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## Review Article

# Rheumatic fever and rheumatic heart disease in Bangladesh: A review

A.K.M. Monwarul Islam<sup>a,\*</sup>, A.A.S. Majumder<sup>b</sup><sup>a</sup> Assistant Professor, Department of Cardiology, Jessore Medical College, Jessore, Bangladesh<sup>b</sup> Director and Professor, National Institute of Cardiovascular Diseases, Dhaka, Ex-Director, National Centre for Control of Rheumatic Fever & Heart Diseases, Dhaka, Bangladesh

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## ABSTRACT

Rheumatic fever (RF) and rheumatic heart disease (RHD) are the most-common cardiovascular disease in young people aged <25 years, globally. They are important contributors to cardiovascular morbidity and mortality in Bangladesh. Classical risk factors, i.e. poverty, overcrowding, ignorance, and insufficient health care services were responsible for the high incidence and prevalence of these diseases over the last century. In concert with the progresses in socioeconomic indicators, advances in health sectors, improved public awareness, and antibiotic prophylaxis, acute RF came into control. However, chronic RHD continues to be prevalent, and the actual disease burden may be much higher. RHD predominantly affects the young adults, seriously incapacitates them, follows a protracted course, gets complicated because of delayed diagnosis and is sometimes maltreated. The treatment is often palliative and expensive. Large-scale epidemiological and clinical researches are needed to formulate evidence-based national policy to tackle this important public health issue in future.

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## 1. Introduction

Rheumatic fever (RF) and rheumatic heart diseases (RHDs) are important medical and public health issues, because they are common and are important causes of cardiovascular morbidity and mortality especially in developing world. Over 15 million people around the world suffer from RHD, which kills hundreds of thousands of people a year, and is the most common acquired heart disease in children and young people in developing countries.<sup>1</sup> Acute RF – the precursor to RHD – results from an abnormal autoimmune response to group A

beta-hemolytic streptococcus (GABHS) infection in a genetically susceptible host. It affects the heart, joints, brain, and subcutaneous tissue; however, when affected, heart valves bear the brunt of RF. Although penicillin is effective in the prevention of the disease, treatment of advanced stages uses up a vast amount of resources, which makes disease management especially challenging in emerging nations.<sup>2</sup>

Bangladesh has been experiencing epidemiological transition from communicable disease to non-communicable disease. The overall mortality has decreased significantly over the couple of decades. But deaths due to chronic diseases, specially the 'fatal four', i.e. cardiovascular disease (CVD),

\* Corresponding author.

E-mail address: [drmonwarbd@yahoo.com](mailto:drmonwarbd@yahoo.com) (A.K.M. Monwarul Islam).<http://dx.doi.org/10.1016/j.ihj.2015.07.039>

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cancer, chronic respiratory disease, and diabetes, are increasing in an alarming rate.<sup>3</sup> RF and RHD are contributors to one of the four, i.e. CVD. In the past few decades, incidence and prevalence of acute RF have decreased much, but chronic RHD continues to be rampant in this population.

## 2. Rationality of the review

Data related to RF and RHD in Bangladesh are often insufficient, suffer from statistical flaws and are not readily available. Many articles were published in local, non-indexed journals which are not available online and difficult to procure. Recognizing these limitations, the present review has been planned to compile the available data on this important public health issue. This review will hopefully stimulate future research and act as a valuable source of information.

## 3. Methods

Data have been collected from the articles available from MEDLINE and BanglaJOL supported by the International Network for the Availability of Scientific Publications (INASP) up to the year 2014. Besides this, local journals which are not available online but recognized by the Bangladesh Medical and Dental Council have also been considered.

## 4. Epidemiology of RF and RHD in Bangladesh

RHD ranks among the leading causes of non-communicable diseases in low-income and middle-income countries and accounts for up to 250,000 premature deaths every year worldwide.<sup>4</sup> In a recent systematic review and meta-analysis including 37 populations in endemic regions around the world, the pooled prevalence of RHD among children and adolescents ( $\geq 5$  years to  $< 18$  years) detected by cardiac auscultation was 2.9 per 1000 people and by echocardiography it was 12.9 per 1000 people, with substantial heterogeneity between individual reports for both screening modalities.<sup>5</sup> Historically, RF and RHD were generally believed to be diseases of temperate climates and rarities in tropical countries. In 1930, RF was reported to be non-existing in this part of the world.<sup>6</sup> In the early 1950s, non-existence of RF in tropical climate was claimed by Paul White, who advised the rheumatic family to take permanent residence in the tropics to avoid RF.<sup>7</sup> Boyd states 'in the tropics, where hemolytic streptococci are rarely found in the throat, scarlet fever is uncommon and RF is very uncommon'.<sup>8</sup> In 1957, Ibrahim quoted that, his medical teachers Drs. D.N. De, J.C. Banerjee, and A.K.M. Abdul Wahed, Professors of Medicine of Calcutta and Dacca Medical Colleges, always state that 'RF is as common in Bengal as in other parts of the world, where its incidence is frequent'.<sup>9</sup> In the course of 5 years from January 1949 to December 1953, out of 19,011 patients admitted in Medical Wards of Dacca Medical College, East Pakistan, acute RF and RHD constituted 606 cases (acute RF 85, RHD 521).<sup>9</sup> The exact incidence and prevalence of RF and RHD in Bangladesh are not known. Only a limited number of small-scale hospital, school, and community surveys are

available. Another limitation is that acute RF, recurrence of RF, and chronic RHD have been described together arbitrarily, and their separate values are often obscure. In the 2nd half of the last century, RF and RHD constituted a significant proportion of admissions in general hospitals, and a lion's share of cardiovascular admissions.<sup>10–12</sup> However, the situation gradually improved. During July 1995 to June 1997, out of 4410 cardiac patients admitted in 13 regional and tertiary care hospitals across the country, 13% were due to RF and RHD.<sup>13</sup> Probably the community prevalence of RF and RHD was first reported in 1976, which was 7.5/1000 in general population, i.e. the second-most prevalent cardiac disease (hypertension 11.0/1000), and even more prevalent than IHD (3.3/1000).<sup>14</sup> In 1984, almost similar prevalence was found in a rural population.<sup>15</sup> Subsequent surveys involving rural,<sup>16</sup> mixed,<sup>17</sup> and urban<sup>18</sup> population found lower prevalence of RF and RHD. High prevalence of RF (43.9/1000) and RHD (5.05/1000) was reported in a school survey involving 4349 children aged 4–17 years in Dhaka City in 1984–1985.<sup>19</sup> Subsequent school surveys revealed lower prevalence.<sup>20–23</sup> Most of these studies suffer from methodological flaws and lack uniformity in criteria used for diagnosis. Over the past 3 decades, like many other parts of the world, the incidence and prevalence of acute RF in Bangladesh decreased; however, RHD continues to be an important public health problem here. Current prevalence of RF and RHD is not exactly known, however, may be  $< 1/1000$  in general population. Recently, conventional and portable echocardiography is being used increasingly in studies concerning RF and RHD, as a result, more and more subclinical cases of RHD are being diagnosed. So, the prevalence of RF and RHD estimated so far may not be accurate, and the true prevalence of RHD may be much higher in Bangladesh as well (Table 1).

Data on prevalence of streptococcal sore throat in Bangladesh are sparse. In a study<sup>24</sup> carried out in 1982–1984, out of 7542 throat swab specimens from sore throat patients, beta hemolytic streptococci (BHS) were found in 20.22%. Anti-streptolysin O (ASO) titer was determined in 5678 cases of this study, 17.11% showed raised titer, i.e.  $> 200$  Todd units. Prevalence of BHS found in subsequent studies ranged from 11 to 33% in different populations<sup>25–30</sup>; 6–21.5% of the BHS belonged to group A.<sup>26–29</sup> Considering these figures, the prevalence of BHS in Bangladeshi children and young adults may be 20% on an average, of which 15% may be of group A. Highest incidence of streptococcal sore throat was found during August to December (Table 2).<sup>31</sup>

## 5. Emerging issues in epidemiology of RF and RHD

Traditionally, RHD was diagnosed by auscultation for a heart murmur with a stethoscope in those with a history of acute RF. Echocardiography, introduced later on, has proven to be more sensitive and specific than auscultation, and introduction of echocardiography in studies on RF and RHD leads to detection and inclusion of previously unrecognized cases of subclinical carditis, which exists at rates several times higher than that diagnosed by examination alone.<sup>32,33</sup> RHD detected on echocardiography without an associated clinically pathological cardiac murmur is referred to as 'subclinical

**Table 1 – Prevalence of RF and RHD in Bangladesh.**

Reference	Year	Place	Age (years)	RF & RHD prevalence	No. screened	Echo	Type of study
Malik <sup>14</sup>	1976	Dhaka City and a village	Different ages	7.5/1000, combined RF and RHD	7062	No	Community project
Hussain <sup>15</sup>	1984	Rural	Different ages	7.8/1000		No	Community project
Ahmed et al. <sup>16</sup>	1991	Rural	5–15	RF 1.2/1000; RHD 1.3/1000	5923	Yes, in selected cases	Community project
Haque et al. <sup>17</sup>	1992	Dhaka City and rural areas	5–15	3.6/1000, combined RF and RHD	Urban 9875, rural 5923	Yes, in selected cases	School and house to house survey
Hossain et al. <sup>18</sup>	2005–2006	Dhaka City	5–22	RF 0.5/1000; RHD 0.4/1000	10,017	Yes, in selected cases	Community project
Banoo et al. <sup>19</sup>	1984–1985	Dhaka City	4–17	RF 43.9/1000; RHD 5.05/1000	4349	No	School survey
Janan <sup>20</sup>	1978–1979	Dhaka City	5–25	RF 8.5/1000	3428	No	School survey; studied RF cases only
Mahmud et al. <sup>21</sup>	1989	Dhaka City	5–18	RF 0.85/1000; RHD 2.8/1000	5011	Yes, in selected cases	School survey
Begum et al. <sup>22</sup>	1990–1991	Dhaka City	5–18	RF 2.37/1000; RHD 0.189/1000	10,538	Yes, in selected cases	School survey
Majumder et al. <sup>23</sup>	2004	Rural	5–16	RF 4.22/1000; RHD 0/1000		No	School survey

RF: rheumatic fever; RHD: rheumatic heart disease.

RHD'. The advent of portable echocardiography raises the possibility that people with previously undiagnosed RHD, including those without a known history of acute RF, can be diagnosed and secondary prophylaxis started at an earlier stage of the illness than previously possible, thus potentially reducing morbidity and mortality.<sup>34</sup> However, despite greatly

improved sensitivity, specificity of portable echocardiography is still a concern, and the natural history of RHD in children with subclinical abnormalities detected by echocardiographic screening remains largely unknown, and long-term follow-up studies are needed.<sup>35</sup> Recently in 2012, World Heart Federation (WHF) proposed new criteria for echocardiographic diagnosis

**Table 2 – Prevalence of streptococcal sore throat in Bangladesh.**

Reference	Year	Place	Age (years)	No. screened	Culture positive for BHS (%)	Group A BHS (% of BHS)	ASO titer
Chowdhury and Rahman <sup>24</sup>	1982–1984	Dhaka City	Different ages	7542	20.22%		17.11% > 200 Todd units
Hussain and Rahman <sup>25</sup>	1987	Dhaka City	Different ages	1510	19.3%		
Rouf et al. <sup>26</sup>	1992	Patients attending NCCRF&HD	5–15	2224	18.3%	20.8%	
Rouf et al. <sup>27</sup>	1992	Dhaka City	5–15; school children	329	33.0%	7.6%	100–300 IU/ml in 88%
Faruq et al. <sup>28</sup>	1993	Dhaka City	School children	601	22%	18.9%	39% of BHS positives has raised ASO titer
Ahmed et al. <sup>29</sup>	1999	Narayanganj	School children	6890 total; 2175 sore throat	19.68% of sore throat cases	21.5%	
Haque et al. <sup>30</sup>	2001	Dhaka	<10	200	11%		

NCCRF&HD: National Centre for Control of Rheumatic Fever and Heart Diseases, Dhaka, Bangladesh; BHS: beta hemolytic streptococcus; ASO: anti-streptolysin O.

of RHD.<sup>34</sup> This endeavor of WHF will hopefully provide standardization of RHD diagnosis, increasing the specificity.

## 6. Risk factors of RF and RHD in Bangladesh

Like other developing countries, Bangladesh has most of the recognized risk factors making her a fertile soil for RF and RHD. Its geographical condition, climate, socio-economic condition, and prevalence of streptococcal infection are as marked as any other country where RF is known to be prevalent.<sup>9</sup>

### 6.1. Poverty

Bangladesh is a developing country with a population of about 153 million. At the time of independence in 1971, the country was desperately poor, and densely populated, with an agrarian economy subject to frequent natural disasters.<sup>36</sup> In 1974 World Atlas ranking of per capita income, Bangladesh came the 2nd lowest, slightly ahead of Rwanda.<sup>37</sup> Henry Kissinger labeled Bangladesh as a country without hope.<sup>38</sup> Poverty and income inequality remain a persistent challenge in Bangladesh. The gross national income per capita is only 2030 (PPP int. \$) whereas the global average is 12,018; 43.3% of the population in Bangladesh lives on <\$1 (PPP int. \$) a day (MDG 1) – which is almost double the global average of 22.7%.<sup>39</sup> According to the Nutrition, Health and Demographic Survey of Bangladesh-2011 (NHDSBD-2011),<sup>40</sup> 14.4% household sometimes and 11.2% household often face food shortage at national level. Among the households experiencing at least some sort of food shortage, 81% households sometimes and 14% households often remain anxious about the next meal. Such a poor background can explain the prevalence of RF and RHD in Bangladesh.

### 6.2. Overcrowding

Bangladesh has one of the highest population densities in the world, with an average of 964 inhabitants per square kilometer; only Singapore and small city-states such as Bahrain or the Vatican have higher figures.<sup>41</sup> Due to financial stringency, people tend to live in a crowded environment. As a result of economic transition, rural people migrate to the cities, often residing in the slums with minimum facilities. Slums now make up about a third of the city corporations, and in 20 years, slums will be half of the city corporations.<sup>42</sup> On an average, each household consists of 4.35 to 5.0 members<sup>40,43–45</sup>; 70% of the households in Bangladesh have 3 to 5 members.<sup>40</sup> One of the most practical indicators of the extent of crowding in households is the number of rooms used for sleeping. Crowding in one sleeping room facilitates the risks of infection. Forty-two percent households use only 1 room, and 35.7% household use 2 rooms for sleeping nationally,<sup>40</sup> with per capita availability of bed room space approximately 5 m<sup>2</sup> (55 square feet).<sup>45</sup> Such an overcrowding makes them prone to streptococcal infection. A retrospective study to see the status of housing and living environment of the patients of RF attending the National Centre for Control of Rheumatic Fever & Heart Diseases (NCCRF&HD), Dhaka, from 1993 to 1996 showed that family comprising of more members, type of residing house especially Kutcha house (houses made from

mud, thatch, or other low-quality materials), and house consisting of less living rooms increases the incidence of RF. Fifty four percent patients out of 477 came from a family comprising of ≥7 members and 41% from a family comprising of 4–6 members; 50.1%, 32.9%, and 17% resides in Kutcha, Pucca (houses made with high quality materials throughout, including the floor, roof, and exterior walls) and semi-Pucca (houses that have fixed walls made up of Pucca material but roof is made up of the material other than those used for Pucca house) house, respectively; 67% and 27.9% of the patients came from the house consisting of 1–2 and 3–4 living rooms, respectively.<sup>46</sup>

### 6.3. Malnutrition

Malnutrition, especially protein energy malnutrition is an important public health problem in Bangladesh. Presence of malnutrition weakens the immune system of the body, making them easy prey to streptococcal infection. Nearly half of children in Bangladesh have chronic malnutrition. Prevalence of stunting (low height-for-age) in children <5 years was 42% in 2010.<sup>47</sup> In the NHDSBD-2011, at national level in children <5 years the prevalence of stunting (low height-for-age) is about 40.2% in both girls and boys, severe stunting 17%; wasting (low weight-for-height) 25.3% in girls and 22.3% in boys, severe wasting 6.5% in girls and 7.2% in boys; and underweight (low weight for age) about 45% in both girls and boys, severe underweight is 17.3% in girls and 15.3% in boys.<sup>40</sup> According to the Household Income and Expenditure Survey 2010 (HIES-2010), per capita per day food intake was 1000 g, protein intake 66.26 g, and total calorie intake 2318.3 kcal.<sup>44</sup> In a case-control study<sup>48</sup> carried out in NCCRF&HD, higher risk of RF was observed for low height for age, low weight for age, low upper arm circumference for age, and low consumption of eggs, milk, chicken, pulses, fruits, and roti (home-made bread). Reduced risk was observed for soybean oil consumption. Also, low serum albumin concentrations and body iron stores were found to increase the risk of acquiring RF in Bangladeshi children.<sup>49</sup>

### 6.4. Inadequate health care facilities

Health care facilities in Bangladesh are often inadequate. In 2011, the percentage of gross domestic product (GDP) allocation for health was 3.8%, which is much lower than the values of low income (5.2%) and global (9.1%) averages. In terms of per capita total expenditure on health at average exchange rate, the country spent USD 27 in 2011; again under half the regional (World Health Organization (WHO) South-East Asia Region) average of USD 69, and far below the global average of USD 1007.<sup>39</sup> Bangladesh is one of the health workforce crisis countries in the world. On a per capita basis, there are fewer practicing physicians in the Bangladesh, i.e. 3.6/10,000 population; the regional (WHO South-East Asia Region) and global averages are 5.6 and 14.1, respectively. The availability of nursing and midwifery personnel is 2.2/10,000 population; the regional (WHO South-East Asia Region) average is 15.3, and global average is 29.2. Also, for 10,000 population, only 6 hospital beds are available.<sup>39</sup> Often the rural people and people residing in slums in cities suffer from scarcity of quality

treatment. The underlying reasons presumably include poverty, ignorance, and difficult commutation. A recent study<sup>50</sup> in a remote rural area in Bangladesh showed that only 47% of the 765 randomly chosen patients sought treatment for their illness from a healthcare provider; out of them, 65% consulted non-graduate village doctors and consultation with graduate (MBBS) doctors was low at 14%. Of the 407 household members who did not seek care for their illness, 40% did not have enough money to consult a healthcare provider.

### 6.5. Ignorance

Besides poverty and scarcity of resources, ignorance appears to play important role in the prevalence of acute RF and RHD in Bangladesh. Literacy rate in Bangladesh is low, 38.22% people have got no education, only 55.08% of those aged  $\geq 5$  years can write a letter for communication.<sup>51</sup> These people often cannot realize the importance of timely proper treatment of ailment, existing healthcare facilities, and their rights, and they easily become the victim of delayed treatment or maltreatment. According to the HIES-2010,<sup>44</sup> the main reason of non-treatment for ailments is the perceived non-serious nature of the disease (56.54%) followed by high cost of treatment (15.57%), and nonsupport from the family (3.89%). Also, 40.21% received treatment from pharmacy/dispensary/compounder followed by private doctor (24.46%) and government doctors in private practice (14.34%). In a study involving rural population, only half (49.8%) of the sore throat cases sought treatment; 38.8% from medicine shops, 27.2% from qualified doctors, 13.6% from hospitals, and 13.6% from homeopathic practitioners.<sup>52</sup> The situation was equally gloomy in a more recent study.<sup>50</sup> Such an attitude favors streptococcal infection getting untreated, resulting in complications, i.e. RF and consequent RHD.

### 6.6. Social stigmata

Social stigmata often hinder to timely proper treatment, especially of chronic RHD. Younger people, especially the females of lower socioeconomic class are mainly affected by chronic RHD. Despite improvement in women empowerment as a whole, females are often neglected in the society; their illness is relatively overlooked; medical attention is often delayed or denied, meanwhile, they are maltreated, and the disease becomes complicated. Sometimes, in case of RF or established RHD, treatment or prophylaxis is not adopted, continued, or is kept confidential during and after marriage. The worst thing is that they may ultimately be divorced.

### 6.7. Genetic factors

The likelihood of genetic susceptibility to acute RF is high, given the increased occurrence of acute RF among families and monozygotic twins. A recent systematic review and meta-analysis of twin studies of concordance of acute RF in order to derive quantitative estimates of the size of the genetic effect, the pooled probandwise concordance risk for acute RF was 44% in monozygotic twins and 12% in dizygotic twins, and the association between zygosity and concordance was strong (odds ratio (OR) 6.39; 95% confidence interval, 3.39–12.06;  $p < 0.001$ ); the estimated heritability across all the studies was

60%.<sup>53</sup> The HLA-D8/17 and HLA-DR7 types are the most represented.<sup>54</sup> The variability in reported HLA alleles associated with acute RF and RHD could be due to genetic differences in the populations studied or differences in local streptococcal strains.<sup>54</sup> However, the contribution of genetics and ethnicity to the high prevalence of RF and RHD in Bangladeshi population has not been studied.

### 6.8. Lack of compliance to secondary prophylaxis

Lack of compliance to secondary prophylaxis of RF and RHD is especially important, because it leads to recurrent acute or clinically silent RF and consequent more chance of development or worsening of chronic RHD. In a study involving 106 patients of acute RF at Dhaka Shishu Hospital in 1987–1989, only 1% used secondary prophylaxis regularly and 9% used irregularly.<sup>55</sup> Another study during 1990–1992 showed that, out of 74 children who received first dose of injectable penicillin for secondary prophylaxis in a hospital, 22.9% never came back for the second dose; 10.8% attended the hospital irregularly because of ignorance (6.75%) and financial stringency (4.05%).<sup>56</sup> Interestingly, in a hospital-based study, secondary prophylaxis was discontinued prematurely by the physicians in 82.92% cases.<sup>57</sup> Recurrences of RF was observed in a study involving 56 cases of RF and RHD, who were on injectable penicillin; after 4 years of prophylaxis, there was 12.5% recurrences, which was more common in case of 4-weekly regimen.<sup>58</sup>

The pattern of risk factors related to RF and RHD in Bangladesh has remained more or less unchanged over decades.<sup>9,59,60</sup> A hospital-based case-control study<sup>59</sup> carried out more than a decade ago found that RF was significantly associated with low income, poor living conditions (substandard house), and poor nutritional status (low height for age). RF and RHD were found to share almost similar risk factors in a more recent study.<sup>60</sup> Women, urban resident, dwellers in brick-built house, having  $>2$  siblings, offspring of working mothers, illiterate mother, and those who did not brush teeth after taking meals were more likely to develop RF and RHD.

## 7. Trends of RF and RHD in Bangladesh

Until recent past, RF was a common disease in Bangladesh, constituting considerable portion of hospital admissions. Classically, the disease affects the children and young adults, most commonly between 5 and 15 years of age; in a hospital-based study in Bangladesh, 90% of the acute RF patients were aged 4–15 years and 3%  $<5$  years.<sup>61</sup> The age reference range for occurrence of RF in Bangladesh was suggested to be 5–22 years in a study.<sup>62</sup> Subsequently, like some other parts of the world, there was a definite trend toward steady decline in incidence and prevalence of RF in the country.<sup>63</sup> On the other hand, despite lower incidence of clinically apparent acute RF, continuing high incidence and prevalence of chronic RHD is a reality. In this population, RHD has a malignant course, and the natural history is accelerated as evidenced by the lower mean age of the patients, younger age for the initial attack of RF, and short interval between the initial attack of RF and onset of symptomatic valvular disease.<sup>64</sup> In a study of 776 patients of mitral stenosis (MS), 38% belonged to juvenile age group, i.e.

<20 years; male predominance, short duration of symptoms, high degree of incapacity, low incidence of atrial fibrillation (AF) and embolism, rapid development of pulmonary hypertension, and high incidence (80%) of active Aschoff's bodies in the sub-endocardium were the remarkable features.<sup>65</sup> Sometimes, the disease is diagnosed for the first time during pregnancy or childbirth, endangering the life of both mother and child. In a study involving 25 pregnant women with MS, there was high maternal morbidity, but rare mortality, and miscarriage rate was 32%.<sup>66</sup>

The RF patients were managed by the cardiology and medicine departments of various secondary and tertiary health care institutions. ASO titer and throat swab culture were important diagnostic tools. Echocardiography was initially not available; for the first time, it was introduced in 1980 in Bangladesh (Islam MN, Professor of Cardiology and Former Director, NICVD; Zafar MA, Professor of Cardiology and Former Director, NICVD, personal communication, 15 Oct 2014). Oral and imported injectable penicillins were used for prophylaxis. National Institute of Cardiovascular Diseases (NICVD), the state-of-the-art institution for CVDs, was established in 1978, and was formally opened on the 3rd April 1981. Soon after its inception, management of heart disease as a whole got momentum, and became more organized. After a decade, with a view to control and prevention of RF and RHD, Government of Bangladesh started a 5-year pilot project in 1988 in collaboration with the Government of Japan through technical cooperation program of Japan International Cooperation Agency (JICA); NCCRF&HD was established on 1st November 1988. RF and RHD cases were diagnosed and managed more efficiently, and besides curative services, preventive and promotive services were delivered. A large number of research works were conducted, and manpower was trained abroad. RF became virtually a subject of social movement, leading to improved public awareness.

Despite much progress, considerable fallacies exist in relation to diagnosis, management, and prophylaxis of RF and RHD in Bangladesh. RF is often diagnosed, better to say, misdiagnosed, on the basis of raised ASO titer which is an easily available and commonly asked test, sometimes with no, or only mild joint pain. Mechanical musculoskeletal pain, and mild febrile illness or vague ailments are sometimes diagnosed and treated as and prophylaxis given for RF. In a hospital-based study, out of 82 children receiving long-term penicillin therapy, only 7.31% had documented evidence of RF by Jones' criteria.<sup>57</sup> Streptococcal infection is presumably a common phenomenon in Bangladesh, especially in low socioeconomic class, and raised ASO titer merely supports its occurrence. About 60–80% of the healthy population may show an elevated ASO titer (>300 IU/ml in children) in developing countries like ours,<sup>67</sup> single raised ASO titer may not equate to acute RF, so paired sera collected at an interval of 4–8 weeks with 2-fold increase or decrease has been suggested to give a more meaningful interpretation.<sup>68</sup> Similarly, a negative ASO titer does not exclude the diagnosis of acute RF.<sup>69</sup> A study to find out the reference value of streptococcal antibodies among apparently healthy primary school children in rural Bangladesh found the geometric mean titer to be 241 IU/ml and 222 IU/ml, and the upper limit of normal values (80th percentile) to be 390 IU/ml and 340 IU/ml for ASO and

anti-deoxyribonuclease B, respectively.<sup>70</sup> On the other hand, use of Jones' criteria appears to be neglected even by the physicians. However, once 'diagnosed', these patients are kept on oral or intramuscular penicillin prophylaxis for years together. A portion of these cases are presumably of post streptococcal reactive arthritis, other inflammatory arthropathies, or even fibromyalgia or hypovitaminosis D. Hypovitaminosis D affects almost 50% of the population worldwide. Patients with vitamin D deficiency may present with musculoskeletal pain. High prevalence of hypovitaminosis D has been reported in Bangladeshi population.<sup>71–73</sup> Some patients presenting with musculoskeletal symptoms and provisionally diagnosed as RF may actually be cases of hypovitaminosis D.

Though acute cases of acute RF are uncommon at present in Bangladesh, clinically silent subclinical cases of carditis continue to occur, which is evidenced by the high prevalence of chronic RHD. Actually, prevalence of RHD in a population provides a better indicator of the real frequency of RF.<sup>74</sup> Chronic RHD itself has a relatively long natural history, and clinical manifestations may occur only in moderate or severe disease, leading to delay in diagnosis. In a clinical study on the pattern of mitral valvular disease conducted in a peripheral tertiary hospital in Bangladesh,<sup>75</sup> significant delay was found in 56% patients; illiteracy and ignorance was found to be the cause in 28% cases, poverty in 24%, and misdiagnosis in 14%; 12% patients adopted indigenous treatment. The common clinical features of mitral valvular disease, particularly, breathlessness, is taken as for bronchial asthma especially by the non-graduate medical practitioners. Cough and hemoptysis accompanied by pulmonary hypertension associated with severe mitral stenosis, is sometimes misdiagnosed as pulmonary tuberculosis even by the less experienced doctors.<sup>75</sup> People with established chronic RHD, especially mitral valvular disease, suffer from chronic morbidity compromising their productivity and leading to loss of job. In a study involving 1427 patients, 61% were severely incapacitated by the disease,<sup>64</sup> while 63% of 245 isolated MS patients aged <20 years were in New York Heart Association (NYHA) class III or IV in a separate series.<sup>76</sup> One well-recognized complication of rheumatic mitral valvular disease is AF, which was present in 2% in juvenile MS in a study.<sup>76</sup> The AF in RHD, is usually refractory to cardioversion. Anticoagulants are often under-prescribed, presumably due to undue fear of bleeding on the part of physician, or inadequate access to proper monitoring on the part of the patients, specially those residing in remote and rural areas. These patients sometimes develop stroke, further worsening their sufferings and compromising productivity. In a study involving 245 isolated MS patients aged <20 years, 3% patients presented with systemic thromboembolism.<sup>65</sup>

## 8. Changing scenario in Bangladesh

Initial success in control of RF and chronic RHD is probably the result of intense, specific primary and secondary prevention measures adopted nationally in eighties and nineties in the last century. On the other hand, the present achievement in this arena appears mostly passive, i.e. the by-product of the country's socioeconomic transition in general, aiding in

primordial prevention. A number of surveys and census indicate socioeconomic transition of Bangladesh.<sup>39-45,51</sup> The key finding of HIES-2010<sup>44</sup> is that the standard of living of the population in general has improved very significantly in recent years. This is reflected in reduced incidence of poverty with stability in the distribution of income and expenditure; increased nutrition from a more diversified food consumption basket; and higher level of living in terms of non-food indicators.

Bangladesh has made considerable progress in achieving the Millennium Development Goals (MDGs). According to the latest report, the country is on track or has already achieved 5 of the 8 MDG goals<sup>77</sup>; remarkable progress has been made in the areas of poverty alleviation, primary school enrolment, gender parity in primary and secondary level education, lowering the infant and under-5 mortality rate and maternal mortality ratio, improving immunization coverage, and reducing the incidence of communicable diseases. Poverty declined 1.8% annually between 2000 and 2005, and 1.7% annually between 2005 and 2010, number of poor people decreased from nearly 63 million in 2000, 55 million in 2005, and to 47 million in 2010. Despite a growing population, the proportion of poor people declined by 26% in 10 years.<sup>78</sup> In terms of MDGs, 2 years ahead of time, in 2013, it has been possible to reduce poverty to 26.2%, whereas the goal was to bring poverty down to 29% by the year 2015.<sup>77</sup> According to the HIES-2010,<sup>55</sup> per capita per day intake of food items has increased by 5.4% to 1000.0 g in 2010 from 947.8 g in 2005 at the national level. The overall calorie intake per capita per day increased by 3.56% to 2318.3 kcal in 2010 from 2238.5 kcal in 2005; protein intake has increased to 66.26 g per capita per day in 2010 from 62.52 g per capita per day in 2005. The average size of household has continued to decrease. It has declined from 4.84 in 2005 to 4.5 in 2010.<sup>55</sup> Access to education has increased. Literacy rate of population aged 7 years and over stands at 57.91% at national level, compared with 51.9% in 2005.<sup>44</sup> The proportion of people benefiting from at least one public safety net program has increased; in 2010, 24.57% of the households reported to have received benefit during the last 12 months from at least one type of program, in contrast, only 13.06% households reported to have received benefit from Social Safety Net Programs (SSNP) in 2005.<sup>44</sup>

Besides decline in poverty and improvement in lifestyle, Bangladesh has achieved considerable success in health sector in recent decades. This success might be attributed to a pluralistic health system with many stakeholders, including government and non-governmental organizations, who pursue women-focused, equity-oriented, nationally targeted programs, such as those in family planning, immunization, oral rehydration therapy, maternal and child health, tuberculosis, vitamin A supplementation, and others.<sup>36</sup> Health care facilities have increased in both public and private sectors; day by day, specialist services are becoming available even in rural and remote areas including Upazila level (subunit of a district, analogous to that of a county or borough of Western countries). Other factors playing important role in controlling acute RF include easy availability and widespread use of antibiotic (though may not be appropriate/supportable) by the registered and unregistered medical practitioners, which might lead to treatment of streptococcal sore throat, among other causes, preventing RF.

Echocardiography is being more widely used for diagnosis of cardiac diseases. At present, majority of the machines used are probably not dedicated echo machines, rather they are ultrasonography devices able to perform 2D and M-mode studies, and the expertise of the echocardiographers may not always be up to the mark. However, despite these pitfalls, they are playing role as least as a screening tool for diagnosis of established cases of chronic RHD. Though in limited scale, transesophageal echocardiography (TEE) is available for better evaluation as well.<sup>79</sup>

Side by side of better diagnosis, treatment facilities have also increased. In the recent decades, treatment modalities of chronic RHD especially mitral valvular disease have gone through evolution, which has been reflected in Bangladesh as well. Classically, severe cases of MS with suitable valve morphology were managed by surgery, i.e. closed mitral commissurotomy (CMC). For the first time, a few cases of CMC were done in Institute of Post-Graduate Medicine & Research (IPGMR) in 1973 by Prof. Ali Ashraf, and then in National Institute of Diseases of Chest & Hospital (NIDCH) in 1979 by Prof. SR Khan (Ahmed NU, Professor of Cardiac Surgery, personal communication, 25 Dec 2013). CMC started in NICVD in 1980, and since then, a good number of cases were done at low cost with good results.<sup>79-81</sup> In a study involving 1500 CMCs, done in NICVD between June 1980 and June 1990, 30% patients were of juvenile age group, i.e. up to 20 years, and the results were encouraging with 30-day mortality 2%, restenosis 18%, and significant mitral regurgitation 4% in long-term follow up.<sup>80</sup> Subsequently, with the introduction of percutaneous transvenous mitral commissurotomy (PTMC) in 1996, MS patients were managed by this modality predominantly, because PTMC is less invasive, leaves no scar in the chest wall, requires more or less similar cost, and the outcomes are good.<sup>82,83</sup> However, open mitral commissurotomy (OMC) is being used for suitable, complicated cases, like before. On the other hand, for mitral valve replacement, some bioprostheses were used initially, which were later almost replaced by metalloprostheses. Initial ball-and-cage metallic valves are out of use nowadays, and majority of the prostheses used today are bileaflet valves. Despite presence of indications, anticoagulants are not given in many high-risk patients with chronic RHD, because of fear of bleeding and lack of adequate monitoring facility. Single or dual antiplatelets are used more commonly, sometimes, without sticking to the guidelines. However, the practice is gradually changing.

Like many other countries, with the control of communicable diseases, non-communicable diseases including CVDs, are getting more attention even in Bangladesh. Among the CVDs, coronary artery disease is being given the topmost priority, and side by side, RF and RHD are receiving less attention. In fact, at present, no specific program for control of RF and RHDs exist in the country. In the past, NCCRF&HD played important role in overall management of RF and chronic RHD. Subsequently, with the control of acute cases of RF, its role decreased, which is at present mainly limited to health education, and epidemiological research. The institution lacks facilities for interventional and surgical management of RHD. In this way, despite promise, it seems to be under-utilized.

## 9. Future directions

In recent years, there is a surge of interest in RF and RHD in regions of the world where these diseases mostly occur.<sup>84</sup> Global organizations, including the WHO and the WHF, are also paying increasing interest, and showing greater efforts in controlling RF and RHD. The WHF has made a major commitment to leading the charge on RHD control, taking the mantle from the WHO.<sup>84</sup> The WHF's mission is to 'minimize the burden of RHD and eliminate RF', for which it has set the goal of achieving a 25% reduction in premature deaths from RF and RHD among individuals aged <25 years by 2025.<sup>1</sup> The targets of the WHF are: to ensure that 90% of countries with endemic RHD have integrated and comprehensive control programs by 2025; to ensure the availability of high-quality benzathine penicillin G for 90% of patients with RHD in 90% of countries with a high burden of this disease within 10 years; to foster at least one prominent public figure as an 'RHD champion' in every country where RHD is endemic, to establish at least one hub of training, research, and advocacy for RF and RHD in each WHO-defined geographic region by 2025; and to test a GABHS vaccine in phase III clinical trials in RHD-endemic countries within 10 years.<sup>1</sup> Bangladesh can align herself with the international communities, formulate appropriate policies, and act accordingly to combat RF and RHD. Under the auspices of WHO and WHF, the country can utilize her extensive network of non-Government Organizations (NGOs) like the Bangladesh Rural Advancement Committee (BRAC) and Association for Social Advancement (ASA), who are already boosting the Government's effort to control communicable diseases like TB. Data related to different aspects of RF and RHD in Bangladesh are inadequate. Large, preferably nationwide epidemiological and clinical studies should be carried out to gain reliable information on this important public health issue. RF and RHD can be declared a notifiable disease, and a national registry can be formulated to keep the record of and track the RF and RHD cases. Renovation of NCCRF&HD may be done to boost up research in RF and chronic RHD and render point-of-care services involving medical, interventional, as well as, surgical modalities of treatment. It can be a reference center for RF and RHD in South Asia. The existing *Doctors' Manual on Rheumatic Fever*<sup>85</sup> is more than a decade old, so it should be updated. Appropriate guidelines may be formulated in relation to RF and RHD to bring about uniformity and rationality in existing practice. Guidelines formulated by the WHO, the Indian Academy of Pediatrics, the National Heart Foundation of New Zealand and the Cardiac Society of Australia and New Zealand, and the WHF can be considered.<sup>34,86–90</sup> Introduction of portable echo machine may lead to more versatile use of this useful tool for the diagnosis and follow up of RF and RHD, and gathering reliable data for research. Side by side, proper and adequate training in echocardiography should be ensured, because, at present, this sector appears to be relatively neglected in Bangladesh, and the country seriously lacks competent echocardiographers. The PTMC hardwires and prosthetic valves are quite expensive; local manufacture and probable reuse can cut down the cost to a significant extent. More research is needed on bioprosthesis, so that hassles of

anticoagulation can be avoided. Treatment of RF and consequent RHD is clumsy, expensive, and is often only palliative; timely prevention can only reduce this great taxation. Further economic upliftment, better housing and lifestyle may be helpful in this regard. CVD prevention should be integrated with primary health care. Cardiovascular health promotion should be part of the national media strategy and the health education curriculum. Intensive research, may be in collaboration with international organizations, should be undertaken to explore the different aspects of RF and RHD in Bangladesh.

## 10. Conclusion

Despite much advancement, RF and RHD are prevalent in Bangladesh. At the advent of the new millennium, we know little about our real situation. The existing disease burden may actually represent the tip of the iceberg. We have no more time to lapse. Large-scale, preferably, nation-wide survey and clinical research should be conducted to determine the different aspects of RF and RHD in Bangladesh. The information available thereby, would help to formulate national policy to combat this public health problem more efficiently in future.

## Conflicts of interest

The authors have none to declare.

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