Streptococcal pharyngitis, rheumatic fever and rheumatic heart disease: Eight-year prospective surveillance in Rupnagar district of Punjab, India

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ABSTRACT

Background. Rheumatic fever (RF)/rheumatic heart disease (RHD) continue to be a neglected public health priority. We carried out a registry-based control project, prospective surveillance and sample surveys to estimate the burden of disease.

Methods. We trained healthcare providers and established a surveillance system for the 1.1 million population of Rupnagar district in Punjab. In sample surveys conducted among schools, physicians examined the sampled children. Children with a cardiac murmur were investigated by echocardiography. Throat swabs were obtained from a sub-sample, and group A streptococci (GAS) were identified and emm typed by standard laboratory methods. We estimated the morbidity rates for RF/RHD from surveillance data and school surveys using a correction factor to account for under-registration of cases in the registry.

Results. A total of 813 RF/RHD cases were registered from 2002 to 2009. Of the 203 RF and 610 RHD cases, respectively, 51.2% and 36.7% were males. In the age group of 5–14 years, RF was more common (80%) than RHD (27%). The prevalence of RF/RHD in 5–14-year-old students was 1.0/1000 (95% CI 0.8–1.3). The school survey indicated that about two-thirds of the RF/RHD cases were enrolled in the hospital-based registries. Based on the school survey, the prevalence of RF/RHD was estimated to be 143/100 000 population. In the registry, the annual incidence of acute RF was estimated to be at least 8.7/100 000 children in the age group of 5–14 years. The prevalence of GAS was 2% (13/656) in children with sore throat and 0.5% (14/2920) among those not having sore throat. Typing of 27 GAS revealed 16 emm types. We estimate that about 1000 episodes of GAS pharyngitis lead to one episode of acute RF.

Conclusion. RF/RHD continue to be a public health problem in Punjab, India.
to patients with RF/RHD to prevent GAS infection, thereby preventing recurrence of RF. Primary prophylaxis, i.e. timely and appropriate treatment of GAS pharyngitis to prevent RF is also important in populations where this strategy was implemented. RF/RHD control programmes based on secondary prophylaxis have been sustained within primary healthcare settings using case registry, which can be utilized not only for monitoring the programme but also to gain insights into the epidemiology of the disease. Yet, most countries, including India, do not have a national RHD control programme. Hence, a RF/RHD control project, primarily on the basis of the secondary prophylaxis strategy, was initiated in Rupnagar district of Punjab in 2002 by the Indian Council of Medical Research which institutionalized prospective surveillance and registration of cases. We analysed the surveillance data and conducted sample surveys in schools to study the epidemiology of RF/RHD and GAS pharyngitis in the source population of the registry.

METHODS

Study area

The study was conducted in Rupnagar district of Punjab located in northwest India. Punjab is one of the most economically developed states of India. As per the Census of India 2001, Rupnagar district had a population of 1.1 million (urban 362 407 and rural 753 701) residing in 880 villages and 8 towns. The sex ratio was 871 women per 1000 men. There were 244 872 children in the age group of 5–14 years. The main occupation of the population is agriculture. Health infrastructure consisted of 6 primary health centres, 17 mini-primary health centres, 62 subsidiary health centres, 128 sub-health centres, 7 hospitals and 110 private medical practitioners. There were 785 primary, 278 middle and 212 secondary schools in the district.

RF/RHD registry

One master registry was established at the district headquarters in 2002, which was supported by 13 sub-registries at the block headquarters. A sub-registry was also set up with one of the private medical practitioners. In April 2006, S.A.S. Nagar (Mohali) district was carved out of Rupnagar and Patiala districts. Five of the sub-registries, which were part of Rupnagar district, continued to function as part of S.A.S. Nagar district. Besides these, a new sub-registry had been established at the civil hospital of Dera Bassi which was earlier part of Patiala district but was transferred to S.A.S. Nagar district. Thus, in Rupnagar and S.A.S. Nagar districts, 15 sub-registries had started functioning in 2007.

Medical officers (167), pharmacists (115), laboratory technicians (32), health supervisors (61) and multipurpose health workers (271) from the health department were oriented about the RF/RHD surveillance and case registration in the registry. From the education department, 1960 primary school teachers were oriented about the signs and symptoms of RF/RHD in formal training sessions, whereas high school teachers (2716) were oriented about RF/RHD during school health programmes.

Patients reporting to either a general outpatient department or referred by health workers or school teachers were examined by doctors who followed standard diagnostic procedures, i.e. Jones criteria (1992) for confirmation of diagnosis and registration of the case. History, clinical examination including auscultation for heart sounds by the doctor were used to suspect/diagnose cases with RHD. Suspected cases were confirmed by the cardiologist in a tertiary care hospital using echocardiography. A case registration sheet, filled for each case by the physician, was available for analysis. The case diagnosis included the following five categories: (i) acute RF; (ii) past history of RF with documentation; (iii) past history of RF without documentation; (iv) RHD with rheumatic activity; and (v) RHD.

School survey

The study area for school surveys comprised all the educational blocks of Rupnagar district. After obtaining permission of the Education Department for conducting the school health survey, a list of all government schools with the number of students in each class was prepared. A sample size of 25 000 children was estimated for each survey. A systematic random sampling method was used to select government schools. A private school was included in the survey if it existed in the vicinity (1 km radius) of the sampled government school. Those students who had not come to the school on the day of survey because of some reason were also included by inviting them to the school for the medical examination. The school dropout rate was 5%–10% in Punjab.

The school survey team consisted of a physician and a social worker. On reaching the school, the social worker introduced the physician to school head/principal, sought active cooperation of the class teacher for the health examination, recorded the demographic information such as age and sex of the child in a school health form and allocated an identification number. The physician conducted the clinical examination including auscultation for heart sounds, asked whether the child had symptoms/signs of RF/RHD during the past years and whether he/she was regularly receiving antibiotics (oral/injections). The findings of the health examination were recorded on a structured form. For each child with a cardiac murmur, the physician filled up an echocardiography referral card. An appointment for echocardiography was made in consultation with a cardiologist. In a tertiary care hospital, the cardiologist examined each case of cardiac murmur and did an echocardiography. Fourteen children could not undergo echocardiography as they had migrated out of the district.

Using standard methods, the physician took a throat swab specimen of a sub-sample of students who had sore throat and those who did not have sore throat on the day of survey. Throat swabs were transported to the laboratory on the same day.

In the first school health survey, conducted during 2002–04, the sampled schools had 25 801 primary schoolchildren (5–9 years); 378 students could not be examined due to various reasons, i.e. migration of family (58), participation in festivals (80), transfer to other schools (50) and absence from the village (190) at the time of survey. In the second school survey, conducted among 25 580 children in the age group of 5–14 years during 2004–07, 535 students could not be examined due to various reasons, i.e. migration of family (38), participation in festivals (293), transfer to other schools (46) and absence from the village (158) at the time of survey.

Laboratory methods

Throat swabs were streaked on blood agar plates, incubated at 37°C in 5%–10% CO2 for 24 hours. Beta-haemolytic colonies were identified and GAS was confirmed using the streptex kit (Murex, Biotech Ltd, UK). Genomic DNA from GAS was isolated and emm gene PCR was done by using standard methods. Nucleotide sequencing was done and emm type identified using BLAST search and CDC website.
Statistical analysis

The incidence/prevalence of RF/RHD was estimated by using the denominator population from the Census of India 2001. While estimating the incidence of acute RF, children with a past history of RF or patients with RHD with rheumatic activity were not included. The registry estimate of the incidence/prevalence of RF/RHD in the age group of 5–14 years was compared with estimates from the school surveys to ascertain the completeness of case registration.

The prevalence of RHD in school survey among the age group of 5–14 years was used to estimate the prevalence of RHD in all age groups of the population by using estimation methods developed by WHO.23 Briefly, this involved estimation of RHD cases in the age >14 years (number of cases in 5–14-year-olds × 5.5, a factor based on the ratio of RHD cases in 5–14-year-olds compared to >14-year-olds in population surveys).

The incidence of pharyngitis among school-age children (5 episodes/child/year) observed in a neighbouring district was used to estimate the number of pharyngitis episodes in the study district.24 The proportion of GAS among children with sore throat used to estimate approximate number of streptococcal sore throat episodes among 5–14-year-olds in the school survey was used to estimate the number of GAS pharyngitis episodes in the study district. The average number of cases of acute RF registered per year was used to compute the incidence of acute RF per 1000 episodes of GAS pharyngitis; 95% confidence intervals (CI) were computed using Epi Info computer package.

RESULTS

A total of 813 patients with RF/RHD were registered during 2002–09 (Table I). Of these, 203 had RF (category 1–3). The frequency of RHD cases was higher among females. As shown in Fig. 1, RHD cases were mostly in the age group of 10–14 years followed by 15–19 years and 20–24 years (median age 27 years) and the highest frequency of RF cases was in the age group of 10–14 years followed by 5–9 years (median age 13 years). About 80% of children with RF and 27% of children with RHD were in the age group of 5–14 years.

A total of 42 deaths occurred among children with RF/RHD registered during 2003–09. Verbal autopsy, done in 40 deaths, indicated that the underlying cause in most of the deaths (35) was RHD. The estimate of annual death rate due to RF/RHD was 245 (RHD prevalence 1.0/1000 × 244 872 children in the age group of 5–14 years), whereas only 162 children (66%) were enrolled in this age group. In the registry, the annual incidence of acute RF was at least 8.7/100 000 children in the age group of 5–14 years or 2/100 000 population. Based on the school survey, the prevalence of RF/RHD was 1.0/1000 (95% CI 0.8–1.3; Table II); prevalence in government schools and private schools was 1.2 and 0.3/1000, respectively.

Using the 2001 Census population, the number of children with RHD among school-age children (5–14 years) was estimated to be 245 (RHD prevalence 1.0/1000 × 244 872 children in the age group of 5–14 years), whereas only 162 children (66%) were enrolled in this age group. Thus, in school surveys, the prevalence of RF/RHD was 1.0/1000 (95% CI 0.8–1.3; Table II); prevalence in government schools and private schools was 1.2 and 0.3/1000, respectively.

In the school surveys, 324 cases of cardiac murmur were detected. Echocardiography, done in 310 cases, revealed 50 RHD and 59 cases of congenital heart disease. One child was diagnosed to have RF without carditis in each of the two school surveys, and 2 children of RHD were diagnosed in both the surveys. Thus, in school surveys, the prevalence of RF/RHD was 1.0/1000 (95% CI 0.8–1.3; Table II); prevalence in government schools and private schools was 1.2 and 0.3/1000, respectively.

In children with RF/RHD identified in school surveys, using auscultation followed by echocardiography, mitral valve was most commonly affected. Mitral regurgitation was present in 19 (trivial 1, mild 6, moderate 8 and severe 4). Thickening of the anterior mitral valve leaflet (AMVL), posterior mitral valve leaflet (PMVL), and AMVL as well as PMVL was observed in 13, 2 and 3 children, respectively along with mitral regurgitation. Mitral and tricuspid regurgitation was noticed in 4 children. Mitral stenosis was diagnosed in 3 children. Mitral regurgitation as well as mitral stenosis was present in 2 children. One child each had thickened AMVL with aortic regurgitation and aortic stenosis, and thickened AMVL with aortic regurgitation.

The prevalence of GAS was 2% (13/656) among children with sore throat and 0.5% (14/2920) among those who did not have sore throat. The emm typing of 27 GAS specimens revealed 16 emm types. The most common (frequency) were emm 57 (5), 15.1

<table>
<thead>
<tr>
<th>Table I. Sex-wise distribution of rheumatic fever (RF) and rheumatic heart disease (RHD) cases registered in Rupnagar district, Punjab, India, 2002–09</th>
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</thead>
<tbody>
<tr>
<td>Diagnostic categories</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>1. Acute RF</td>
</tr>
<tr>
<td>2. History of RF with documentation</td>
</tr>
<tr>
<td>3. History of RF without documentation</td>
</tr>
<tr>
<td>4. RHD with rheumatic activation</td>
</tr>
<tr>
<td>5. RHD</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Fig 1. Age-wise distribution of rheumatic fever (RF) and rheumatic heart disease (RHD) cases registered in Rupnagar district, Punjab, India, 2002–09
In Rupnagar, all cases could not be registered. A comparison of the estimation from the school survey indicates that about 66% of cases were registered. Hence, the estimate based on registry would underestimate the burden of RF/RHD. In Fiji, even an active surveillance programme had found that all cases of RF/RHD were not notified in the public health system. One reason could be that mild RHD cases do not present to a medical institution. Some of the cases may not have sought clinical attention or could have presented to private practitioners/institutions and therefore were missed by our survey. One of the registries set up in the private sector had registered 51 cases, which indicates that some cases of RF/RHD were indeed in the care of private medical practitioners.

Unlike other studies, in the acute RF cases of Rupnagar district, the proportion of carditis (25.6%), arthralgia (16.3%) and chorea (4.4%) was lower but arthritis (69.5%) was higher, and erythema marginatum and subcutaneous nodules could not be detected. Carditis and arthralgia are considered to be two prominent features of acute RF in India. Hospital-based studies from Delhi, Chennai and Mumbai have reported higher rates of carditis (33.3%, 67.5% and 42%) and arthritis (66.6%, 44.2% and 67.6%), respectively, but the rates of erythema marginatum and subcutaneous nodules were low. Higher rates of chorea were reported in Delhi (20.5%) and Mumbai (18.8%). Arthralgia was reported in 19.6% of cases in the Delhi study. The clinical profile of cases registered in the community setting could be different from those registered in hospitals or some symptoms and signs may have been missed in Rupnagar district as the examinations were done by medical officers in primary care settings. Prospective community-based studies with standardized data collection by research staff are needed to accurately describe the profile of acute cases of RF. In RHD cases, predominantly the mitral valve was involved (97%), followed by aortic (22.3%) and tricuspid valve (10.5%), which is similar to earlier studies, though the proportion of isolated aortic valve involvement was found to be lower (1.3%).

School surveys are considered to be a valid means to estimate the burden of RHD in the community. It is well known that surveillance systems operating within the existing health infrastructure usually under-report the burden of disease as was the case in this study. However, even school surveys may underestimate the burden of disease in India because a large number of children coming from the low socioeconomic strata never attend school or are often absent/taken out of school, particularly if sick. In Punjab, school enrolment rates are high (90%–95%) and dropout rates are low (5%–10%); hence, we believe our study is more inclusive. Prevalence rates of RHD are higher in the lower socioeconomic group, who generally attend government schools compared to those who attend private schools. Moreover, some cases with a mild murmur can be missed in surveys conducted in schools. Hence, prevalence rates of RF/RHD estimated from school surveys should also be interpreted with caution.

The registry-based estimation of burden of RF/RHD is generally lower than the surveys conducted in schools. Hence, direct estimation of burden of RF/RHD in the community would require conducting sample surveys that cover the entire population. Such surveys are difficult to organize compared to school surveys. Hence, the prevalence of RHD in school surveys among the age group of 5–14 years has been used to estimate the burden of disease in the entire population with the help of a correction factor which ranges from 5 to 7. We used a correction factor of 5.5 based on the

<table>
<thead>
<tr>
<th>Survey period</th>
<th>Age group (years)</th>
<th>Sex</th>
<th>Children examined</th>
<th>RF/RHD (echo-cardiography)</th>
<th>RF/RHD Prevalence/1000 (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>2002–04</td>
<td>5–9</td>
<td>Boys</td>
<td>13610</td>
<td>18</td>
<td>1.3 (0.8–2.1)</td>
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<td></td>
<td></td>
<td>Girls</td>
<td>11435</td>
<td>8</td>
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<td>2004–07</td>
<td>5–9</td>
<td>Boys</td>
<td>6239</td>
<td>10</td>
<td>1.6 (0.9–2.9)</td>
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<tr>
<td></td>
<td></td>
<td>Girls</td>
<td>5160</td>
<td>9</td>
<td>1.7 (0.8–3.3)</td>
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<tr>
<td>10–14</td>
<td>Boys</td>
<td>6230</td>
<td>2</td>
<td>0.3 (0.1–1.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Girls</td>
<td>5813</td>
<td>5</td>
<td>0.9 (0.3–2.0)</td>
<td></td>
</tr>
</tbody>
</table>

*One case of RF without RHD was identified in each school survey among the age group of 5–9 years. † Two children with RHD were detected in both the survey periods.
methodology for estimation used in a WHO publication. Using these methods of estimation, the prevalence of RHD in Rupnagar district of Punjab was estimated to be 143/100 000 population.

The prevalence of RHD could be higher in states with poor socioeconomic indicators. Such states form a large part of the population in India. The burden of RF/RHD could be similar to that of cancer in India. However, India still does not have a national RF/RHD control programme, whereas a national cancer control programme is functioning for several decades, despite the fact that RHD is a preventable disease of children and adolescents, which primarily affects poorer segments of population. Management of RHD is expensive and does not offer a permanent cure. Valve replacement surgery requires long-term anticoagulation therapy with careful monitoring. Most of the patients with RHD belong to underprivileged communities who often live in remote rural areas where facilities for monitoring of anticoagulation therapy are generally not available.

Some investigators have opined that RF/RHD has been declining in India. They have based their assessment on the proportion of hospital admissions due to RHD and/or school surveys that have been conducted over a period of several decades in various geographic regions of India. These comparisons could be biased, as over the years treatment-seeking pattern might have changed and survey design, populations sampled, especially clinical assessment methods (auscultation followed by echocardiography) may also have differed. Now several peripheral-level health institutions provide care for RF and RHD whereas such facilities were earlier available only in a few tertiary care institutions. Findings from this study do not support a decline in RF/RHD in Rupnagar district as the age distribution still shows a peak in the age group of 5–14 years. A peak in the later age group (middle age) would have indicated a decline in the incidence of RF/RHD in the recent past, i.e. lower prevalence of RHD among children and adolescents compared to adults. Surveillance data from registries can provide a trend of the disease that school surveys cannot assess. School surveys often differ in design and methodology and do not provide follow-up data as children included in a primary survey would not be seen again.

Owing to limited resources available to us, we used clinical methods (auscultation) for initial screening and echocardiography for confirmation of RF/RHD. Recently conducted school surveys have used echocardiography for screening as well as confirmation of RHD in school surveys and found the prevalence to be 15–20 times higher. These findings indicate that RHD detected by auscultation may represent only the tip of the iceberg and the burden could be much more than what is generally believed. However, criteria for diagnosing RF/RHD by echocardiography still have limitations and we do not know much about children with ‘subclinical RHD’, i.e. those who have no history/symptoms of RHD but echocardiography suggests a valve damaged by RHD. Whether secondary prophylaxis will be beneficial in sub-clinical cases of RHD detected by echocardiography, needs to be investigated.

Another unique feature of our study was the estimation of the burden of GAS pharyngitis in the same community where RF/RHD surveillance has been functioning and sample surveys had been conducted in schools for establishing the burden of disease. Many studies have indicated that GAS pharyngitis is endemic in India. On an average, 5–14-year-old children in urban slums suffer from one episode of streptococcal pharyngitis per year. The rural community had a much lower annual incidence of 0.1 episode per child. It seems, most children get infected with at least one or the other type of GAS during their school years. How many of these infections result in RF can be roughly estimated. Earlier studies in the USA had estimated that 100 episodes of GAS throat infections led to only 0.3 to 3 cases of RF in endemic and epidemic situations, respectively. Recent studies from developed countries report an incidence of GAS similar to what has been reported in our community, but acute RF cases occur rarely. The widespread use of antibiotics for the treatment of pharyngitis is considered to be responsible for the decline in RF in developed countries. However, outbreaks of RF have also occurred in these countries. The appearance of specific serotypes and clones of the same serotypes have been found to be associated with outbreaks of acute RF in USA. Hence, surveillance of GAS types should be part and parcel of RF/RHD surveillance programmes to identify strains that have epidemic potential.

Several emm types of GAS were found to be prevalent in Rupnagar district which are different from the ones that are usually associated with the occurrence of RF. This finding is in line with earlier studies indicating that several emm types circulate in India. This variation implies that the amino terminal M protein-based vaccines may not be effective in this community as the emm types included in this vaccine are different from the ones reported by us and from earlier studies in India.

In summary, RF/RHD continue to be an important public health problem in Rupnagar district of Punjab despite the relatively higher socioeconomic status (per capita income of Rs 141 per year 2006–07) of this district compared to many other districts of India and other developing countries. The higher prevalence of RHD in the younger age groups indicates that the disease is not on the decline. Prospective surveillance in registry-based programmes, set up within the existing health infrastructure for controlling RHD may not have complete registration of all cases, but it can be used for monitoring disease trends and for conducting sentinel surveillance for GAS types. Registry-based secondary prophylaxis programmes can prevent recurrence of acute cases of RF; however, many acute cases of RF continue to occur, which calls for formulation and implementation of primary prevention strategies.

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Conflict of interest. None.

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