976-89	Italy	Children	Slight increase in ARF hospitalisations during 1980s in Milan
(198)	1986	Italy	All	3547 deaths due to RHD in Italy. Project approx 70,000 cases with acquired valve disease, of which about 30% RHD (21,000)
(199)	1987-95	New Zealand	All	7/62 heart transplants for RHD
(200)	1988-91	New Zealand	All	RHD cause of 1.4% admissions for heart failure
(201)	1990s	Norway		1990-92, 99 cases of ARF reported from Norwegian Hospitals - possibly represents an increased incidence
(39)	1951-86	Spain	All	Dramatically reduced ARF and RHD mortality since 1970
(202)	1986-90	Sweden	21-64	RHD SMR 56 for employed, 293 for unemployed. Overall, 26% unemployed
(202)	1986-90	Sweden	21-64	RHD one of the most important avoidable causes of death, especially in unemployed
(203)	1980-89	Texas	All	SMR RHD for blacks 1.6, and for Hispanics 1.0
(37)	1985-90	USA	All	No real change in national hospital admissions with ARF or RHD. Age adjusted death rates for ARF + RHD = 26.2 per million (1979) to 16.7 (1988)

APPENDIX 4

Studies since 1980 documenting the association of rheumatic heart disease and infective endocarditis

Ref	Year of study	Country	Age	Proportion of IE with RHD as predisposing factor	Rank of RHD as predisposing factor	Notes / mortality
(204)	1980-89	Denmark	All	1.5%	Not stated	
(205)	1982-92	France	Children	10%	Not stated	0% in children born in France
(206)	1977-92	USA	Children	5%	Not stated	
(207)	1994-95	Brazil	12-20y	63%	Most common	Mortality 42%
(208)	1977-85	Ethiopia	>13y	86%	Most common	
(209)	1995-97	India	All	56%	Most common	Mortality 30%
(210)	1981-91	India	All	42%	Most common	Mortality 25%
(211)	1984-90	India	Children	49%	Most common	
(212)	1987-88	India	Adults	68%	Most common	Mortality 21%
(43)	1980-94	Israel	Adults	37%	Most common	Incidence IE 1.2 per 100,000 in 1990s. Deduced incidence of RHD related IE = 0.44 per 100,000
(213)	1982-92	Ivory Coast	All	30%	Most common	
(214)	1983-94	Morocco	>11y	63%	Most common	Mortality 29%
(182)	1982-89	Nigeria	Children	66%	Most common	
(215)	1992-96	Slovakia	All	30%	Most common	Mortality 22%
(216)	1974-99	Turkey	Adults	65%	Most common	

APPENDIX 5

Population based studies of the incidence of acute post-streptococcal glomerulonephritis

Ref	Year of study	Place	Age	APSGN incidence (per 100,000 per year)
(54)*	1970-1994	Italy	>15y	0.29
(55, 56)*	1986-1990	France	All	0.15
(57)	1985	Singapore	<12y	10.8
(58)	1988-97	New Zealand	5-14y	8.1 (All) ~48 (Maori) ~80 (Pacific Islander)
(59)	1981-84	New Zealand	Children	50.5 (Maori) 46.5 (Pacific Islander) 5.9 (Other)
(60)	1993-95	Australia	<15y	239 (Aboriginal) 6 (non-Aboriginal)
(141)	1979-80	French Caribbean	<20y	~20
(217)	1980-89	Chile	<15	18.1
(67)	1986-91	Nigeria	<15y	24.3
(61)	1980-83	Kuwait	Children	17.8
(66)	1980-84	Kuwait	Children	19.5

* Biopsy-based study only, so likely under-ascertainment

APPENDIX 6

Population-based studies of the incidence of invasive group A streptococcal infections

Ref	Year of study	Place	Age	Incidence (per 100,000 per year)	Mortality
(218)	1991-96	Australia	All	32.2 (Indigenous) 6.4 (non-Indigenous)	13%
(219)	1996-2001	Australia	All	82.5 (Indigenous) 10.2 (non-Indigenous)	7%
(78)	1992-93	Canada	All	1.5	15%
(79)	1981-93	Denmark	All	1.6	23%
(220)	1986-91	Denmark	All	2.3	22%
(80)	2000	England and Wales	All	1.7	
(221)	2001	France	All	1.7	
(222)	1981-94	Israel	All		21%
(223)	1997-98	Israel	All	3.7	5%-14%
(224)	1990-94	Israel	<15y	4.8	
(74)	1998-2002	Kenya	<15y	13.0	25%
(225)	1993-94	Norway	All	3.9	
(226)	19929-6	Ontario, Canada	<18y	1.9	4%
(77)	1987-95	Sweden	All	2.3	11%
(227)	1993-96	Sweden	All	2.6	16%
(228)	1994	UK	All		18%
(229)	1990-99	UK	All	1.35	
(81)	1985-90	USA	All	46.0 (Native American) 2.7 (White)	20%
(76)	1994-95	USA	All	5.2	14.4%

APPENDIX 7

Studies since 1980 documenting population or community-based prevalence of scabies and/or pyoderma

Ref	Year of study	Place	Age (years)	Number surveyed	Prevalence pyoderma	Prevalence scabies
(230)	1994	Ethiopia	All	768	"Common"	"Common"
(231)	1991	Tanzania	All	936	0.3%	6% all ages 8.5% <15y
(232)	1994	Portugal	All	1000	0.7%	1.2%
(233)	1998	Taiwan	Primary school age	3029	0.8%	1.4%
(234)	1993	Kenya	School age	5780	0.9%	8.3%
(234)	1999	Kenya	School age	4961	1.6%	7.7%
(236)	1994	Tanzania	All	1114	1.7%	5.0%
(237)	1994*	Mexico	All	1528	1.8%	1.7%
(238)	1988-89	Malawi	All	34,000	6%	3%
(239)	1998*	Malaysia	All	356	7.0%	11.9%
(240)	1983	Mozambique	<15	798	11 to 17%	
(241)	1989	Ethiopia	School age	1842	11.6%	1.7%
(242)	1989	Vanuatu	All	18223	11.7% all ages ~16% <10y 28% <5y	16% all ages 24% <10y
(243)	1981*	Brazil	6-16	9955	12.2%	3.0%
(244)	1993-94	Mali	<13	1817	12.3%	4.3%
(245)	1995*	Malaysia	Children	41	20%	
(246)	1998*	Tanzania	All	800	~20%	4% all ages
(247)	2000	Australian Aboriginal	<6	217	22.5%	35%
(248)	1986	Nigeria	All	1960		35%
(249)	1984	Solomon Islands	All	10224	43% all ages 52% <15y	1.3% all ages 3% <10y
(13)	1997	Samoa	5-17		43.6%	4.9%
(250)	1994	Australian Aboriginal	All	125	49% all ages 69% <16 29% >16	29% all ages 32% <16 25% >16
(251)	2000	Australian Aboriginal	<17	129	64%	
(252)	1995	Australian Aboriginal	<15	130	90%	

* Publication date (study date not given)

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