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The Descriptive Epidemiology of Acute Rheumatic Fever and Rheumatic Heart Disease in Low and Middle-Income Countries

Das De Sudeep[1,*], Krishna Sredhar[2]

[1]Institute of Public Health, University of Cambridge, UK
[2]Department of Elderly Medicine, Leeds Teaching Hospitals NHS Trust, UK
*Corresponding author: sdasde@gmail.com

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Abstract Acute rheumatic fever (ARF) and Rheumatic heart disease (RHD) have been declining in developed nations. In low and middle-income countries, however, they continue to be a major cause of mortality and morbidity. It is estimated that RHD causes 200000-250000 premature deaths every year and is the leading cause of cardiovascular death in developing nations. This review aims to describe the background, pathogenesis and epidemiology of acute rheumatic fever and rheumatic heart disease in developing nations. The paper also highlights some of the public health measures, which can be undertaken to reduce the heavy disease burden of ARF and RHD in theses countries.

Keywords: *acute rheumatic fever (ARF), rheumatic heart disease (RHD), epidemiology, Group A β haemolytic Streptococcus (GABHS)*

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1. Introduction

Acute rheumatic fever (ARF) is a consequence of pharyngeal infection with Group A β haemolytic Streptococcus (GABHS). It is a result of an exaggerated immune response to group A streptococcus in a susceptible host. There is a range of symptoms associated with ARF, with damage to the valve tissue of the heart or rheumatic heart disease (RHD) being the only chronic sequela, leading to significant morbidity and mortality. The progression from acute rheumatic fever to rheumatic heart disease is thought to be driven by episodes of recurrent infections resulting in a prolonged inflammatory response in the cardiac valvular tissue [1]. The pathogenesis of acute rheumatic fever and rheumatic heart disease is illustrated in Figure 1. [2] It is estimated that approximately 60 percent of subjects with ARF will develop RHD [1]. From a historical perspective, it was William Charles Wells' landmark publication [3] in 1812 that made a definitive link between ARF and its cardiac manifestation. The infective aetiology of ARF was recognized by Poynton and Paine in 1900 [4] and Beattie in 1904 [5]. Since the 1900s, the aetiolgy of valvular heart disease in developed nations has gradually shifted from rheumatic to degenerative. In developing nations, however, valvular heart disease is still predominantly caused by rheumatic heart disease. It is estimated that approximately 80-85% of children younger than 15 years live in areas where RHD is endemic. RHD causes 200000-250000 premature deaths every year and is the leading cause of cardiovascular death in developing nations. [6] The objective of this paper is to describe the epidemiology of ARF and RHD in low and middle-income nations, as well as to highlight the public health measures, which can be undertaken to improve the heavy disease burden, which ARF and RHD carry in these countries.

2. Methodology

2.1. Search Strategy

Table 1. Search strategy

Search Limits	
English language Date of publication: 1 January 1980- 10 November 2012	
MeSH search terms	
("Rheumatic Fever" OR "Rheumatic Heart Disease") AND ("Incidence" OR "Prevalence" OR "Epidemiology") NOT ("North America" OR "Europe")	
Inclusion criteria	Exclusion criteria
1. Low/Middle income countries 2. Incidence/Prevalence of ARF/RHD 3. Epidemiological data on person, place, or time	1. Non cardiac manifestations of ARF/RHD 2. Diagnostic Techniques in ARF/RHD 3. Articles on treatment 4. Articles on prevention 5. Studies based in developed nations

A literature search was performed on PubMed to identify studies that described the epidemiology of acute rheumatic fever and rheumatic heart disease. The studies were then selected based on pre-specified inclusion and exclusion criteria listed in Table 1.

The above search strategy revealed 1767 articles. Articles were assessed for relevancy based on the title and the abstract. Duplicate articles were excluded. A total of 6 studies on acute rheumatic fever, 11 on rheumatic heart disease and 5 review articles were identified for this paper.

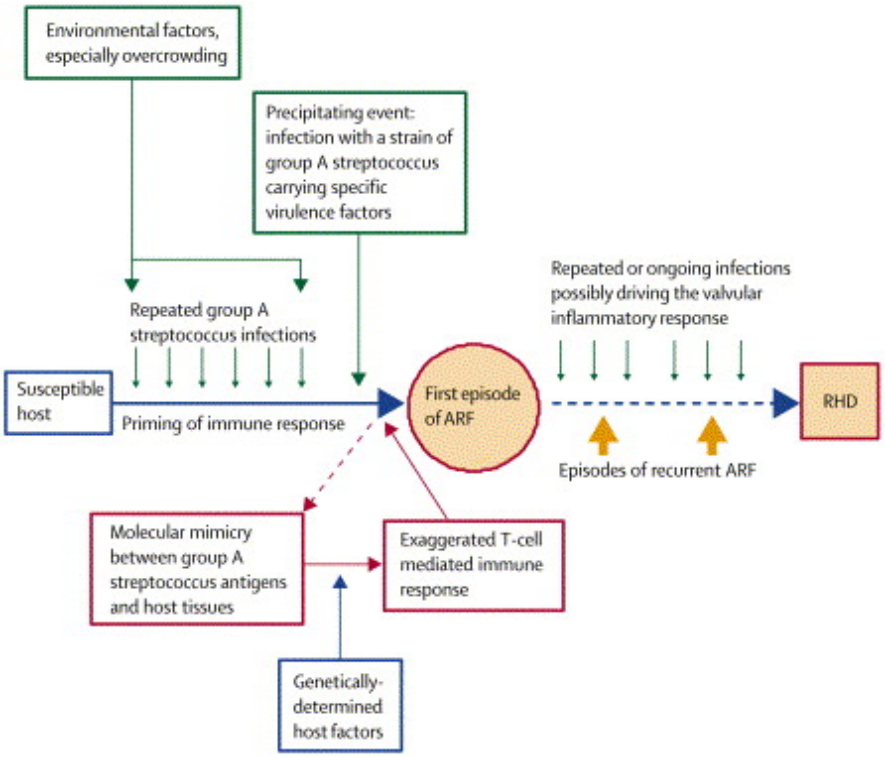

Figure 1. Pathogenetic pathway for ARF and RHD [2]

2.2. Definitions and Case Ascertainment

Jones [7] first described the diagnostic criteria for ARF in 1944. (Duckett- Jones criteria) They have since been modified several times, most recently in 2002. [8] They can be divided into major and minor criteria as summarized in Table 2.

Table 2. Duckett-Jones criteria. Major and Minor criteria for the diagnosis of acute rheumatic fever [9]

Major criteria	Minor criteria
Migratory polyarthritis	Arthralgia
Carditis	Fever
Erythema marginatum	First degree heart block
Sydenham chorea	Elevated inflammatory markers (ESR, CRP)
Subcutaneous nodules	

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Diagnosis of acute rheumatic fever with the *Revised Jones Criteria* can only be made in the presence of either 2 Major or 1 Major and 2 Minor criteria, together with evidence of recent streptococcal infection, shown either by microbiology of throat swabs or serological tests. Diagnosis of ARF with the *Modified Jones Criteria*does not require microbiological or serological evidence of recent streptococcal infection.

Rheumatic heart disease (RHD) is a late complication of ARF caused by chronic inflammation of the valvular tissue. The mitral valve is most commonly involved with either mitral stenosis or mitral regurgitation being the most common clinical manifestations.

Diagnosis of RHD is made based on a clinical history of previous streptococcal throat infections, the presence of a cardiac murmur on auscultation and echocardiographic confirmation.

2.3. Measures of Disease Occurrence

The literature reviewed mainly reported the incidence of acute rheumatic fever and prevalence of rheumatic heart disease, with one study reporting the annual incidence of newly diagnosed cases of RHD [10]. Data was retrieved from population-based studies, hospital based studies and from specialty clinics. There were both prospective and retrospective studies. There was no data from surgical or autopsy series in the developing nations. The national health registries were also not as well developed or updated like in the developed nations. There were variations in the diagnostic criteria for ARF in some developing nations with limited laboratory resources to identify streptococcal infections. In these countries, diagnosis is based on clinical criteria alone and laboratory evidence of Group A streptococci is a minor criteria. *(Modified Jones criteria).*

In studies where there was no direct measure of annual incidence, the total number of cases over the study period was divided by the population at risk, and then by the number of years of the study period. In studies where there was a significant difference in the population (due to immigration/emigration) at risk over the time period of the

study (i.e the denominator), the average incidence over the years was calculated.

With regards to prevalence data on RHD, some of the studies did not employ echocardiography to diagnose RHD, relying mainly on clinical findings. This would result in under-reporting of the prevalence of RHD. Conversely there were population-based screening studies, which utilized echocardiography to determine the prevalence of RHD, incorporating subclinical or asymptomatic cases of RHD. This led to significantly higher rates in the prevalence of RHD.

3. Results

3.1. Acute Rheumatic Fever

The literature reporting the incidence of acute rheumatic fever has been summarized in Table 3.

Table 3. Summary of data for Acute Rheumatic Fever incidence

Study	Place/Year	Study Duration (Years)	Population size at risk	Mean Annual Incidence (per 100000)	Target Age (Years)	Gender	Study characteristics/Method of diagnosis
Grover et al [11] 1993	N India/1988-91	3	31200	51	5-15	24 M 24 F	Prospective study, data collected from primary health care registries in rural community/revised criteria used
Majeed et al [12] 1993	Kuwait/1984-88	5	382885	23	5-14	40 M 48 F	Prospecivestudy , data collected in primary care centres and referred to regional hospital for case ascertainment/revised criteria used
Eltohami et al [13] 1997	Qatar/1984-94	11	60000-100000	11.2	4-14	51 M 35 F	Hospital based study.Retrospective from Jan 84-Aug 86, prospective from Aug 86-Dec 94/revised criteria used
Omar et al [14] 1995	Malaysia/1981-90	10	NA	15.8	6-11	1.39M : 1 F	Retrospective hospital based/modified criteria used
Steer et al [15] 2009	Fiji/2005-07	2	316314	15.2	All ages (Median age of diagnosis 10.4)	17 M 16 F	Prospective hospital based/revised criteria used
Talbot et al [16] 1984	New Zealand/1978-82	5	129765	88 (Maoris) 9.3 (Non-maoris)	< 30	1M: 1.2 F NA	Retrospective based on hospital registries/revised criteria used

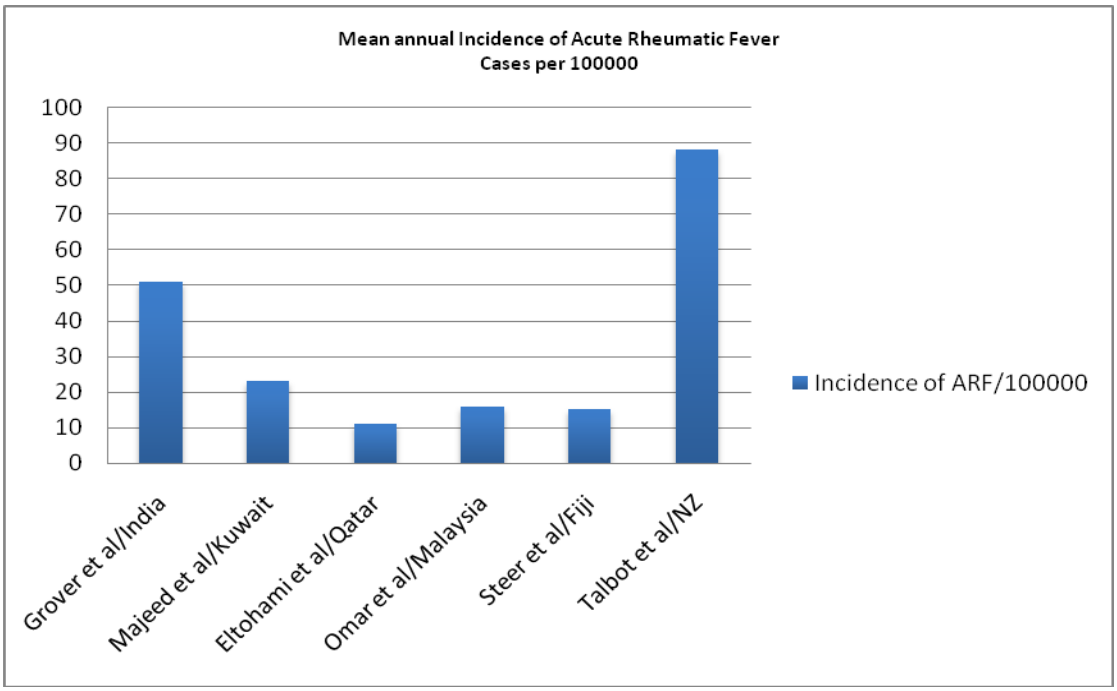

Figure 2. Mean annual incidence of ARF by study

Overall, there was a scarcity of quality data on the incidence of acute rheumatic fever in the developing world, especially for sub-Saharan Africa and China. There was one study from India [11], two studies from the Middle East [12,13], one study from Southeast Asia [14], one study from Fiji [15] and one study from New Zealand. [16] The study from New Zealand was chosen as it reported the incidence of ARF in indigenous Maoris, who were a low or middle income population.

The study from India [11] was a population based prospective study in a rural community in North India with an at risk population of 31200. Data was collected from primary health care centres in the villages. The study period was over 3 years and the mean annual incidence was 51/100000 population.

Majeed et al [12] conducted a study in Kuwait over 5 years on a target population of children aged 5-14 years. This was a prospective study where suspected cases in primary care centres were referred to the regional hospital where they were ascertained.The population at risk was 382 885. The average annual incidence was 23/100000.

The other study in the Middle East was based in Qatar [13].This was a hospital based study and data was acquired from the only paediatric inpatient facility in the country, hence assuming all the new onset rheumatic fever cases in the country would be included. A total of 86 children were diagnosed with ARF over an 11-year period. Taking into account differences in the population at risk over the years, an average incidence rate of 11.2/100000 was calculated.

The Malaysian study [14] was based in a paediatric unit in a teaching hospital in Kuala Lumpur. Hospital records of children diagnosed with ARF were gathered from 1981-1990. There were 134 patients in total diagnosed with ARF over the time period. The incidence of ARF was 15.8/100000, with the majority of cases occurring between 6-11 years of age.

In Fiji [15], the study was a hospital based prospective study conducted over a 23-month period. Altogether there were 37 cases of ARF diagnosed during the study period.

The average incidence of ARF in children aged 5-15 was 15.2/100000.

The study by Talbot et al [16] was conducted in New Zealand over a 5-year period. This was a retrospective hospital based study. The target age group was under the age of 30 and the source population size was 129765. The mean annual incidence of ARF was 88/100000 in the Maoris (indigenous people) and 9.3/100000 in non-Maoris.

The incidence of ARF by study is summarized in Figure 2.

3.2. Rheumatic Heart Disease

The data retrieved on the prevalence of rheumatic heart disease is presented in Table 4. There was one study based in South Africa (!0), which calculated the incidence of new cases of rheumatic heart disease per year. This was a retrospective hospital based study at a tertiary care centre. The annual incidence of new RHD cases reported was 23.5/100000. The rest of the studies were population based prospective studies. Most of the studies were school surveys with a target population of school children and adolescents aged between 5-17 years. One study by Rizvi et al [17] conducted a community based household survey ranging over all age groups. There were studies from the Indian subcontinent [17,18,19] with the prevalence of RHD varying from 5.7/1000 in Pakistan [17] to 51/1000 in Bikaner, North India [18]. Studies from Sub-saharan Africa, Southeast Asia, Central America and the Pacific region also noted high prevalence rates of 30.4/1000 [20], 21.5/1000 [20], 48/1000 [21] and 55.2/1000 [22] respectively. There was a study from China [23], which reported a prevalence of 1.86/1000 in the adult population.

Table 4. Summary of data for Rheumatic Heart Disease prevalence

Study	Place/ Year	No. of cases	No. screened	RHD Prevalence (cases/1000)	Target Age (Years)	Gender	Echo-based screening	Study Characteristics
Rizvi et al [17] 2004	Pakistan/1993-94	54	9430	5.7	All ages(mean age of diagnosis 29.5)	20 M 34 F	No	Prospective Community survey
Periwal et al [19] 2006	N.India/2005	50	3002	16.7	5-14	35 M 15F	No	Prospective School survey
Maneesha et al [18] 2010	N. India/2007-08	54	1059	51	6-15	27M 27F	Yes	Prospective School survey
Longo-Mbenza et al [24] 1998	Kinshasa,Africa/1996	59	2648	22.2	5-16	33M 26F	No	Prospective School survey
Carapetis et al [25] 2008	Tonga,Pacific/2003-04	159	4794	33.2	3-15 (mean 8)	NA	No	Prospective School survey
Wang et al [23] 2006	China/2001-02	15	8080	1.86	> 18 (mean age of diagnosis 48.3)	4M 11F	No	Prospective Community study
Marijon et al [20] 2007	Cambodia/2001-02	8 79	3677	2.2 21.5	6-17 (median12)	1M: 1.3F	No Yes	Prospective School survey
Marijon et al [20] 2007	Mozambique/2005	5 66	2170	2.3 30.4	6-17 (median 11)	1M: 1.7F	No Yes	Prospective School survey
Ben M Reeves et al [22] 2010	Fiji/2008	4 20	362	11 55.2	5-14 (median 10)	1M: 1.5F	No Yes	Prospective School survey
Paar et al [21] 2010	Nicaragua 2006-09	150 11	3150 (paeds) 489 (adults)	48 22	5-15 (mean 9.5) 20-35 (mean 27.4)	67M 83F 1M 10 F	Yes Yes	Prospective Community study

The studies either ascertained RHD by clinical assessment, followed by echocardiographic confirmation of suspected cases, or echocardiographic screening of all the cases in the study. The studies, which employed echocardiographic screening, reported significantly higher prevalence rates of up to 10 times compared with studies, which relied on clinical assessment. The prevalence of RHD by study is illustrated in Figure 3. The difference in prevalence rates of RHD between studies using clinical methods and echocardiographic screening is summarized in Figure 4.

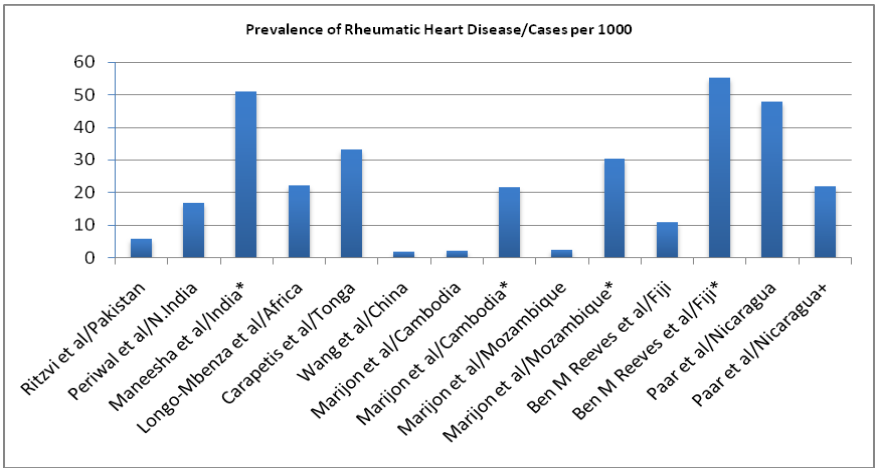

Figure 3. Prevalence of RHD by study (*Echo based screening studies, + Study on adults)

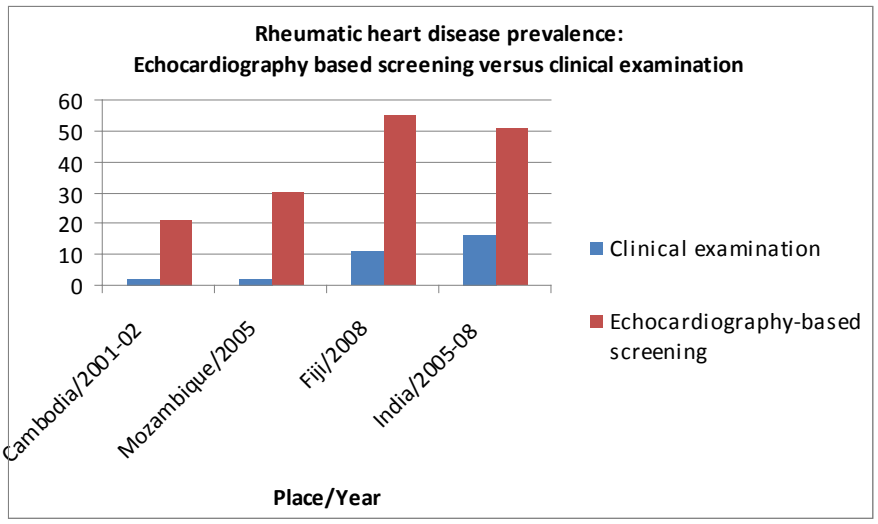

Figure 4. Echocardiography versus clinical examination

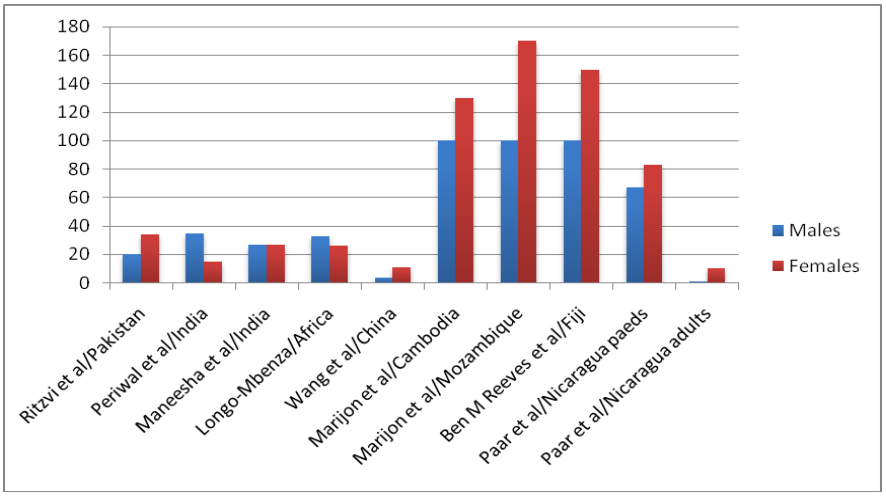

Figure 5. Prevalence of RHD by gender

3.3. Target Population

3.3.1. Gender

In the 6 studies [11-16] which reported the incidence of ARF, there was no difference between males and females.

In terms of RHD, Karen Sliwa et al [10] reported that 68 % of newly diagnosed cases of RHD were females. For the remaining 10 studies [17-25] that reported data on prevalence of RHD, 7 of the studies revealed a female predominance, 1 showed no difference and 2 studies revealed a higher prevalence in males. The prevalence of rheumatic heart disease by gender in these studies is illustrated in Figure 5.

3.3.2. Age

The studies reporting the incidence of ARF mainly targeted a population aged between 5-18 years with a median age of presentation ranging from 11-14 years of age. The study by Steer et al [15] targeted all age groups and reported a median age of diagnosis of ARF of 10.4 years with an interquartile range between 8.7-14.3 years.

With regards to the prevalence of RHD, most of the studies were based on school children. Rizvi et al [17] conducted a community-based study across all age groups and the mean age of the subjects diagnosed with RHD was 29.5 years.

In the study by Karen Sliwa et al [10], which targeted a population above the age of 14, the median age of diagnosis of RHD was 41 (interquartile range 30-55) in males and 42 (interquartile range 31-55) in females.

3.4.Geography

The distribution of the incidence of ARF varied between the regions with the highest rates of 88/100000 being reported in indigenous Maoris in New Zealand [16] and an incidence of 51/100000 reported in the Indian subcontinent [11]. The studies from the Middle East [12], Southeast Asia [14], the Pacific Islands [15] and North Africa [13] reported an incidence of 23, 15.8, 15.2 and 11.2 per 100000 population respectively.

The data on RHD prevalence revealed the highest rates in the Pacific Islands (55.2/1000 in Fiji [22], 33.2 in Tonga [25]), India(51/1000) [18] and Africa (30.4/1000 in Mozambique, 22.2/1000 in Kinshasa) [20,24].

3.5. Time

Literature retrieved on the worldwide epidemiology of ARF [1,6,9] revealed an overall decrease in incidence of ARF in all regions with the exception of the Western Pacific. The general decline in ARF incidence can be attributed to the earlier recognition in ARF, the more widespread use of appropriate antibiotics for Group A Beta haemolytic streptococcus (GABHS), and improved living conditions. The increase in incidence in the Western Pacific can possibly be explained by improved recognition and reporting of ARF in this region. One other possibility is that the Western Pacific consists of many small, isolated populations (small denominator) and a small outbreak of ARF can be calculated as a high incidence level.

The prevalence of RHD is increasing worldwide [9]. Given the decline in the incidence of ARF, this is likely to be explained by improved treatment options available for RHD resulting in longer survival, rather than an increase in the disease. The more recent studies, which have utilized echocardiography based screening to diagnose RHD, have also led to higher prevalence rates of RHD being reported [20].

4. Discussion

4.1. Epidemiological Challenges

The studies reviewed were conducted at different time periods and to compare data between studies on incidence, prevalence as well as demographic factors would be inaccurate. Multiple factors such as awareness of the disease, better diagnostic methods as well as changes in the socioeconomic climate of the various countries could have contributed to the differences in the data observed.

There was also variation between studies on the methods used for case ascertainment and measuring disease occurrence.

The revised Jones criteria for diagnosing ARF require microbiological or serological evidence of streptococcal infection. In studies where there were no resources to identify streptococcal infections, the diagnosis of ARF was made only on clinical grounds (modified Jones criteria) and this would have led to under reporting of the true incidence rates.

Studies which utilized echocardiography based screening to diagnose RHD reported up to 10 times higher prevalence rates compared to studies which used clinical screening methods.

With regards to study design, studies, which were prospective, population based and used active surveillance methods would have been more representative of the true incidence and prevalence rates. In contrast, retrospective studies presenting data from specialty referral clinics or hospital registries tend to under report the incidence and prevalence rates.

4.2. Acute Rheumatic Fever and Rheumatic Heart Disease

Data from reviews done on the incidence of ARF [2] across all ages reveal that the peak incidence of acute rheumatic fever is in children aged 5-14 years. The highest reported incidence rates are in indigenous populations of New Zealand and the Western Pacific with rates ranging from 80-100 per 100000. There is no documented difference in ARF incidence between the genders.

RHD prevalence is highest in adults aged 20-50 years [10]. This difference in age of presentation between ARF and RHD can be explained by 1) RHD being a result of recurrent attacks of ARF over years and 2) RHD being asymptomatic for years after the first attack of ARF.

Several studies [17,20,21,22,23] have revealed a higher prevalence of RHD in females in low and middle income countries and researches have attributed several reasons including genetic and social factors. It is established, for example, that women are genetically more predisposed to many autoimmune diseases, and researchers postulate that similar processes contribute to the higher prevalence of RHD observed in women. Social factors include women having limited access to health care in many developing nations, as well as being in physical contact more with children, possibly increasing the risk of repeated exposure to group A streptococcus [6].

4.3. Public Health Interventions

Improved social and economic conditions, together with the use of penicillin have virtually eradicated ARF and RHD in the developed world. In low and middle-income nations, however, rheumatic heart disease still remains the major cause of cardiovascular death in children and young adults. The WHO [26] reports that at least 15.6 million people have RHD, 300000 of approximately 0.5 million people who acquire ARF annually eventually develop RHD, and 200 000-250 000 premature deaths each year are directly attributable to ARF or RHD [6].

The cornerstone of any public health measure to reduce the disease burden of ARF and RHD involves prevention. Community based prevention involves attempts to reduce overcrowding and improving hygiene and access to better health care. It is worth noting that the decline in ARF incidence rates in the USA and Europe preceded the antibiotic era and can be attributed to improved socioeconomic conditions [27].

Primary prophylaxis involves the prescription of antibiotics, namely penicillin in group A streptococcal (GAS) pharyngitis to eradicate the bacteria and prevent ARF. In countries where there are limited laboratory resources to diagnose GAS pharyngitis, the indiscriminate use of penicillin to treat anyone presenting with a sore throat may be a cost effective option to prevent ARF, especially in children and adolescents in endemic areas [1].

Secondary prophylaxis aims at preventing recurrent attacks of ARF, which is a major risk factor for RHD [2].This entails long term treatment with oral or ideally intra-muscular benzylpenicillin which ensures better compliance rates [6].

Optimal treatment of ARF and RHD involves establishing better registries and promoting active surveillance by training healthcare workers to diagnose ARF and RHD. Quality data from updated registries was lacking in many of the low and middle-income countries, especially Africa and China.

The more recent studies [18,20,21,22] have raised the question of echocardiography based screening programmes to diagnose RHD. This would diagnose patients with asymptomatic or subclinical RHD who could potentially be a target for secondary antibiotic prophylaxis. For screening criteria to be satisfied however, it is necessary to prove that any early intervention can improve prognosis. It has not yet been proven that secondary prophylaxis for all patients with subclinical RHD is the best clinical option. Current guidelines recommend the use of secondary antibiotic prophylaxis for children with “significant subclinical rheumatic heart disease” as defined by specific echocardiographic criteria [28]. Further research into including all patients with subclinical disease needs to be evaluated and studies are also needed to examine the cost-effectiveness of such screening [28].

Future goals in the prevention of ARF will centre on vaccine development against Group A Streptococcus with researchers having completed phase 2 trials of a vaccine in adults. The treatment of RHD will focus on more minimally invasive and cost effective interventions made available in middle and lower income nations [6].

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