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REVIEW

The worldwide epidemiology of acute rheumatic fever and rheumatic heart disease

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Abstract: Acute rheumatic fever (ARF) and rheumatic heart disease (RHD) are significant public health concerns around the world. Despite decreasing incidence, there is still a significant disease burden, especially in developing nations. This review provides background on the history of ARF, its pathology and treatment, and the current reported worldwide incidence of ARF and prevalence of RHD.

Keywords: rheumatic fever, rheumatic heart disease, group A streptococcus, epidemiology

Introduction

Acute rheumatic fever (ARF) is a postinfectious, nonsuppurative sequela of pharyngeal infection with *Streptococcus pyogenes*, or Group A β hemolytic *Streptococcus* (GABHS). Of the associated symptoms, only damage to the valve tissue within the heart, or rheumatic heart disease (RHD), can become a chronic condition leading to congestive heart failure, strokes, endocarditis, and death. While the incidence and prevalence of ARF and RHD have been decreasing in developed nations since the early 1900s, they continue to be major causes of morbidity and mortality among young people in developing nations. It is estimated that there are over 15 million cases of RHD worldwide, with 282,000 new cases and 233,000 deaths annually.[1]

More recent data using echocardiography to screen for RHD in developing nations have lead to a marked increase in the recognized prevalence in these regions.[2–6] With these new data, there has been an increased awareness and interest in ARF and RHD, which stimulated this review of the literature to provide information on the pathogenesis, diagnosis, and treatment for ARF and RHD, and an updated estimate of the worldwide incidence and prevalence.

Background

Although physicians in Europe had been describing clinical components of ARF since the 1500s, it was William Charles Wells' seminal publication in 1812 that definitively linked ARF with carditis.[7] The entire clinical spectrum of ARF (from tonsillitis to carditis) was first described by Cheadle in 1889.[8] The infectious etiology of ARF was long suspected, especially given the seasonal variation in outbreaks, and in 1900 Poynton and Paine described a diplococcus isolated from patients with ARF, which they implicated as a causal organism for the disease.[9] *Micrococcus* (or *Streptococcus*) *rheumaticus* was isolated from a patient with ARF in 1904, and was noted to be "indistinguishable from strains of *Streptococcus pyogenes*".[10] Into the 1930s, theories implicating viruses as causal agents for ARF surfaced,[11] and are still being investigated today.[12,13]

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Methods

An extensive literature search for any articles about "acute rheumatic fever" or "rheumatic heart disease" was performed in August 2010 using PubMed. Articles reporting data of the incidence of ARF or prevalence of RHD were reviewed. In order to maximize the available information, non-English language articles were included if it was possible to obtain an English translation of either the abstract or the entire article.

To generate trends of ARF incidence and RHD prevalence over time, data from various countries were clustered by World Health Organization (WHO) region – Africa, the Americas, Southeast Asia, Europe, Eastern Mediterranean, and Western Pacific. Data reported from any countries within a WHO region for a given year were averaged together to provide a value for that year. These data were plotted for the time period 1970 to 2009, and trend lines were calculated with quadratic regression for each WHO region and are reported in the graphs. Regional incidence and prevalence estimates were not weighted by the underlying population.

The last major WHO report on the worldwide prevalence of ARF and RHD reported data through 1990.[14] This year was used as a cutoff to create 2 eras: 1970 through 1990, and 1991 through the present. ARF incidence and RHD prevalence rates for each reporting country during these eras were graded and plotted on a world map to show the changes in disease burden and geographic location with time in more detail than the trend plots.

Jones criteria for each of the WHO regions were compared using one way ANOVA with post-hoc analysis to identify significant differences in criteria between regions.

Diagnosis

The diagnostic criteria for ARF were first developed by Jones in 1944[15] and have since been modified in 1965,[16] 1984,[17] 1992,[18] and 2002.[19] The criteria are divided into Major and Minor criteria (Table 1). Diagnosis is made by the presence of either 2 Major or 1 Major and 2 Minor criteria, *plus* evidence of recent streptococcal infection, either by a pharyngeal swab

culture positive for GABHS, positive rapid GABHS antigen test or rising serologic antibody titers (antistreptolysin O [ASO], DNAse B, or streptokinase).[18]

The Major criteria are migratory polyarthritis, carditis, Sydenham chorea, erythema marginatum, and subcutaneous nodules. Polyarthitis is redness, swelling, and intense pain of multiple, usually large, joints that can change from one location to another as the disease progresses. Carditis is typically valvulitis and has traditionally been diagnosed by a new murmur suggestive of valvar regurgitation, but echocardiography has been used more in recent years to aid in the diagnosis (see below). There may be myocarditis or pericarditis in addition to the valvulitis. Sydenham chorea, or St. Vitus' dance, is rapid, uncontrolled movements of the trunk or extremities. There can also be worsening school performance, behavioral changes, and emotional lability. Erythema marginatum is a transient rash with central pallor and red, serpiginous (snake-like) borders found on the trunk and extremities. Subcutaneous nodules are painless, flesh-colored bumps, usually found on the extensor surfaces of the arms and legs.[18]

The Minor criteria are arthralgias, fever, elevated acute-phase reactants, and first degree heart block. Arthralgia is pain, often in multiple joints, without associated redness or swelling. Of note, a patient can have either arthritis or arthralgia as a Jones criterion, but not both. Fever, usually at least 39°C, is common in early ARF. Acute-phase reactants are nonspecific laboratory markers of inflammation in the body. The typical ones measured are erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), both of which are expected to be elevated during an episode of ARF. These markers can also be followed as signs of resolution of ARF. First degree heart block is diagnosed by prolongation of the PR interval on electrocardiogram (Figure 1). Having first degree heart block does not predict whether a patient will develop RHD.[18]

There has been controversy over the use of Doppler echocardiography in the diagnosis of ARF.[19,20] Many argue

Table 1 Major and Minor Jones criteria for the diagnosis of acute rheumatic fever[18]

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

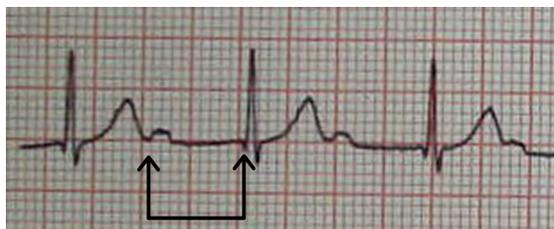**Abbreviations:** CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Figure 1 Electrocardiogram demonstrating first-degree heart block in a patient with acute rheumatic fever. The PR interval is noted by the arrows, and is markedly prolonged at 300 milliseconds (normal for an adult is less than 200 milliseconds).

that echocardiography can help to diagnosis subclinical RHD, especially among high-risk populations.[21–24] However, since it is not known how much valvar regurgitation is "normal", there is concern for overdiagnosis of carditis by relying on Doppler echocardiography.[19] The current American Heart Association guidelines recommend the use of Doppler echocardiography as a supplement to diagnosis, but evidence of valvar regurgitation should not be used as a Major or Minor criterion.

Pathophysiology

Even though ARF has been recognized as a disease entity for at least 150 years, a clear understanding of the pathophysiology still eludes modern physicians. The role of GABHS infection as an initial event is clear, and has been supported by outbreaks of ARF following outbreaks of pharyngitis, as well as rising antistreptococcal antibodies in patients with ARF.[25] ARF is believed to be an autoimmune reaction to GABHS infection. Genetically determined host susceptibility has long been presumed, especially given the tendency for outbreaks to occur within families and the relatively few cases of ARF that develop given the high prevalence of GABHS pharyngitis and pharyngeal carriage.[26] Many studies have investigated the role of HLA alleles, which are located on chromosome 6, in ARF susceptibility, and while there have been no universal associations, HLA-DR7 has been the most frequently associated with ARF and RHD.[27–45]

While the exact mechanism by which certain genes can confer an increased susceptibility to ARF has not been delineated, there are theories about the roles played. HLA molecules process antigens within a host cell and present them on the cell surface to T cells, which can then attack the antigen or activate B cells to produce antibodies to the antigen. If the HLA molecules present antigens that resemble both *Streptococcus* and human tissues, then host cells can be attacked. This is called molecular mimicry and will be discussed more below. Another protein that has been associated with ARF and RHD is the inflammatory cytokine, tumor necrosis factor-α (TNF-α), which is also located on chromosome 6 near the HLA alleles. TNF-α may be upregulated in patients with increased ARF susceptibility, leading to an increased inflammatory response in these patients, and subsequent development of ARF.[30] A third factor, mannose-binding lectin (MBL), binds to various sugar molecules on the cell surface and helps to mark foreign cells for immune cells to eliminate. RHD patients with mitral valve damage have been found to have high levels of MBL

in their blood, while those with aortic valve damage have low levels.[30]

The theory of cross-reaction between GABHS and heart tissue has been explored for at least 60 years. Cavelti first identified anticardiac autoantibodies in ARF in 1945, and subsequently demonstrated that anticardiac and antiskeletal muscle antibodies were produced in rats, but only in the presence of killed streptococci.[46,47] These antibodies could subsequently react to, and damage, host tissue without the continued need for streptococci to be present.[48] In 1962, Kaplan and colleagues demonstrated a cross-reactivity between human heart tissue and GABHS[49] and later anticardiac antibodies in patients with ARF.[50] Further study has led to the identification of the M-protein on the GABHS cell membrane as the likely antigen for inducing the production of antibodies that cross-react with human heart tissue.

The cross-reactivity is believed to occur through molecular mimicry, where all or part of a foreign antigen resembles at least some portion of host tissue. In ARF and RHD, the foreign antigen is the M-protein and it cross reacts with cardiac myosin, which induces T-cell mediated attack of the heart tissue and valves. Once valve tissue is damaged and inflamed, proteins that are normally intracellular can become exposed to invading immune cells and lead to the development of more autoantibodies directed at different component proteins of valve tissue.[30] This leads to further inflammation and scarring of heart valve tissue and chronic RHD. All four heart valves can be involved in rheumatic carditis; however there is a marked predominance of mitral valve involvement. This has recently been associated with higher levels of MBL,[30] but is not clear why more MBL leads to damage of the mitral valve. Since all heart valves develop from the same tissue, they should be equally susceptible to attack from an autoantibody.[51]

Once heart valves have been damaged, they do not function properly, and blood is allowed to leak backward, or regurgitate. In severe cases, this can cause acute congestive heart failure, which can be the presenting symptom of ARF. Figure 2a shows normal cardiac anatomy and Figures 2b and 2c show echocardiograms demonstrating a thickened, regurgitant mitral valve. In addition to the usual treatment for ARF, these patients require medical management for their heart failure. Patients that recover from the initial rheumatic carditis are likely to have permanent valve damage, and over time the affected valves can become stenotic in addition to regurgitant. Severe valve stenosis or regurgitation can eventually warrant surgical repair or replacement of
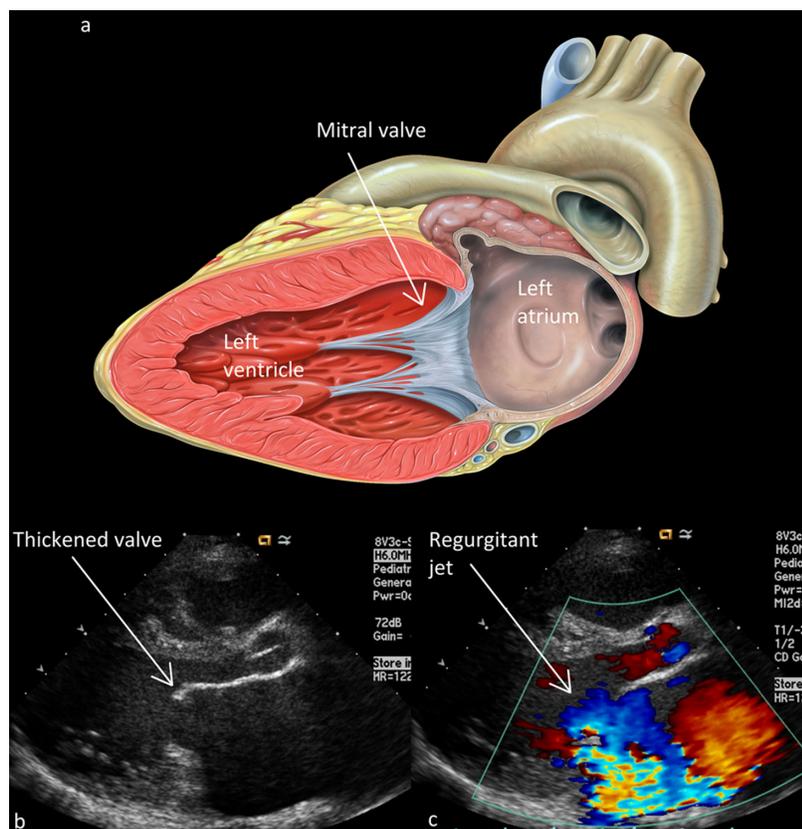
Figure 2 a) Artist rendition of normal left heart anatomy, demonstrating the left atrium connected to the left ventricle via a mitral valve.[52] **b)** Two-dimensional echocardiogram of the left heart, demonstrating a thickened anterior leaflet of the mitral valve. **c)** Two-dimensional echocardiogram with color Doppler, demonstrating moderate-to-severe mitral valve regurgitation (blue jet).

the affected heart valves. A recent review of 361 cardiac surgeries for rheumatic disease (RHD, neonatal lupus, systemic lupus, Kawasaki disease, or juvenile rheumatoid arthritis) among 261 North American patients from 1985 to 2005 found that 55% of the surgeries were for RHD (160 patients, 200 procedures) with 3 in-hospital deaths.[53] In various series of patients with endocarditis, RHD was the underlying cause in 15% to 76.6% of cases, with mortality from endocarditis ranging from 29% to 36%.[54–57] The cost of surgical intervention for RHD is approximately US$25,000, which is enough to fund 1 year of an RHD screening program in a small developing nation.[58] Early detection of ARF and RHD through screening programs can reduce the morbidity of chronic RHD and surgeries for heart valve repair or replacement.

There appears to be molecular mimicry involved in the development of Syndeham chorea as well. Numerous studies have provided evidence for anti-neuronal antibodies to the basal ganglia in patients with Sydenham chorea.[59] Kirvan and colleagues recently found a carbohydrate component of the streptococcal cell wall that cross-reacts with gangliosides in the cell membrane of neurons in the basal ganglia. Not only

does this cause inflammation and damage neurons, but since gangliosides are involved in cell signaling, neuronal pathways can be disrupted as well.[60] One function of the basal ganglia is inhibition of motor impulses. Damage to this area can explain the unusual movements associated with Sydenham chorea.

Investigators have used MRI to examine the brains of patients with Sydenham chorea to determine the etiology of the movement, speech and behavioral issues. One of the earliest reports of brain MRI findings in acute Sydenham chorea demonstrated increased signal intensity in the caudate nucleus, a component of the basal ganglia, with associated edema and shifting of brain matter.[61] This appeared to correlate with pathologic findings seen in varying case series which show blood vessel inflammation, occlusion and necrosis in early disease, and degenerative changes in recurrent chorea.[61,62] Subsequent case series have demonstrated acute changes in the caudate nucleus (some of which progressed to cystic changes on subsequent studies)[63] and others with lesions in the subcortical white matter, which may be the cause of speech and behavioral symptoms.[64]

Table 2 Antibiotic regimens for treatment of group A streptococcal pharyngeal infections.

Antibiotic	Dose	Duration
Penicillin V	250 mg by mouth 2 to 3 times daily (≤27 kg) or 500 mg by mouth 2 to 3 times daily (>27 kg)	10 days
Benzathine penicillin G	600,000 units intramuscular (≤27 kg) or 1,200,000 units intramuscular (>27 kg)	Once
Amoxicillin	50 mg/kg by mouth daily	10 days
Cephalosporin[a] (first generation)	Drug-dependent	10 days
Clindamycin[a]	20 mg/kg/day divided in 3 doses by mouth	10 days
Clarithromycin[a]	15 mg/kg/day divided in 2 doses by mouth	10 days
Azithromycin[a]	12 mg/kg by mouth daily	5 days

Notes: [a]In penicillin-allergic patients. Note, up to 5% of patients allergic to penicillin may also be allergic to cephalosporins.
Source: American Heart Association, Inc.[66]

Treatment
Primary prevention
There are several approaches to reduce the impact of ARF. The first line is primary prevention through the recognition of GABHS pharyngitis and treatment with appropriate antibiotics. Antibiotic therapy initiated within 9 days of onset of pharyngitis is effective in preventing ARF.[65,66] Oral penicillin V is still the first line treatment in patients whom compliance can be expected, and there has never been documentation of GABHS isolates that are resistant to penicillin. For patients in whom compliance with an oral regimen is a problem, a single intramuscular dose of benzathine penicillin G (BPG) can be given at the time of GABHS pharyngitis diagnosis. Patients that have a hypersensitivity to penicillin may be treated with a first-generation cephalosporin, but as many as 5% may also be allergic to cephalosporins. Macrolides, including erythromycin, clarithromycin, and azithromycin, are another alternative, although there have been GABHS strains that demonstrate macrolide resistance. Fluoroquinolones, tetracyclines, and sulfonamides are not recommended to treat GABHS pharyngitis.[65,66] Full details of antibiotic treatments for GABHS pharyngitis are shown in Table 2.

Another intriguing area of research for the past 40 years in ARF prevention is GABHS vaccine development. While there are many potential vaccine candidates, the extracellular M-protein on the surface of GABHS cells has become the primary target, and there are currently 4 vaccines in development targeting the M-protein.[67,68] Part of the complexity in vaccine development is the high variability
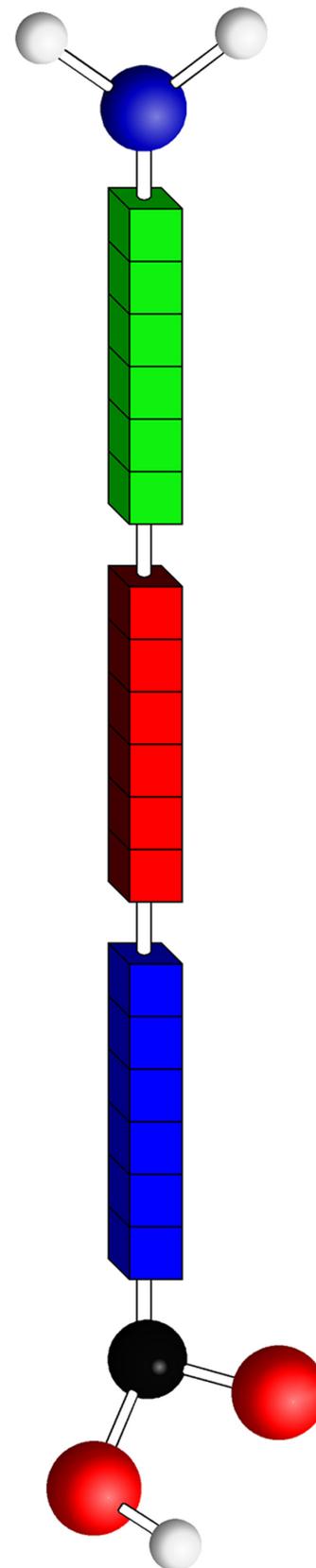

Figure 3 Schematic drawing of the M-protein structure with the conserved (blue), variable (red), and hypervariable (green) regions. Note that the conserved region is closest to the cell membrane.

of the M-proteins, with over 150 M-types identified. Figure 3 shows a schematic of the structure of the M-protein, with conserved, variable, and hypervariable regions. The hypervariable region is exposed to the host immune system and is the portion that distinguishes each M subtype. For the 26-valent GABHS vaccine, the decision about which M-types to include was based on the United States Centers for Disease Control's Active Bacterial Core Surveillance of the Emerging Infections Program Network. The 26 chosen strains were those associated with pharyngitis, invasive disease, and ARF, so-called "rheumatogenic" strains.[69] It is important to note that these strains are based only on data from the United States, which will be discussed more later. The other three M-protein-based vaccines in development target the conserved region of the M-protein, and are likely to provide protection against a wider range of M-types.[68] Since ARF is thought to be due to an autoimmune response to the M-protein and molecular mimicry of the heart valve tissue, there is concern that vaccination could actually cause ARF. This was seen in an early M-protein vaccine trial in the 1960s where all patients receiving the vaccine developed antistreptococcal antibodies, but 3 of 21 also developed ARF, compared to 5 of 447 controls.[70,71]

Acute treatment

Salicylate therapy for the symptoms of ARF was first attempted successfully by Maclagan in 1876.[72,73] Since then, a variety of treatments have also been attempted for ARF, including irradiation of the heart,[74] administration of ascorbic acid and orange juice,[75] or heparin,[76] and prolonged confinement to a hyperoxic chamber.[77] While aspirin has remained the mainstay of ARF therapy, the exact action of effect is unclear, but seems to be related to the anti-inflammatory properties. This has prompted the study of other anti-inflammatory medications.

A large multi-center study in the United States and United Kingdom in 1955 compared the efficacy of aspirin, cortisone, and adrenocorticotropic hormone for the acute treatment of the symptoms of ARF. They found that there was no difference in final outcomes; the hormonal treatments caused more rapid resolution of some symptoms, but at the cost of higher recurrence rates.[78] A more recent meta-analysis confirmed these results and found no significant reduction in the development of RHD with corticosteroids compared to aspirin.[79] Given the higher likelihood of side effects from steroid treatment, aspirin has remained the first line treatment for uncomplicated ARF.[21] Treatment with aspirin usually causes marked improvement in the joint manifestations of ARF within 24 to 48 hours, which can help distinguish ARF from other arthritides which do not resolve as quickly. For those who cannot tolerate aspirin, naproxen has been used as an alternative anti-inflammatory agent.[80,81] Some groups do recommend the use of corticosteroids for carditis in patients who are in severe heart failure.[21,22] Anti-inflammatory medications are given until the inflammatory markers normalize, usually 4 to 6 weeks.

There have been studies showing decreased severity and duration of chorea with prednisone therapy.[82] Paz and colleagues[82] performed a placebo-controlled study on a group of 37 children with Sydenham chorea, treated 22 with prednisone, and found a quicker resolution of chorea symptoms in the treatment group. Given the inflammatory changes seen on pathologic specimens,[61,62] corticosteroid treatment for chorea is a logical choice. However, the progression to degenerative changes seen in recurrent chorea makes corticosteroids less likely to be of any benefit in this group.

Secondary prophylaxis

Those patients who develop ARF are at high risk to develop subsequent attacks when infected with GABHS, and so this population is best treated with secondary antibiotic prophylaxis after their initial attack (Table 3). Patients who have recurrences of ARF are at risk to develop carditis, if they had not already, or worsen existing valve damage. Antibiotic choices are similar to those for GABHS pharyngitis. Secondary antibiotic prophylaxis is only effective when there is high compliance,[66,83] so many healthcare providers prescribe intramuscular BPG every 4 weeks to ensure adequate serum penicillin levels. Studies in areas highly endemic for ARF have found that BPG dosed every 3 weeks provides better prevention of recurrent ARF.[84] If patients are compliant with oral regimens, these can be equally effective.

Secondary antibiotic prophylaxis should be given to individuals most at risk for GABHS pharyngeal infections. These include children, people living in crowded conditions

Table 3 Antibiotic regimen for secondary prophylaxis of acute rheumatic fever.

Antibiotic	Dose
Benzathine penicillin G	600,000 units intramuscular (≤27 kg) or 1,200,000 units intramuscular (>27 kg) Every 4 weeks (3 weeks in high-risk areas/populations)
Penicillin V	250 mg by mouth twice daily
Sulfadiazine	0.5 g by mouth daily (≤27 kg) or 1 g by mouth daily (>27 kg)
Macrolide[a]	Drug-dependent

Notes: [a]In penicillin-allergic patients. Note, up to 5% of patients allergic to penicillin may also be allergic to cephalosporins.
Source: American Heart Association, Inc.[66]

Table 4 Reported incidence of acute rheumatic fever (ARF) (per 100,000 persons) from 1930 through 1970

Years	Country	Subgroup	ARF (/100,000)
1930–1964	Sweden[85]		25 → 1.3
1935–1949	United States (Minnesota)[86]		35–65
1948–1953	England (Bristol/Sheffield)[87]		25.5–55
1949–1961	United States (Colorado)[88]		12–14
1950	Costa Rica[89]		120
1952	Peru[90]		27
1952–1957	Sri Lanka[91]		112
1960–1964	United States (Maryland)[92]		15.6
1960–1964	United States (Utah)[93]		4.7–6.4
1963–1965	United States (New York)[94]	African Americans	47
1963–1965	United States (New York)[94]	Puerto Ricans	78
1963–1965	United States (New York)[94]	Whites	23
1963–1969	United States (Tennessee)[95]	African Americans	44.4
1963–1969	United States (Tennessee)[95]	Whites	21.9
1966	Denmark[85]		1.5
1965–1966	Fiji[96]	Fijians	13
1965–1966	Fiji[96]	Indians	140
1970	United States (Arizona)[97]	Papago tribe	92

(military recruits, college students), parents, teachers, and healthcare workers. The American Heart Association guidelines state that individuals who have had ARF without carditis should be treated until the age of 21 years or 5 years after their last attack, whichever is longer. Those with RHD should be treated until 40 years of age or 10 years after their last attack, whichever is longer. The most important component of these guidelines is the need to assess each patient's clinical situation to determine if they have continued high-risk exposure to GABHS which could warrant lifelong prophylaxis. It is also recommended to continue prophylaxis after heart valve

Table 5 Reported prevalence of rheumatic heart disease (RHD) (per 1000 persons) from 1935 through 1970

Years	Country	RHD (/1000)
1935–1964	United States (Minnesota)[86]	20.6 → 12
1949–1951	United States (Colorado)[88]	6.7
1958–1961	Japan[98]	4.6 → 2.1
1961	USSR[99]	10–30
1964–1965	Pakistan (Karachi)[100]	1.8
1966	India (Chandigarh)[101]	1.8
1970	Taiwan (Taipei)[102]	1.4
1970	Uruguay[103]	1

replacement surgery, as any of the four cardiac valves can be affected by ARF.[65,66]

Results

Of the 164 articles reviewed for ARF incidence and RHD prevalence data, 85 utilized population-based screening, national health registries, prospective disease surveillance, surgical series, or autopsy series. Seventy-nine studies were retrospective reviews of hospital admissions or discharges for ARF or RHD, data from specialty referral clinics, or studies from which the data collection methods could not be determined. In order to maximize the available data, all studies were included.

The literature review revealed data on the incidence and/or prevalence of ARF and RHD in 100 countries around the world. Tables 4 and 5 show the reported incidence of ARF and prevalence of RHD for the era before 1970. Figures 4 through 7 present the incidence of ARF and prevalence of RHD during the 1970 to 1990 and 1991 to present eras.

Figures 8 and 9 are graphs of the trend of ARF incidence and RHD prevalence for each WHO Region. The reported incidence of ARF is decreasing in all WHO Regions except for the Americas where it appears to be increasing slightly and the Western Pacific, where it appears to be steadily increasing. The reported prevalence of RHD is increasing in all regions except for Europe, where it appears to be decreasing.

Table 6 shows the percentages of patients with the Major and Minor criteria for each WHO region and for all reported studies combined. There was a slight male predominance in all ARF cases, and the only significant difference between regions was a higher male predominance in Southeast Asia compared to the Western Pacific ($P = 0.049$). Overall, carditis occurred in 60% of cases, but the Americas had significantly fewer cases than the Western Pacific or Southeast Asia ($P = 0.005$ and 0.019, respectively). Arthritis also occurred in 60% of all cases and Southeast Asia had significantly fewer cases than the Americas, Europe and the Eastern Mediterranean ($P = 0.002$, 0.011 and 0.013, respectively). There were more cases of erythema marginatum in the Americas than in Southeast Asia ($P = 0.015$), and in the Western Pacific than in both the Eastern Mediterranean and Southeast Asia ($P = 0.015$ and 0.003, respectively). The Americas also had more cases of chorea than the Eastern Mediterranean ($P = 0.025$). Fever and an elevated ESR were reported less often in Africa than any of the other regions, and ESR elevation was less in Southeast Asia than in the Eastern Mediterranean and Western Pacific ($P = 0.019$ and 0.041, respectively). Elevated
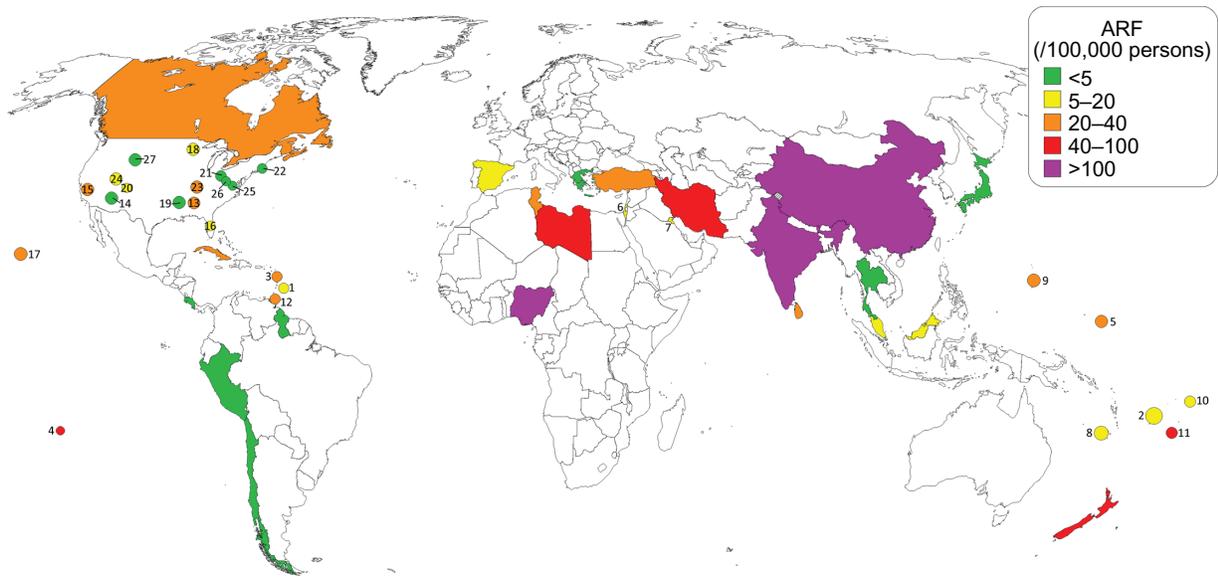
Figure 4 Map showing reported worldwide incidence of ARF from 1970 through 1990.[86,97,104-156] (1) Barbados,[104,105] (2) Fiji,[112] (3) French Antilles,[113] (4) French Polynesia,[112] (5) Federated States of Micronesia,[114] (6) Israel,[120] (7) Kuwait,[123-125] (8) New Caledonia,[112] (9) Northern Mariana Islands,[133] (10) Samoa,[112] (11) Tonga,[112,136] (12) Trinidad,[137] (13) Alabama,[140] (14) Arizona,[97] (15) California,[141,142] (16) Florida,[143] (17) Hawaii,[144-146] (18) Minnesota,[86] (19) Mississippi,[147] (20) Navajo Reservation,[148] (21) Ohio,[149,150] (22) Rhode Island, [151] (23) Tennessee,[152] (24)Utah,[93] (25) Virginia,[153] (26) West Virginia,[154,155] (27) Wyoming.[97]

ASO titer was more common in the Americas, Europe, Eastern Mediterranean, and Western Pacific than in Africa ($P = 0.002$, 0.022, <0.001, and 0.036, respectively), and in the Americas and Eastern Mediterranean than in Southeast Asia ($P = 0.026$ and 0.005, respectively). Regional ARF recurrence rates ranged from 8% to 34%, with Europe having significantly fewer recurrences than the Americas, Eastern Mediterranean, Western Pacific, and Southeast Asia ($P = 0.013$, 0.004, 0.025, and 0.001, respectively); Africa had

fewer recurrences than Southeast Asia ($P = 0.049$). There was no difference in subcutaneous nodules, arthralgia, or first-degree heart block between all 6 regions. There were not enough data available to compare differences in Major and Minor criteria between the two eras to evaluate for changes in presenting Jones criteria over time.

The reported M-types are presented in Figure 10, showing M-types from developing nations (Figure 10a), developed nations (Figure 10b), and both combined (Figure 10c). For
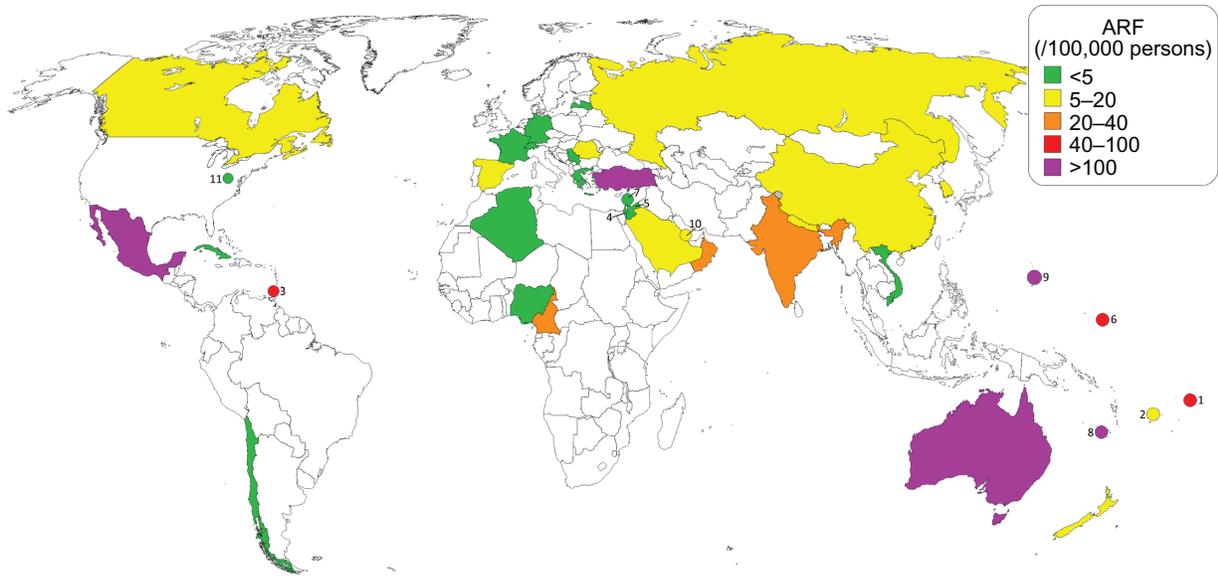

Figure 5 Map showing reported worldwide incidence of ARF from 1991 through present.[40, 108, 111, 115, 120, 139, 156-200] (1) American Samoa,[159,192] (2) Fiji,[169-171] (3) Grenada,[175] (4) Israel,[120,178] (5) Jordan,[179] (6) Kosrae, Federated States of Micronesia,[181] (7) Lebanon,[182] (8) New Caledonia,[185] (9) Northern Mariana Islands,[133] (10) Qatar,[190] (11) West Virginia.[199]
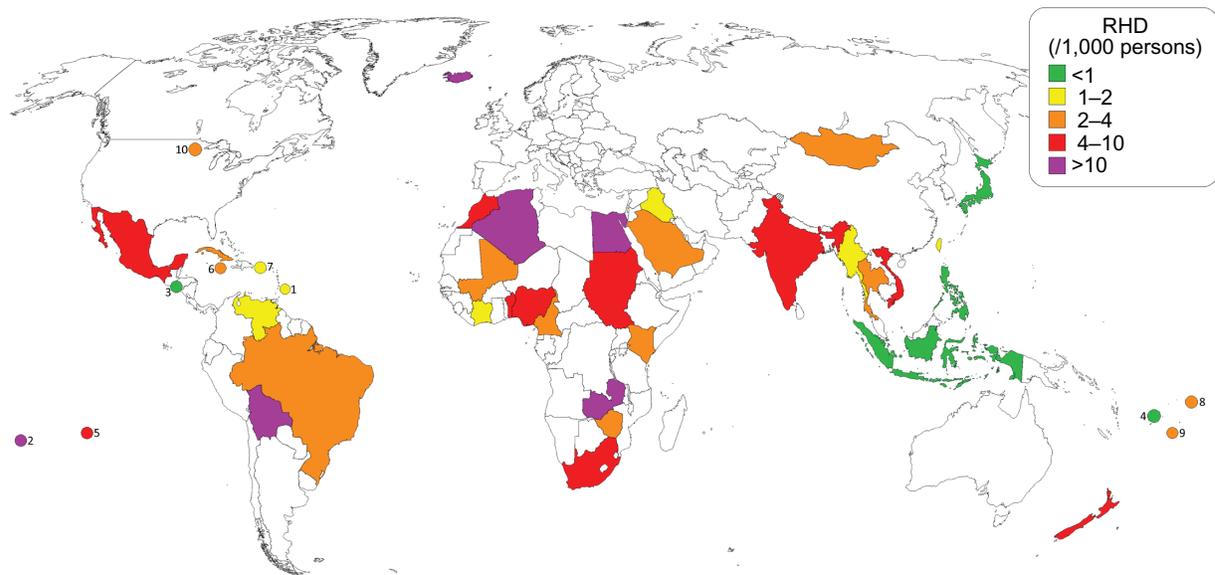
Figure 6 Map showing reported worldwide prevalence of RHD from 1970 through 1990.[14,21,86,90,99,102-104,111,112,118,128,132,136,201-216] (1) Barbados,[104] (2) Cook Islands,[21] (3) El Salvador,[202] (4) Fiji,[112] (5) French Polynesia,[112] (6) Jamaica,[202] (7) Puerto Rico,[103] (8) Samoa,[112] (9) Tonga,[112,136] (10) Minnesota.[86]

comparison, in Figure 10 the 26 M-types present in the GABHS vaccine currently being tested are noted by an asterisk.[69,241]

Discussion

This is the most comprehensive review of the incidence and prevalence of ARF and RHD in the English literature to date. The inherent limitations to the methods of many reviewed studies, especially those presenting data from specialty referral clinics or hospital admissions, do not allow calculation

of exact incidence rates. However, these data make clear that ARF and RHD still exist in significant numbers around the world, which is a disappointment from a public health standpoint.

As might be expected, practice patterns for ARF diagnosis vary across countries. In Africa, where public health resources are limited, only 50% of patients diagnosed with ARF had laboratory evidence of a recent streptococcal infection demonstrated by an elevated or rising ASO titer. All patients diagnosed with ARF were treated accordingly.
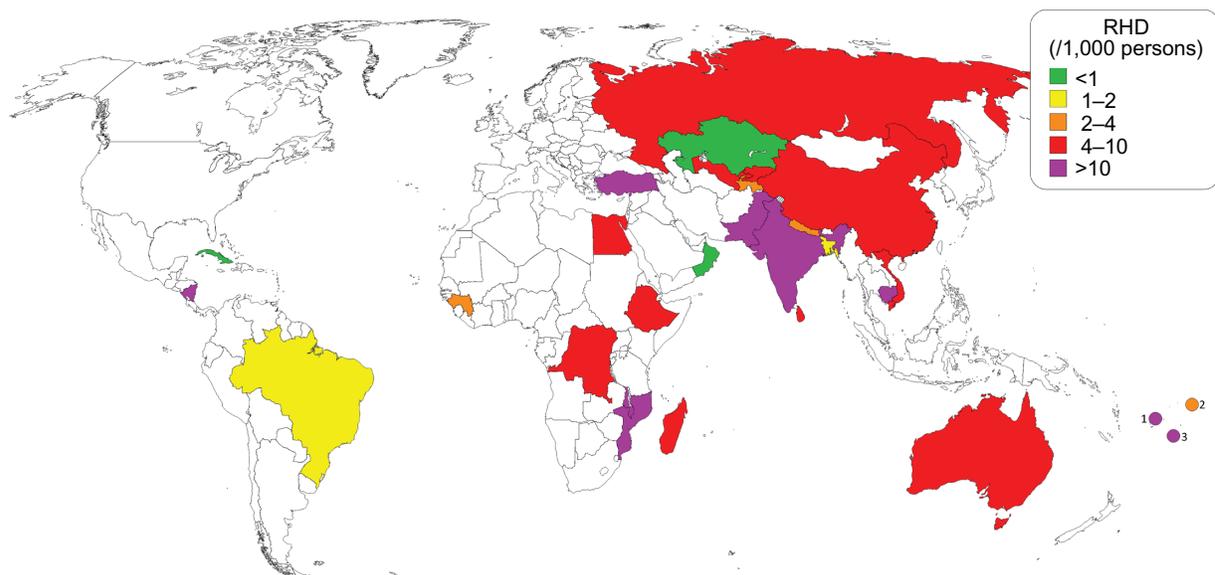

Figure 7 Map showing reported worldwide prevalence of RHD from 1991 through present.[2-6,21,111,160,168,169,176,177,189,191,192,197,217-240] (1) Fiji,[169,228] (2) Samoa,[192] (3) Tonga.[3]
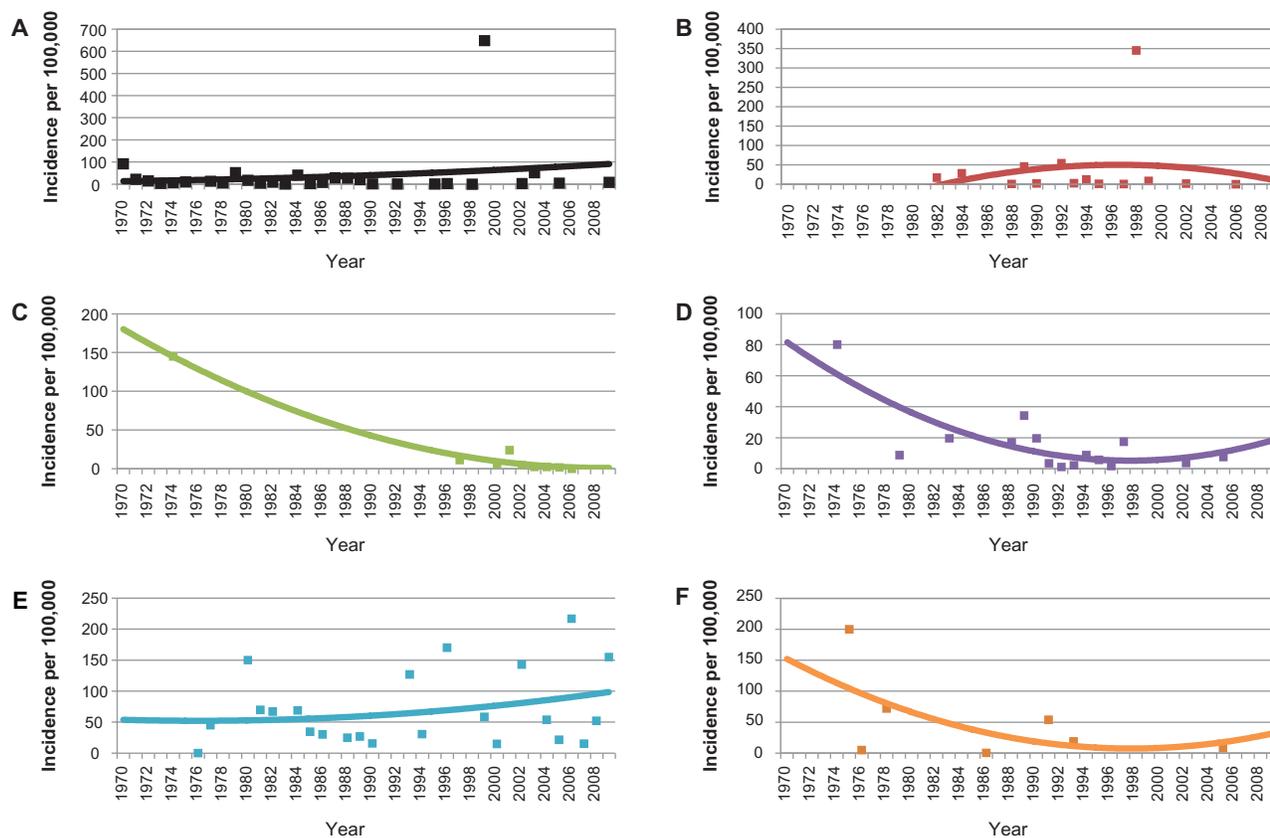
Figure 8 Trends of acute rheumatic fever incidence per 100,000 persons for each WHO region, **A)** The Americas, **B)** Europe, **C)** Africa, **D)** Eastern Mediterranean, **E)** Western Pacific, and **F)** Southeast Asia. Points represent reported incidence from the literature.

Similar practice patterns can be noted in the other poorer WHO regions – Western Pacific and Southeast Asia. Because of the endemic nature of ARF in these regions and the marked impact of progression to chronic RHD, it is reasonable to be aggressive with ARF diagnosis and treatment.

The decrease in ARF incidence is consistent with prior studies that have shown the incidence to be decreasing since the early 20th century. This trend has been attributed to improved living conditions, the use of antibiotics for GABHS pharyngitis and possibly shifting GABHS serotypes. The upward trend in our calculated incidence of ARF in the Americas is likely due to the high incidence reported from Mexico in 1995, which is easily seen as an outlier in the maps in Figures 4 and 6. The apparent increase in incidence in the Western Pacific is more likely improved recognition and reporting of ARF in this region. The reported incidence is only now approaching an average 100/100,000 people, which is likely what the true incidence has been. One possibility for the high incidence of ARF in the Western Pacific region is that many of the countries are small island nations. These countries have small, relatively

isolated populations, and so even a small outbreak of ARF can be calculated as a high incidence level, given relatively small denominators.[133,161]

The prevalence of RHD appears to be increasing worldwide. Given that the incidence of ARF has been decreasing in most regions, it is not likely due to increases in the disease. Major advances in medical and surgical treatments for RHD have led to increased survival, which has contributed to an increased prevalence of RHD. RHD is also more rigorously sought out, and newer studies relying on echocardiography to enhance the diagnosis of RHD have shown that subclinical carditis exists at rates up to 10 times higher than that diagnosed by examination alone.[2–6] Recognition of subclinical carditis will identify those children who would benefit from secondary antibiotic prophylaxis and hopefully prevent the progression to clinically significant RHD. Population-wide echocardiographic screenings may be subject to length time bias or pseudodisease, and the children diagnosed are likely to be among the majority of ARF patients in whom carditis resolves within a year of initial attack. Nevertheless, their increased likelihood
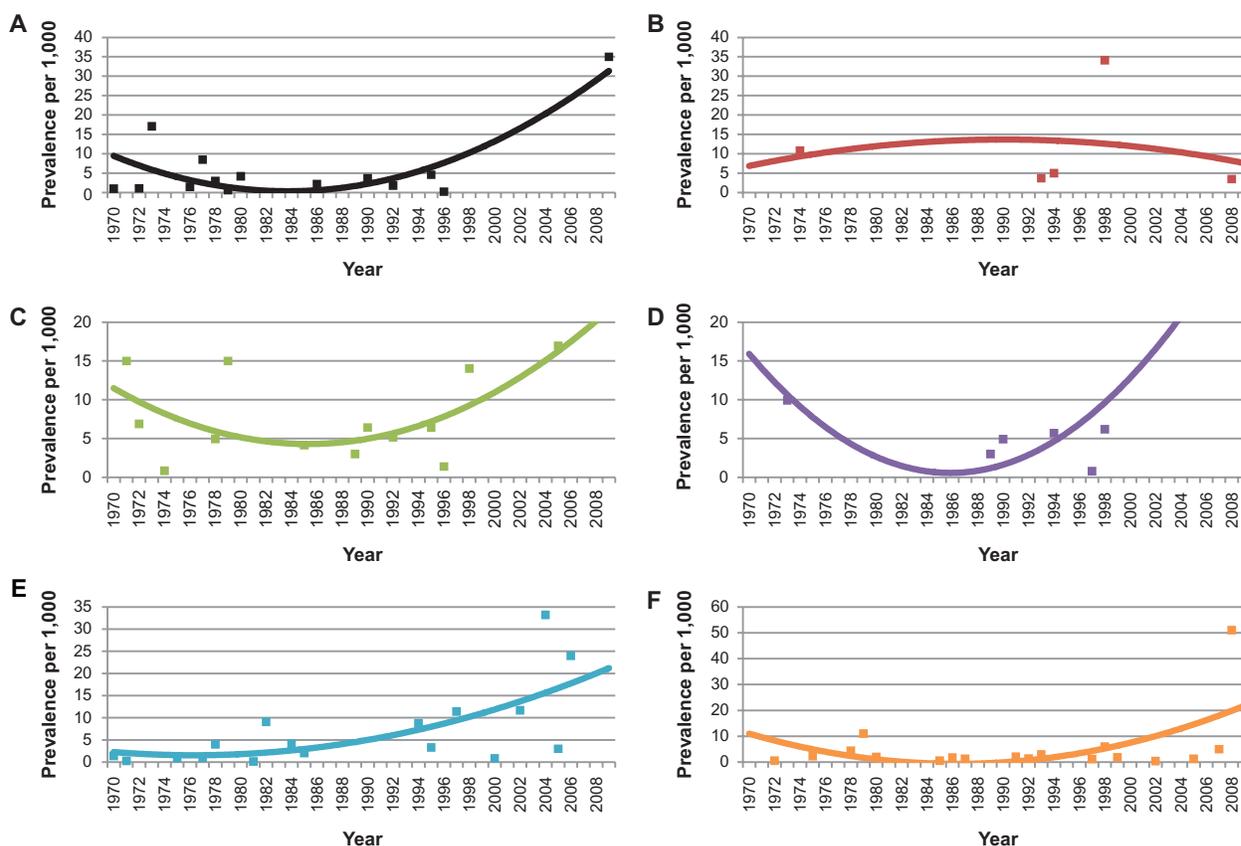
Figure 9 Trends of rheumatic heart disease prevalence per 1000 persons for each WHO region, **A**) The Americas, **B**) Europe, **C**) Africa, **D**) Eastern Mediterranean, **E**) Western Pacific, and **F**) Southeast Asia. Points represent reported prevalence from the literature.

of recurrent ARF, and worsening of prior valvar lesions, makes it appropriate that these children receive secondary antibiotic prophylaxis.

Given the relative ease and low cost of GABHS pharyngitis treatment to prevent ARF occurrence, there is little excuse for hundreds of thousands of new cases of ARF annually. Authors cite varying reasons such as patients not seeking care for pharyngitis, poor compliance with

antimicrobial regimens, or even ARF without a clinically apparent preceding sore throat as missed opportunities to prevent ARF.[242,243] A recent meta-analysis of the treatment of GABHS pharyngitis to prevent ARF concluded that there would be an approximately 60% reduction in cases of ARF if pharyngitis was appropriately treated, especially in endemic areas.[243] These are similar to Gordis' findings from the 1970s in Baltimore.[242] Implementing systematic sur-

Table 6 Percentage of major and minor criteria by WHO region and for all reported studies

WHO region	Males	Recurrences	Major criteria					Minor criteria				
			Carditis	Arthritis	EM	Chorea	Nodules	Arthralgia	Fever	↑ PR	ESR	ASO
The Americas	54.7%	22.0%	52.8%	64.4%	7.8%	15.3%	3.8%	40.9%	63.9%	23.3%	84.2%	79.4%
Europe	54.7%	7.9%	62.0%	65.7%	5.5%	12.3%	8.0%	43.1%	68.9%	26.3%	81.5%	78.3%
Africa	50.1%	17.9%	63.3%	48.9%	1.7%	8.8%	4.8%	55.5%	35.4%	22.7%	52.9%	48.7%
Eastern Mediterranean	54.4%	27.9%	60.3%	63.5%	2.8%	8.0%	1.6%	34.5%	74.8%	20.3%	90.5%	86.9%
Western Pacific	48.2%	22.6%	67.5%	54.3%	11.0%	11.7%	1.5%	35.1%	68.4%	24.7%	91.0%	72.3%
Southeast Asia	57.4%	33.9%	66.0%	46.0%	0.8%	15.4%	4.4%	45.5%	71.3%	28.9%	71.9%	60.9%
All	53.7%	21.9%	59.5%	59.3%	5.9%	12.9%	3.7%	40.7%	65.6%	24.1%	81.4%	75.3%

Note: Proportions are restricted to acute rheumatic fever patients.
Abbreviations: EM, erythema marginatum; ↑ PR, prolonged PR interval on ECG; ESR, increased erythrocyte sedimentation rate; ASO, elevated antistreptolysin O titer.
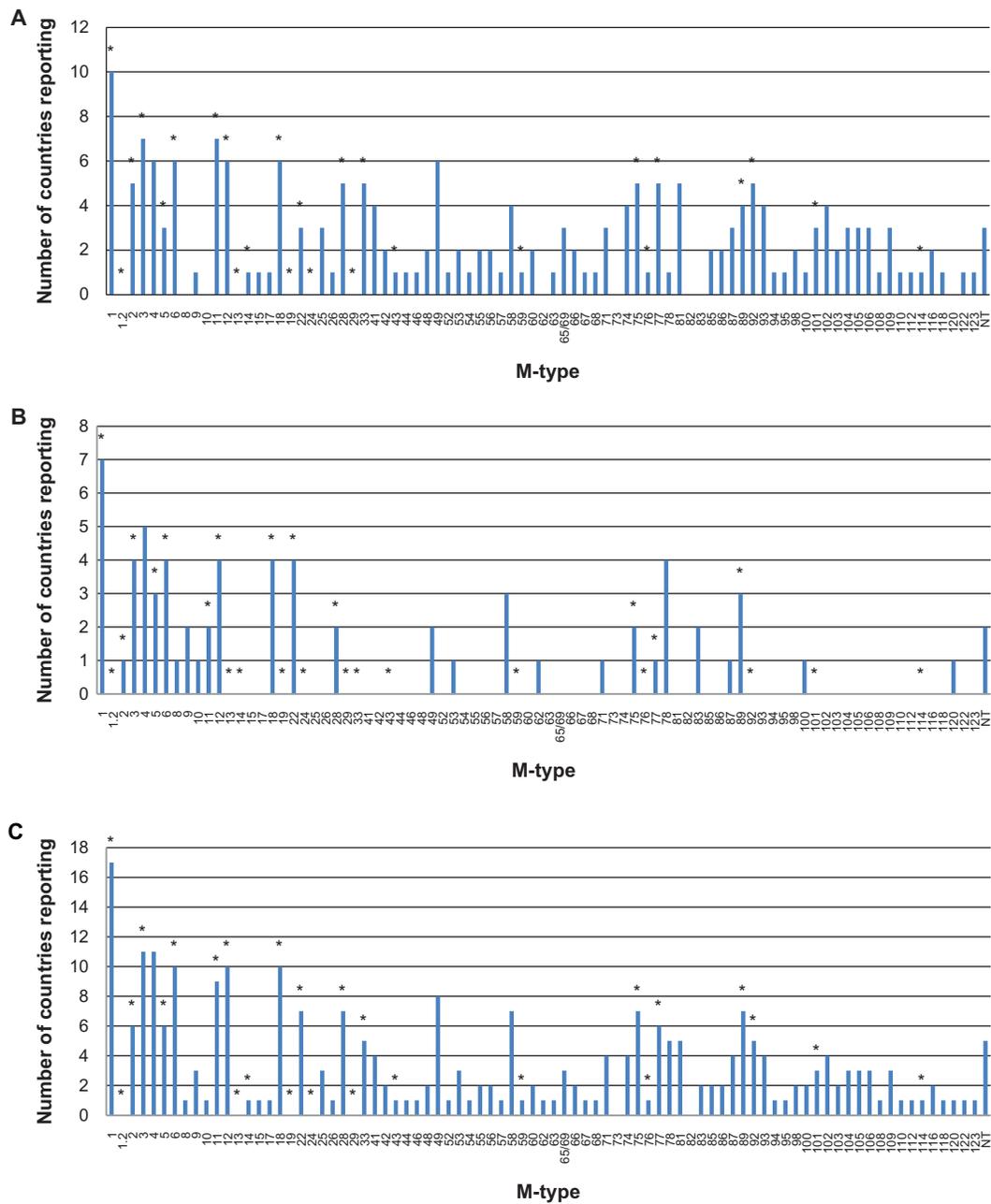
Figure 10 Number of reported occurrences of each streptococcal M-type in **A**) developing nations, **B**) developed nations, and **C**) both combined.
Note: *denotes M-types contained in 26-valent GABHS vaccine.
Abbreviation: NT, nontypeable.

veillance and treatment of GABHS pharyngitis, particularly through school-based programs, is crucial to the control and prevention of ARF.[244] In highly endemic areas, some providers choose to empirically treat patients in the 5- to 15-year age range with fever and complaints of sore throat, even without any laboratory evidence of GABHS infection (M.D.S., personal communication). With the low risk of side effects or induction of antibiotic resistance with penicillin therapy compared with the significant risk associated with ARF, this strategy may be justified.

The likelihood of genetic susceptibility to ARF is high, given the increased occurrence of ARF among families and monozygotic twins.[28,245] The HLA-D8/17 and HLA-DR7 types are the most represented in the literature among patients with ARF and RHD, but there are still many other HLA alleles that are identified in only single studies.[27–45,245] The variability in reported HLA alleles associated with ARF and RHD could be due to genetic differences in the populations studied or differences in local streptococcal strains. Given the current state of the literature, it is hard

to make generalizations about a single "rheumatic" HLA allele, and there are likely multiple HLA alleles that, in combination, increase an individual's susceptibility to ARF and RHD. This is an area that needs continued research efforts to help target ARF prevention strategies to higher-risk populations.

As discussed previously, the availability of a GABHS vaccine would be the best form of ARF prevention, especially since not all patients report upper respiratory infection symptoms or sore throat before their initial ARF occurrence. However, as shown in Figure 10, the M-types present in the 26-valent GABHS vaccine being developed do not represent many of the M-types found in the developing world. Since we do not know all the possible "rheumatogenic" M-types, not vaccinating against prevalent M-types, such as 49, 58, and 81, may be missing the opportunity to prevent many cases of ARF, especially in developing nations where ARF and RHD are endemic. The vaccines that target the conserved region of the M-protein are likely to provide better protection, but they are all currently in the experimental stage.[68]

Rheumatic fever remains a serious public health problem throughout the world. Despite our major advances in medical technology and understanding, we have not eradicated this disease. While a greater understanding of the detailed mechanisms of disease onset will advance scientific knowledge, it may not matter if one person is more susceptible to developing chorea when exposed to streptococcal M-type 19 or another to developing carditis when exposed to streptococcal M-type 49; in the end, both will develop some form of ARF, and the common denominator is exposure to GABHS. Preventing or providing early treatment for streptococcal infections will be the most important step to worldwide ARF eradication. It is hoped that presenting the continued worldwide problem of ARF and RHD will help promote further study into strategies to reduce the burden of this disease.

Disclosure

The authors report no conflicts of interest.

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