

Socioeconomic burden of rheumatic heart disease: An insightful look at in Indian population

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ABSTRACT

Rheumatic heart disease (RHD) continues to be a major health hazard in most developing countries. RHD describes a group of short-term (acute) and long-term (chronic) heart disorders that occur as a result of acute rheumatic fever (RF). Acute RF is a condition in which the connective tissues of the body, the heart, joints, brain, and skin are swollen. It is usually seen in children who are 5–15 years old pediatric and juvenile mitral stenosis (MS), up to the age group of 12 and 20 years, respectively. Cardiovascular disease morbidity and mortality in young people leading to about 250,000 deaths per year. Risk factors for acute RF include poverty, overcrowding, malnutrition, and maternal educational level and employment. RHD, 1990–2015 used multiple sources of data and epidemiological modeling techniques to estimate the global prevalence of and mortality due to RHD over a period of 25 years. India accounted for the highest estimated number of deaths due to RHD globally in 2015 with over 119,000 people were died. Acute RF and RHD have declined in many parts of the world; they continue to be a major cause of cardiovascular morbidity and mortality in India. This is a tremendous national health burden, and since it mainly affects children and young adults, leads to significant social and economic losses. This necessitates thoughtful examination of the primary prevention of this devastating disease, i.e. better understanding and management of Group A streptococcal pharyngitis.

Keywords: Rheumatic heart disease, epidemiology, heart disorders, rheumatic fever, streptococcal

Introduction

Rheumatic fever (RF) is an inflammatory disease that can involve the heart, joints, skin, and brain.^[1] The disease generally develops 2–4 weeks after a streptococcal throat infection. Signs and symptoms include fever, multiple painful joints, involuntary muscle movements, and occasionally a characteristic non-itchy rash known as erythema marginatum.

RF is common worldwide and responsible for many cases of damaged heart valves. In Western countries, it became fairly rare since the 1960s, probably due to the widespread use of antibiotics to treat *Streptococcus* infections. Rheumatic heart disease (RHD) describes a group of short-term (acute) and long-term (chronic) heart disorders that occur as a result of acute RF. Damage to the heart valves is a common result of RF. It is these damages that lead to the defect in the heart. Acute RF is a condition in which the connective tissues of

the body, the heart, joints, brain, and skin are swollen. It is usually seen in children who are 5–15 years old.

On an average, 60% of those with RF develop heart diseases at a later stage of life. All parts of the heart get damaged due to inflammation. The most affected is generally the mitral valve.

While it has been far less common in the United States since the beginning of the 20th century, there have been a few outbreaks since the 1980s. Although the disease seldom occurs, it is serious and has a case fatality rate of 2–5%.

RF primarily affects children between ages 5 and 17 years and occurs approximately 20 days after strep throat. In up to a third of cases, the underlying strep infection may not have caused any symptoms.

The rate of development of RF in individuals with untreated strep infection is estimated to be 3%. The incidence of recurrence with a subsequent untreated infection is substantially greater (about 50%).^[2] The rate of development is far lower in individuals who have received antibiotic treatment. Persons who have suffered a case of RF have a tendency to develop flare-ups with repeated strep infections.

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Pathophysiology of RHD

RF is a systemic disease affecting the periarteriolar connective tissue and can occur after an untreated Group A beta-hemolytic streptococcal pharyngeal infection. It is believed to be caused by antibody cross-reactivity. This cross-reactivity is a Type II hypersensitivity reaction and is termed molecular mimicry. Usually, self-reactive B cells remain anergic in the periphery without T-cell co-stimulation. During a *Streptococcus* infection, mature antigen presenting cells such as B cells present the bacterial antigen to CD4-T cells which differentiate into helper T₂ cells. Helper T₂ cells subsequently activate the B cells to become plasma cells and induce the production of antibodies against the cell wall of *Streptococcus*. However, the antibodies may also react against the myocardium and joints,^[3] producing the symptoms of RF.

Group A *Streptococcus pyogenes* has a cell wall composed of branched polymers which sometimes contain M protein that is highly antigenic. The antibodies which the immune system generates against the M protein may cross react with cardiac myofiber protein myosin,^[4] heart muscle glycogen, and smooth muscle cells of arteries, inducing cytokine release and tissue destruction. However, the only proven cross-reaction is with perivascular connective tissue (citation needed). This inflammation occurs through direct attachment of complement and Fc receptor-mediated recruitment of neutrophils and macrophages. Characteristic aschoff bodies, composed of swollen eosinophilic collagen surrounded by lymphocytes and macrophages can be seen on light microscopy. The larger macrophages may become anitschkow cells or aschoff giant cells. Acute rheumatic valvular lesions may also involve a cell-mediated immunity reaction as these lesions predominantly contain T-helper cells and macrophages Figure 1.^[5]

Burden of RHD in India

The information regarding the burden of disease comes from hospital data, population-based studies, and school surveys. Hospital-based data between 1945 and 1963 indicated that anywhere from 20% to 50% hospital admissions for cardiac patients were for RHD.

Since the hospital-based data do not represent the population of the region, there is a bias toward the worst affected and those seeking admission for procedures. Additional bias may be introduced through changes in the population served by the hospital over many years. With increasing marginalization of the poorer sections of the society, some hospitals may no longer be serving those who are worst affected with RHD. Perhaps, the most important source of bias is the preference of the admitting units. With the emergence of the epidemic of coronary artery disease (CAD), hospital admissions are largely represented by CAD patients in most hospitals.

Population-based surveys for prevalence are very few and scattered. In a study in rural Haryana prevalence of RHD was found to be 2.2/1000 in 5–30-year-old patients.^[6] Mathur *et al.* in a study of the urban population of Agra found RHD in 1.8/1000 in the same age group.^[7] Berry^[8] studied the urban population of Chandigarh and found RHD in 1.23/1000 male and 2.07/1000 in the female

population of all age groups. A recent Indian Council of Medical Research (ICMR) study (between 2000 and 2010) in 10 different, mostly urban, locations of the country found the prevalence to range from 0.2 to 1.1/1000 for RHD and 0.0007 to 0.2/1000 for RF.^[9] ICMR has conducted three school-based surveys in children 5–14 year in age over a period of 40 years between 1970 and 2010. The first survey from 1972 to 1975 was in schools at Agra, Alleppy, Bombay (Mumbai), Delhi, and Hyderabad. The second from 1984 to 1987 included schools at Delhi, Varanasi, and Vellore. The third study included children from 10 centers in the country located at Shimla, Jammu, Chandigarh, Jodhpur, Indore, Kochi, Wayanad, Mumbai, Vellore, and Dibrugarh. It has a wider coverage but not of the whole country. In the first study (1972–1975), 1,33,000 children were evaluated and the prevalence of RHD varied from 0.8 to 11/1000, overall 5.3/1000. The second study (1984–1987) included 53,786 children and the prevalence ranged from 1.0 to 5.6/1000 overall 2.9/1000. The third and the largest study included 1,76,904 school children with a prevalence varying from 0.13 to 1.5/1000 (overall 0.9/1000) in the 5–14 years age range.^[9] Acute RF and RHD have declined in many parts of the world, they continue to be a major cause of cardiovascular morbidity and mortality in India. If one assumes an attack rate of RF of 0.3–3% of all streptococcal sore throats,^[10,11] then there would be between 50,000 and 500,000 new cases of acute RF in India every year. These figures do not account for asymptomatic and subclinical (SC) streptococcal pharyngitis and thus, the actual numbers may be even higher. According to recent epidemiological surveys among school children, the prevalence of RHD varies from 1 to 5.4/1000 school-aged children and the incidence of acute RF varies from 0.2 to 0.75/1000 school-age children 5–15 years of age.^[12–14] Using the 2001 National Census Data information that 23.6% of the total population of India (1027 million) is between 5 and 15 years of age,^[15] one may estimate that approximately 600,000 children <15 years of age are currently suffering from chronic RHD, and that approximately 1,21,000 children are newly diagnosed with acute RF every year. This is a tremendous national health burden, and since it mainly affects children and young adults, leads to significant social and economic losses. This necessitates thoughtful examination of the primary prevention of this devastating disease, i.e., better understanding and management of Group A streptococcal (GAS) pharyngitis.

Prevalence of RHD

The data suggest a progressive decline in RHD from 5.3 to 2.9 to below 1.0/1000 between 1970 and 2010. In the last study, echocardiographic evaluation was performed in all children clinically diagnosed to have a heart murmur and children with congenital heart disease could be excluded from the study. In a study on 1,18,212 schoolchildren 4–18 years of age, a heart murmur was found in 389 normal children. Echo evaluation identified 61 children with RHD giving a prevalence of 0.5/1000 children in Uttar Pradesh^[16] studies from Punjab, Gujarat, Rajasthan, Uttar Pradesh and Tamil Nadu have found the prevalence to range from 0.67 to 4.54/1000 children. The figures are variable but suggest a decline in the prevalence of RHD over time, however, whether they identify a real decline in prevalence is a difficult question to answer. At the same time, the

addition of echocardiographic RHD surveys of normal children has introduced a new dimension to the assessment of disease burden. Most available echocardiographic evaluation studies for the presence of RHD in school children suggest more than 10–20 times higher prevalence of clinically “silent” RHD the reliability or acceptability of the prevalence data based on clinical evaluation alone is not known with certainty. Further, the echocardiographic diagnosis has fallacies and follow up studies of the clinically silent or subclinical RHD are required to establish the significance of disease identified through echocardiography alone Table 1.

Epidemiology of RHD

1. Emerging issues in epidemiology of RHD

Microbial evolution is driven by mutations and underlying mechanisms of genetic exchange, which also play an important role in the emergence and re-emergence of infectious diseases. The reemergence of streptococcal disease is considered within this context. Investigators are pursuing molecular studies to explore the possible genetic relationship between the recent reemerging, virulent GAS and streptococci that caused widespread epidemics of severe scarlet fever in an earlier era. Interest in GAS had waned following the widespread use of penicillin to treat GAS pharyngitis and the concomitant prevention of acute RF (ARF) and RHD. Clinicians also found that, in parallel with this important medical advance, cases of GAS pharyngitis were milder than before. The emergence of new microbes or old editions in new garments stems from genetic evolution. A consequence of this genetic versatility is that microbes can develop new pathogenic vigor, escape population immunity by acquiring new antigens, develop antibiotic or drug resistance, become more transmissible, and escape from the species barrier. Toxigenic *Escherichia coli*, which can cause bloody diarrhea and the uremic syndrome, and GAS, which can cause toxic shock syndrome and the reemergence of RF, very likely have acquired new vigor as a result of genetic events and evolutionary selection. Although this evolution is poorly understood, the “new” GAS agents likely exploit the changing circumstances of the ecosystem brought about by perturbations in nature and human behavior.

2. Risk factors of RHD in India

Risk factors for acute RF include poverty, overcrowding, malnutrition, and maternal educational level and employment.^[17-20] Primordial prevention – i.e., elimination of risk factors within the community at the earliest stage - is linked to socioeconomic development, which directly affects hygiene, access to medical care, and living conditions. In developed nations, the decrease in acute RF incidence started before the antibiotic era and had been attributed to better living conditions in the USA and western Europe.^[21] Although some countries have achieved major economic development, access to hygiene and public health measures are often inequitable across populations.^[22] In any case, economic improvement does not provide complete protection against acute RF and RHD, as shown by disease outbreaks in middle-class children in the USA in the 1990s and in northern Italy more recently Table 2.^[23]

Trends of RHD in India

India accounted for the highest estimated number of deaths due to RHD globally in 2015 with over 119,000 people dying from the ailment, according to a study. India was among the five countries with the largest estimated cases of RHD in 2015, together accounting for 73% of global cases. The number of cases of RHD in India was 13.17 million followed by China with 7.07 million, Pakistan with 2.25 million, Indonesia with 1.18 million, and the Democratic Republic of the Congo with 805,000, according to the study published in *The New England Journal of Medicine*.^[24]

“In 2015, the countries with the highest estimated numbers of deaths due to RHD were India (1,19,100 deaths), China (72,600), and Pakistan (18,900),” it said. The highest estimated age-standardized death rates - more than 10 deaths per 1,00,000 population were in the Solomon Islands, Pakistan, Papua New Guinea, Kiribati, Vanuatu, Fiji, India, Federated States of Micronesia, Marshall Islands, Central African Republic and Lesotho, it added. RHD is a sequela of acute RF, which is usually a disease of poverty associated with overcrowding, poor sanitation and other social determinants of poor health. According to the study, global age-standardized mortality from RHD decreased from 9.2 deaths per 1,00,000 population in 1990 to 4.8 deaths/1,00,000 population in 2015, a decrease of 47.8%. The study, “Global, Regional, and National Burden of RHD, 1990–2015,” estimates 3,47,500 deaths from RHD in 1990 and 3,19,400 deaths in 2015, an 8% decrease.

There is an estimate of the increase in 77% and 82% of RHD since 1990 and 2015, respectively, occurred in locations with an endemic disease pattern. The study titled “Global, Regional, and National Burden of RHD, 1990–2015” used multiple sources of data and epidemiological modeling techniques to estimate the global prevalence of and mortality due to RHD over a 25-year period. The health-related burden of RHD has declined worldwide, but the condition persists in some of the poorest regions in the world, the study concluded.^[24]

Changing Scenario India in Context of RHD

A number of studies have attempted to document RF incidence and RHD prevalence in India. In Future control program vaccine, the ultimate hope for this. For the vaccination, there is a paucity of clinical trials and available in the market are of very high cost.^[25] *StreptAvax*: Sequence of short peptides from the N-terminal region of 26, most common GAS emm- type strains were used in 30 healthy volunteers who showed a significant rise in antibody titer. It has no known cross reaction, but it may not be very helpful in India.^[26] Another Mucosal vaccine based on the conserved region of the protein, a fusion protein containing the C-terminal half of Mprotein expressed in the human oral commensal, *Streptococcus gordonii*.^[26]

Potential Strategies for the Future

Prevention strategies are the most appealing option for sustainable disease control in developing nations. Medical intervention is

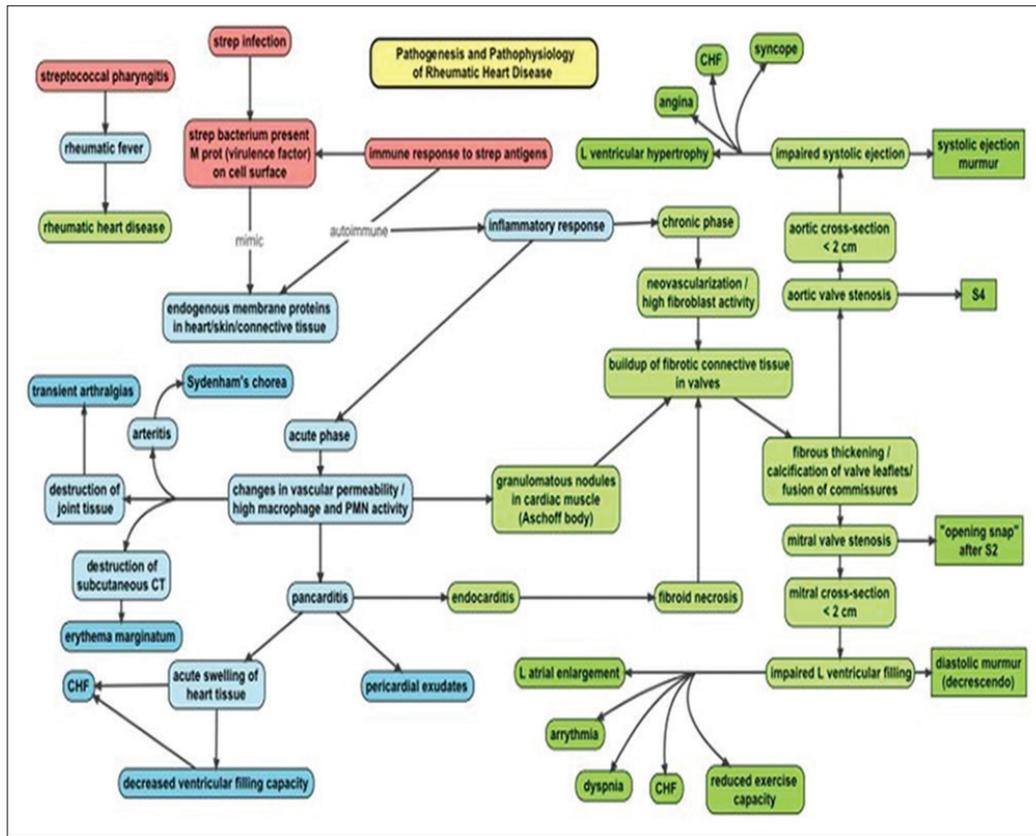


Figure 1: Pathogenesis and pathophysiology of rheumatic heart disease

Table 1: Percentage of RHD in hospital admission

Place	Year	%
Madras	1941	39.5
Calcutta	1965	44.6
Madras	1946	46.8
Bombay	1954	24.7
Delhi	1958	39.1
Shimla	1959	50.6
Agra	1960	35.1
Punjab	1963	27.6

RHD: Rheumatic heart disease

Table 2: Number of cases in RHD in different countries

Country	Number of cases
India	13.17 million
China	7.07 million
Pakistan	2.25 million
Indonesia	1.18 million
Democratic country of Congo (DRC)	805,000

RHD: Rheumatic heart disease

based on the eradication of group A *Streptococcus* with penicillin, which prevents the initial acute RF attack (primary prophylaxis) or disease recurrences (secondary prophylaxis). The efficacy and safety

of antibiotic prophylaxis are well established and should lead to near-complete eradication of advanced RHD when combined with broader changes such as improved living conditions, education, and awareness.^[27-29]

Primordial prevention, i.e., elimination of risk factors within the community at the earliest stage, is linked to socioeconomic development, which directly affects hygiene, access to medical care, and living conditions. In developed nations, the decrease in acute RF incidence started before the antibiotic era and had been attributed to better living conditions in the USA and western Europe.^[21]

Ideally, prophylaxis should prevent the first acute RF attack, particularly if given shortly after a sore throat.^[30] Primary prevention relies on the eradication of GAS carriage through active sore throat screening and by treatment of pharyngitis by oral antibiotics (phenoxymethylpenicillin 250 mg 2 or 3 times daily for patients weighing ≤ 27 kg, phenoxymethylpenicillin 500 mg 3 or 3 times daily for patients weighing > 27 kg; or amoxicillin 50 mg/kg per day for 10 days) or intramuscular antibiotics (benzathinebenzylpenicillin 6,00,000 IU [one injection] for patients weighing ≤ 27 kg, or 1 2,00,000 IU [one injection] for patients weighing > 27 kg).^[31] So far, primary prevention alone as a large-scale strategy has often been neglected in developing countries.^[32] Programs that target subpopulations with a high prevalence of RHD might be more efficient than present practices.^[33]

Conclusion

The incidence of acute RF is higher in India as well as anywhere in the world, and the prevalence of RHD is among the highest in the world. While continuing attention should be paid to increase the cause of disease of poverty, immediate action is needed to improve diagnosis of RHD.

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