RHD in India: are we ready to shift from secondary prophylaxis to vaccinating high-risk children?

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Rheumatic fever (RF) and rheumatic heart disease (RHD) continue to be important public health problems in the developing world. Although the disease burden appears to have declined in parts of India that have experienced an improvement in human development, there are many areas where the disease burden may be high. There is paucity of epidemiological data from poorly served rural populations, urban slums and tribal pockets, where the disease prevalence is expected to be high. Penicillin prophylaxis, particularly secondary prophylaxis has remained the mainstay for prevention of RF and RHD. However, this has not made significant difference to the disease burden over the years, particularly in high-prevalence regions.

An effective vaccine against group A streptococcus (GAS) has the potential of reducing RF–RHD disease burden. However, there are a number of difficulties that need to be overcome before an effective vaccine is made available. Very few vaccines have reached the stage of clinical trials. A number of questions remain about their usefulness for streptococcal strains found in the developing world. There is also the practical issue of identifying the population at risk in the developing world, given the changing epidemiology of the disease.

This article attempts to review the epidemiology of RF–RHD in India today and identify potential problems relating to the use of a vaccine against GAS.

Keywords: Epidemiology, prevention, rheumatic fever, rheumatic heart disease, secondary prophylaxis, vaccines.

Introduction

MOST diseases are the result of a complex interaction among the 'host', 'agent' and 'environment'. If the delicate balance between these components is disturbed, it will result in a disease. The incidence of many of the infectious diseases now under control showed impressive reductions even before the advent of vaccines and antibiotics. This was the result of better living conditions, specifically housing, safe drinking water supply and education resulting from improvement in the socio-economic conditions. This phenomenon of rapid decline of many infectious diseases in the Western world has been noted in diphtheria, pertussis and pulmonary tuberculosis[1]. However, vaccines have also played an important role in rapidly reducing the incidence and severity of many diseases and in eradicating smallpox. It is hard to imagine that we would have reached the threshold of eradicating poliomyelitis without the polio vaccines. Cuba eradicated poliomyelitis[2] with just two rounds of mass immunization with oral polio vaccine held 4 weeks apart in early 1962. This dramatic control or elimination of the disease would not have been possible without the vaccine.

Rheumatic fever (RF) results from complex immunological responses to an infection with group A streptococcus (GAS), about which our knowledge is not complete. Even though there are many gaps in our knowledge about the exact etiology of RF, we now have sufficient evidence to indicate that streptococcal infections play a crucial role in its causation. Hence a vaccine to prevent streptococcal infections seems to be a reasonable way to approach the control of RF.

A sharp decline in RF and rheumatic heart disease (RHD) occurred in industrialized nations all over the world with improving living standards, a few decades before penicillin was introduced. Industrialized nations[1,3,4] now have an average annual RF incidence of <0.5/100,000 and RHD prevalence of <0.05/1000. Improved living standards translate into reduction in over-crowding, better access to health care and more widespread use of antibiotics, all of which allow prompt treatment of streptococcal infections and help abort epidemics[4]. However, the small but significant resurgence of the RF in parts of the United States during the mid-eighties and its persistence thereafter[5], suggested that additional factors also contribute to its occurrence, albeit in a small way. Selected populations in the Pacific Islands also appear to have a high occurrence of RF and RHD that is perhaps best explained by a genetic predisposition. Like many other infectious diseases, RF and RHD continue unabated in the developing world, largely reflecting the relatively poor living standards and health-care availability. The disease burden in various emerging economies appears to

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mirror human development. The effectiveness of penicillin prophylaxis in the prevention of RF and RHD was demonstrated over five decades ago and GAS has remained sensitive to penicillin till now. Yet penicillin prophylaxis does not appear to have had a significant impact on the disease burden in the developing world.

In this article, we propose to examine whether available vaccines against GAS can be considered as the major preventive strategy against RF in India, particularly for those at high risk. We will attempt to first provide an overview of the epidemiology of RF and RHD in India, and briefly summarize the situation with secondary prophylaxis in India. We would then address the following questions:

1. At what stage of development are candidate vaccines against GAS and what would the specific advantages and limitations be in the Indian context?
2. What are the specific logistic difficulties in implementing a vaccination programme for RF–RHD prevention in India?
3. What potential approaches could be used to overcome these logistic difficulties?
4. What could be the areas identified for future research in vaccine development for RF and RHD prevention?

RF and RHD in India: epidemiology and disease burden

A number of studies have attempted to document RF incidence and RHD prevalence in India through a variety of methods[6–24]. School surveys have been the commonest method used. They are traditionally considered useful because the denominator is clear. However, school surveys will miss older patients with RHD and children who do not attend schools. In areas where RF and RHD are on the decline, most patients with RHD tend to be older. Population-based registries have the potential to capture all age groups, but are heavily dependent on referral mechanisms. Hospital-based statistics has serious limitations because only the most seriously affected are represented. Table 1 lists the limitations and advantages of various epidemiological methods for obtaining information on RF and RHD.

It is perhaps impossible to make generalizations on health indices and disease prevalence in India. Statistics from one region would most certainly not apply to the country as a whole. Sharp differences are likely to results from extreme variations in geography, living standards, economy, human-development indices, urbanization and health infrastructure. Given the undeniable relationship between incidence of RF and living standards[4], it is particularly difficult to make generalizations for RF and RHD using data collected from various parts of India scattered over the last five decades (Table 2). All estimates of disease burden in India are therefore crude extrapolations. The problem is further compounded by the absence of uniformity in the methodology used in the various studies.

Notwithstanding the above-mentioned caveats, some patterns appear to be emerging in selected parts of India where the disease has become less prevalent. These include many urban regions and States such as Kerala and Tamil Nadu (Table 2)[22]. Many large institutions have reported a decline in the proportion of hospitalizations from RF and RHD and a progressive reduction in the number of balloon mitral valvotomy procedures and heart valve surgeries for RHD. Hospital admissions for RF have also declined in these institutions. Serial school surveys from the same region over one or more decades have also shown a decline in RF–RHD. These studies are also supported by impressions of senior physicians and cardiologists in the region, who have reported a decrease in the number of patients they see with RF–RHD. The age profiles of patients with RHD are also changing in these regions and have started to resemble the typical Western profile of relatively older patients in their mid-forties. Aggressive forms of RHD such as juvenile mitral stenosis are now seldom encountered in these regions.

We recently conducted a survey of a population of 1.37 million in central Kerala, a region with one of the best health infrastructure and human-development indices in all the whole of India. Information on RF/RHD patients was gathered over 38 months (2003–06) through passive referral mechanism after thorough orientation of health-care professionals and active reporting in a population proportionate sample of 25,228 children from 46 schools. Echocardiography was performed for diagnostic confirmation in all suspected cases. Out of 554 cases of suspected RF/RHD reported from the general population, 355 had RHD and 64 were on penicillin prophylaxis for previous history of RF. Two instances of acute RF were recorded in the first year of surveillance, seven in the second year and five in the last 14 months. Two RHD patients had recurrence of RF. Of the 25,033 schoolchildren surveyed, three were found to have RHD (prevalence of 0.12/1000), and six were on penicillin prophylaxis for a history of RF. The worst-case scenario of RHD prevalence was estimated as 0.16/1000. The prevalence of RHD and incidence of RF in this study is among the lowest reported thus far from the developing world. It appears to support the view that improved access to health care and antibiotics results in a decline in the incidence of RF and prevalence of RHD.

There are data to suggest that RF and RHD may not have declined in the areas of India that have experienced little improvement in human development[25]. Most comparative studies have reported a substantially higher prevalence in the rural regions. Thus parts of the country with the highest prevalence today are likely to be those with the poorest health-care infrastructure. Because of serious limitations in the health-care delivery systems,

Table 1. Epidemiological methods for rheumatic fever (RF) and rheumatic heart disease (RHD)

Study type	Limitations	Advantages
Population registry	Heavily dependent on referral pathways: Health-care infrastructure in the area and willingness of the potential sources of referral. Under-reporting: Mild cases, missed diagnosis – marginalized sections of the population may be missed altogether. Over-reporting: Sampling from outside the study area. Denominator: Dependent on census data, errors may result from under or over estimation of the migrant population	Wide coverage. Relatively easy to organize in areas with well-developed health-care infrastructure.
School surveys	Focus entirely on the 5–15 yrs age group. Limited value in areas with poor school enrolment rates. Affected children may not attend schools (absenteeism). School surveys may yield a much lower prevalence in regions where affected RHD patients are older	Clearly defined denominator. Allows systematic and well-organized surveys. Better suited for RHD and not acute RF.
Hospital statistics	Out-patient clinic and admissions: Only the relatively sick will be represented. Procedure records: Likely to miss valve lesions that do not require a procedure.	Diagnosis is likely to be accurate.
RF–RHD mortality statistics	Inaccuracies resulting from deaths that occur is areas with poor health infrastructure. Decline in mortality may occur without decline in disease burden.	

the magnitude of the problem remains unrecognized in many poorly served regions. Very few systematic surveys are available from rural populations with a poor health care infrastructure, urban slums and tribal colonies. Table 2 summarizes the results of selected studies from India over the last 50 years. The Indian Council of Medical Research (ICMR) is currently looking to document the incidence of RF and the prevalence of RHD in regions with poor access to heath care. It is essential to get as clear an idea as possible about the prevalence and distribution of RF/RHD in India, before making recommendations on prevention. As of now the only realistic form of prevention is secondary prevention that essentially involves administration of penicillin prophylaxis to all patients with RHD, including those who have had RF in the past. This allows targetted prevention of a group of particularly vulnerable individuals. The alternative strategy of administering penicillin to all patients with sore throat is not cost-effective, particularly if large populations are included.

Current preventive strategies for RF–RHD and their efficacy

Among all currently available methods for prevention of RF–RHD, secondary prophylaxis is considered the most cost-effective. This involves regular administration of penicillin to patients with established RHD, or one or more previous episodes of RF. Primary prophylaxis involves prompt treatment of all streptococcal sore-throat infections. This is challenging because it is difficult to diagnose streptococcal sore-throat infection in the community setting. Administration of penicillin to all patients with sore throat is unlikely to be cost-effective, because several thousands will have to be treated to prevent a single episode of RF[26]. Further, many patients with RF do not recall suffering from sore throat.

The success with secondary prophylaxis is critically dependent on patient education. Regular prophylaxis is perhaps more realistic with 3 or 4 weekly benzathine penicillin injections. For high-prevalence regions 3-weekly penicillin is recommended[3]. Compliance with benzathine penicillin injections has been shown to vary from 40 to 86% in reports from India[27–29]. Compliance with oral penicillin is difficult to ensure because many doses may be missed inadvertently. Most studies evaluating compliance with oral penicillin do not involve a strict compliance check in the form of pill counts.

There are reports of erratic availability of benzathine penicillin from parts of India[30]. More importantly, many private physicians are reluctant about administering the injection for fear of anaphylaxis. Primary health centres, district hospitals and some medical colleges in selected states are also reluctant to administer benzathine penicillin injections after the occurrence of episodes of fatal anaphylaxis[30]. There are unsubstantiated reports of selected state governments that have prohibited the use of penicillin injections. A single episode of fatal penicillin anaphylaxis is likely to result in much greater public outcry than recurrences of RF in a sizable number of patients.

Another significant challenge with secondary prophylaxis relates to identification of all candidates who need it. Many patients with RHD do not recall a qualified doctor diagnosing the first episode of RF[26]. Many families choose to seek treatment from alternative systems of medicine for joint pains and therefore, do not receive advice on penicillin prophylaxis. Patients from marginalized sections of the society are particularly unlikely to receive regular penicillin prophylaxis.

Table 2. Studies on RF and RHD from India (1957–2006)

Place of study	Urban/rural/ combined	Author	Year	Age group (yrs)	Method (clinical/ echo)	Sample size	RHD prevalence per 1000	RF incidence per 1000
Different Indian states[6]	Combined (mostly urban)	Padmavati (quoted from Employees state insurance report)	1957–58	Industrial workers	Clinical	1,610,500	0.67	
Different Indian states[6]		Padmavati (quoted from Employees state insurance report)	1958–59	Industrial workers	Clinical	1,610,500	0.56	
Different Indian states[7]	Combined	Padmavati	1978	School children	Clinical		6–11	
Different Indian states[7]	Combined	Padmavati	1978	Employees insurance data	Clinical		1.3	10.9
Vellore, Tamil Nadu[8]	Rural	Koshi	1975–78	4–16	Clinical	3890	4.4	1.7, 1.6, 0
Balabgarh, Haryana[9,10]	Rural	ICMR	1982–90	5–15	Clinical	22,729	1.0	
Varanasi, Uttar Pradesh[9,10]	Combined	ICMR	1982–90	5–15	Clinical	12,190	5.4	
Vellore, Tamil Nadu[9,10]	Predominently rural	ICMR	1982–90	5–15	Clinical	13,509	2.9	
Delhi[11]	Urban	Padmavati	1984–94	5–10	Clinical	40,000	3.9	0.384
Anand, Gujarat[12]	Rural	Patel	1986	8–18	Clinical	11,346	2.03	0.176
Ludhiana, Punjab[13]	Combined	Avasthi	1987	6–16	Clinical	6005	1.3	0.700
Ambala, Haryana[14]	Rural	Grover	1988–91	General population	Echo	114,610	0.09	
Ambala, Haryana[14]	Rural	Grover	1988–91	5–15	Echo	31,200	2.1	0.54
Shimla, Himachal Pradesh[15]	Combined	Thakur	1992–93	5–16	Clinical	15,080	2.98 Rural–4.8 Urban –1.98	
Churu, Rajasthan[16]	Rural	Kumar	1992	5–15	Clinical	10,168	3.34	
Jammu Tawi[17]	Combined	Gupta	1992	6–16	Echo	10,263	1.36	0
Agra, Uttar Pradesh[18]	Urban	Vashistha	1993	5–15	Echo	8449	1.42 Slum–4.1 Urban–0.6	
Aligarh, Uttar Pradesh[19]	Rural	Agarwal	1995	General population	Clinical	3760	6.4	
Srinagar, J&K[20]	Rural	Kaul	1999–2000	5–15	Echo where needed	4125	5.09	
Kanpur, Uttar Pradesh[21]	Combined	Lalchandani	2000	7–15	Clinical	3963	4.54 Urban–2.56 Rural–7.42	0.750 Urban–0.42 Rural–1.20
Vellore, Tamil Nadu[22]	Rural	Jose	2001–02	6–18	Echo	229,829	0.68	
Bikaner, Rajasthan[23]	Urban	Periwal	2003–04	5–14	Echo	3292	0.67	
Gorakhpur, Uttar Pradesh[24]	Urban	Misra	2003–06	4–18	Echo	118,212	0.5	
Cochin, Kerala	Combined	Soman	2003–06	5–16	Echo	25,033	0.12	

Vaccine against GAS: rationale, challenges and concerns

A recent document from the WHO[31] on GAS vaccine development states, 'In light of the current lack of a clear strategy for primary prevention of GAS infections, there is definitely a place for a safe, effective, affordable and practical GAS vaccine'. An effective vaccine against GAS infections would serve us well not just in preventing RF and RHD, but also post-streptococcal glomeru-

Table 3. Practical issues with group A streptococcus (GAS) vaccine development (modified from WHO[31])

Problem identified	Specific issues
Orphan status	Vaccine has not been wholeheartedly accepted by the industry or larger governmental or non-governmental research bodies
Focus on strains in the developed nations	The vaccine in the most advanced stage of development focuses on common strains in the developed nations. GAS strains are completely different in the developing world
Paucity of clinical trials	Only one vaccine appears to have undergone clinical trials of any kind. Most candidate vaccines have not yet been tested for safety and efficacy
Cost of vaccine	Many of the current candidate vaccines depend on expensive technologies; their products could potentially be non-affordable in developing countries with high disease burden

lonephritis, sore throat, impetigo and invasive forms of streptococcal infections. Clearly the overall magnitude of the problem in the developing world and many parts of India is formidable and is likely to remain so in the foreseeable future. The limitations with secondary prophylaxis (above), the devastating consequences of RHD in terms of mortality and loss of productivity together with the failure of tertiary health services to cope with the disease burden are strong reasons to justify a major thrust towards vaccine development.

However, vaccine development for GAS has been a slow and tedious process thus far and several roadblocks need to be overcome[31]. These include the fear of cross-reactivity with host tissue components resulting in rheumatic fever[26], the need to cover for all strains in endemic areas and ensuring industrial partnership in developing an inexpensive product. Table 3 summarizes the difficulties encountered with the development of a streptococcal vaccine. Additional difficulties include problems in identifying the population at risk within endemic zones, given the paucity of information of disease distribution.

Candidate GAS vaccines: at what stage of development are they?

Several GABHS protein components and the streptococcal polysaccharides have been considered for utilization in developing a vaccine[31–39] (Table 4). Most work has been done in relation with the M-protein, considered to be the virulence factor of the GABHS. The M-protein has an amino terminal end that is hyper variable and shows tremendous variety between regions and even within regions. It frequently undergoes genetic recombination that can lead to loss in the opsonizing ability of type-specific antibodies. Vaccines directed at the amino terminal end M-protein are therefore strain-specific[32]. Since more than hundred different strains have been identified it becomes essential that the vaccine must be polyvalent, i.e. it should incorporate all those strains which are present in the community. The problem associated with the M-protein is that the GABHS has a strong tendency for mutations which can occur rapidly[33]. A vaccine made from the locally dominant strains of GABHS may not be effective if the infection is due to a mutant organism.

Specific problems in the Indian context

Vaccine development

Information on prevailing strains of streptococci based on *emm* typing is available from two Indian reference laboratories located in North (PGI Chandigarh) and South India (CMC Vellore)[40]. A large number GAS *emm* subtypes have been identified in them, and there are relatively few strains common to both centres. A significant number of novel strains have been identified in both centres. Based on these data it appears that it is likely to be challenging to develop a polyvalent vaccine that would cover all M-protein serotypes in India. The focus for India should be on alternative approaches to vaccine development. Given the current situation, it may be fair to state that a vaccine for GAS is unlikely to be available for Indian patients in the near future[26].

Identifying patients at risk

The GAS vaccine is likely to work best if administered in vulnerable children. The following questions are likely to be asked once a vaccine becomes available:

What age group should be considered? Intuitively the benefits of the vaccination would be best if the vulnerable group of 5–15 years is covered. Vaccination should perhaps be initiated at 3 years.

Should every child in the vulnerable age group in India be vaccinated? It is fair to assume that here is considerable variability in the RF–RHD burden across various parts of the country. Vaccination may not be a realistic or cost-effective option in areas with very low disease burden. The epidemiological profile of the disease is likely to change substantially over the next several years. By the time a vaccine is developed, data from current epidemiological studies may not be valid.

Table 4. Candidate vaccines for GAS

Name and reference	Composition (major constituents)	Potential advantages	Potential limitations	Clinical trials, if any
StreptAvax[32]	Sequence of short peptides from the N-terminal region of 26 commonest GAS *emm*-type strains (North American and one conserved epitope (spa))	No known cross-reactive epitopes	Unlikely to be effective in India (numerous M-protein types)	Thirty healthy adult volunteers. Well tolerated and safe. More than four-fold increase in antibody titres to 26 of 27 antigens
Minimal conserved epitope in the C-repeat region of the M protein[33]	B-cell epitope within peptide 145 that does not contain any T-cell epitopes combined with seven type-specific determinants on a polymer backbone	May allow protection against a wider range of GAS subtypes	No industrial partner yet	None yet. Preclinical evaluation completed
Mucosal vaccine based on the conserved region of the M protein[34]	Fusion protein containing the C-terminal half of M-protein expressed in the human oral commensal, *Streptococcus gordonii*.	Easily administered, transported and stored in a lyophilized form (avoiding the need for a cold chain)	Some epitopes in the C repeat region react with anti-myosin antibody from ARF sera and induce anti-myosin antibodies in mice. May not protect against skin infections and PSGN	Safety demonstrated through a study on 100 human volunteers. Phase I trials expected soon
Group A streptococcal carbohydrate[35]	GAS carbohydrate conjugated to tetanus toxoid	The GAS carbohydrate is conserved among all GAS strains. So there are no problems with type-specificity	Fear of cross-reactivity	No human trials; no pre-clinical trials
C5a peptidase[36]	Intranasal preparation: Unadjuvanted recombinant inactivated SCPA. Injectable preparation: Adjuvanted formulation of SCPA	Prospect of a simple vaccine that induces local immunity through IgA antibodies	None identified yet. However, there are no clinical data	It is the only candidate GAS vaccine presently being developed with a large industry collaborator, Wyeth Lederle Vaccines
Streptococcal adhesin, fibronectin-binding protein 1 (Sfb1)[37]	Intranasal immunization of mice with either Sfb1 alone or coupled to cholera toxin B subunit (CTB) resulted in SfbI-specific IgG responses in serum and IgA in lung mucosa.	Antibodies do not appear to cross-react with human tissues; impressive local immunity	Only 70% of GAS strains express Sfb1	No clinical or preclinical studies
Streptococcal cysteine protease[38]	Streptococcal pyrogenic exotoxin B (Spe B)	No data available	No data available	No trials yet

How can we identify children at risk for RF? Mapping the entire country for low and high prevalence zones is likely to be unrealistic. Considerable variations are likely within individual states. Based on current data, one potential approach could be to target rural populations and other presumed high-prevalence zones. This strategy may be justifiable if a clear pattern emerges from recent surveillance studies such as that conducted by the ICMR under the Jai Vigyan Mission Mode Project. For example, if there are clear urban–rural differences, or if there is a pattern that suggests a relationship of RHD prevalence to the human development index of the state or region, preventive efforts can be targetted to these regions.

Potential strategies for the future

Although there appears to be no prospect of a vaccine against GAS becoming available in the near future, efforts to develop one should continue. Efforts to type common GAS strains in various parts of India may also need to continue if a polyvalent vaccine is to be developed in the future. Efforts to unravel the pathogenesis of RF following GAS infection should also continue. It is important to recognize that the incidence of GAS infections has not declined, while RF has virtually disappeared[3,4]. Clearly there are aspects of pathogenesis of RF that we do not still understand.

For the present, secondary prophylaxis appears to be the only realistic approach for the control of RF and RHD. The lack of availability of benzathine penicillin is a serious problem that needs to be overcome through governmental intervention. There is continued need for education about the disease among health professionals and the general public, especially in areas with high disease burden. The importance of penicillin prophylaxis needs to be reiterated at all levels. Patients with established RHD and those who have had an episode of RF should receive targetted education on the importance of penicillin prophylaxis.

Areas with potentially high RF–RHD burden should be targetted for disease control. These include tribal pockets, rural populations and urban slums. Continued efforts to obtain accurate data on disease burden should be made from these regions as well as from those parts of India (such as the eastern and northeastern states), with little published data. It is also important to recognize that the epidemiology of RF and RHD in India may be rapidly changing in many parts of the country. A substantial decline in disease burden is likely in those parts of India that are experiencing substantial improvements in human development.

Conclusion

Vaccines should not be seen as a magic bullet to control any disease, disregarding various interactive forces that contribute to disease occurrence. Appropriate and specific protective measures have certainly an important place in the prevention of diseases. This is particularly applicable to RF and RHD. Any public health effort to control RF–RHD should perhaps adopt a holistic approach that includes all facets of disease prevention for an enduring impact on reduction of disease burden.

1. Gordis, L., The virtual disappearance of rheumatic fever in the United States: lessons in the rise and fall of disease. *Circulation*, 1985, **72**, 1155–1162.
2. Mas Lago, P., Eradication of poliomyelitis in Cuba: a historical perspective. *Bull. WHO*, 1999, **77**, 681–687.
3. Rheumatic fever and rheumatic heart disease. World Health Organisation Technical Report Series No. 923, 2004, pp. 1–122.
4. Kumar, R. K., Rammohan, R., Kaplan, E. L. and Narula, J. S., Epidemiology of streptococcal pharyngitis, rheumatic fever and rheumatic heart disease. In *Rheumatic Fever* (eds Narula, J. *et al.*), American Registry of Pathology, Washington, DC, 1999, pp. 41–78.
5. Veasy, L. G. *et al.*, Persistence of acute rheumatic fever in the intermountain area of the United States. *J. Pediatr.*, 1994, **124**, 9–16.
6. Padmavati, S., Epidemiology of cardiovascular disease in India: I. Rheumatic heart disease. *Circulation*, 1962, **25**, 703–710.
7. Padmavati, S., Rheumatic fever and rheumatic heart disease in developing countries. *Bull. WHO*, 1978, **56**, 543–550.
8. Koshi, G., Benjamin, V. and Cherian, G., Rheumatic fever and rheumatic heart disease in rural South Indian children. *Bull. WHO*, 1981, **59**, 599–603.
9. Community control of rheumatic fever and rheumatic heart disease. Report of ICMR Task Force study, ICMR, Delhi 1994.
10. Pilot study on the feasibility of utilizing the existing school health services in Delhi for the control of RF/RHD. ICMR final report, 1990.
11. Padmavati, S., Present status of rheumatic fever and rheumatic heart disease in India. *Indian Heart J.*, 1995, **47**, 395–398.
12. Patel, D. C., Patel, N. I., Patel, J. D. and Patel, S. D., Rheumatic fever and rheumatic heart disease in school children of Anand. *J. Assoc. Physicians India*, 1986, **34**, 837–839.
13. Avasthi, G., Singh, D., Singh, C., Aggarwal, S. P., Bidwai, P. S. and Avasthi, R., Prevalence survey of rheumatic fever (RF) and rheumatic heart disease (RHD) in urban and rural school children in Ludhiana. *Indian Heart J.*, 1987, **39**, 26–28.
14. Grover, A., Dhawan, A., Iyengar, S. D., Anand, I. S., Wahi, P. L. and Ganguly, N. K., Epidemilogy of rheumatic fever and rheumatic heart disease in a rural community in northern India. *Bull. WHO*, 1993, **71**, 59–66.
15. Thakur, J. S., Negi, P. C., Ahluwalia, S. K. and Vaidya, N. K., Epidemiological survey of rheumatic heart disease among school children in the Shimla Hills of northern India: prevalence and risk factors. *J. Epidemiol. Commun. Health*, 1996, **50**, 62–67.
16. Kumar, P., Garhwal, S. and Chaudhary, V., Rheumatic heart disease: a school survey in a rural area of Rajasthan. *Indian Heart J.*, 1992, **44**, 245–246.
17. Gupta, I., Gupta, M. L., Parihar, A. and Gupta, C. D., Epidemiology of rheumatic and congenital heart diseases in school children. *J. Indian Med. Assoc.*, 1992, **90**, 57–59.
18. Vashistha, V. M., Kalra, A., Kalra, K. and Jain, V. K., Prevalence of rheumatic heart disease in school children. *Indian Pediatr.*, 1993, **30**, 53–56.
19. Agarwal, A. K., Yunus, M., Ahmad, J. and Khan, A., Rheumatic heart disease in India. *J. R. Soc. Health*, 1995, **115**, 303–309.
20. Kaul, R. R., Masoodi, M. A., Wani, K. A., Hassan, G. and Qureshi, K. A., Prevalence of rheumatic heart disease in school children (5–15 years) in a rural block of Srinagar, *JK Practitioner*, 2005, **12**, 160–162.
21. Lalchandani, A., Kumar, H. R. P. and Alam, S. M., Prevalence of rheumatic fever and rheumatic heart disease in rural and urban school children of district Kanpur. *Indian Heart J.*, 2000, **52**, 672.
22. Jose, V. J. and Gomathi, M., Declining prevalence of rheumatic heart disease in rural schoolchildren in India: 2001–2002. *Indian Heart J.*, 2003, **55**, 158–160.
23. Periwal, K. L., Gupta, B. K., Panwar, R. B., Khatri, P. C., Raja, S. and Gupta, R., Prevalence of rheumatic heart disease in school children in Bikaner: an echocardiographic study. *J. Assoc. Physicians India*, 2006, **54**, 279–282.
24. Misra, M. *et al.*, Prevalence of rheumatic heart disease in school-going children of eastern Uttar Pradesh. *Indian Heart J.*, 2007, **59**, 42–43.
25. Routray, S. N., Has the prevalence of rheumatic fever/rheumatic heart disease really changed? A hospital-based study. *Indian Heart J.*, 2003, **55**, 152–157.
26. Tandon, R., Is it possible to prevent rheumatic fever. *Indian Heart J.*, 2004, **56**, 677–679.
27. Kumar, R., Thakur, J. S., Aggarwal, A. and Ganguly, N. K., Compliance of secondary prophylaxis for controlling rheumatic fever and rheumatic heart disease in a rural area of northern India. *Indian Heart J.*, 1997, **49**, 282–288.
28. Saran, R. K., Sinha, N., Hasan, M., Bhatia, M. C. and Bhatia, K. B., Is monthly injection of benzathine penicillin adequate for rheumatic fever prophylaxis in our country? *J. Assoc. Physicians India*, 1985, **33**, 641–643.
29. Ravisha, S., Tullu, M. S. and Kamat, J. R., Rheumatic fever and rheumatic heart disease: clinical profile of 550 cases in India. *Arch. Med. Res.*, 2003, **34**, 382–387.

30. Sainani, G. and Sainani, A. R., Rheumatic fever: How relevant in India today. *J. Assoc. Physicians India* (*Suppl.*), 2006, **54**, 42–47.
31. World Health Organisation, Group A streptococcal vaccine development: current status and issues of relevance to less developed countries. Group A streptococcal disease. Discussion papers on child health. WHO, Geneva, 2005; www.who.int/child_adolescent_health/documents/research/en/index.html (accessed 9 May 2007).
32. McNeil, S. A. *et al.*, Safety and immunogenicity of 26-valent group a streptococcus vaccine in healthy adult volunteers. *Clin. Infect. Dis.*, 2005, **41**, 1123–1124.
33. Brandt, E. R. *et al.*, Opsonic human antibodies from an endemic population specific for a conserved epitope on the M protein of group A streptococci. *Immunology*, 1996, **89**, 331–337.
34. Hruby, D. E., Hodges, W. M., Wilson, E. M., Franke, C. A. and Fischetti, V. A., Expression of streptococcal M protein in mammalian cells. *Proc. Natl. Acad. Sci. USA*, 1988, **85**, 5714–5717.
35. Salvadori, L. G., Blake, M. S., McCarty, M., Tai, J. Y. and Zabriskie, J. B., Group A streptococcus–liposome ELISA antibody titers to group A polysaccharide and opsonophagocytic capabilities of the antibodies. *J. Infect. Dis.*, 1995, **171**, 593–600.
36. Ji, Y., Carlson, B., Kondagunta, A. and Cleary, P. P., Intranasal immunization with C5a peptidase prevents nasopharyngeal colonization of mice by the group A Streptococcus. *Infect. Immunol.*, 1997, **65**, 2080–2087.
37. Valentin-Weigand, P., Talay, S. R., Kaufhold, A., Timmis, K. N. and Chhatwal, G. S., The fibronectin binding domain of the Sfb protein adhesin of streptococcus pyogenes occurs in many group A streptococci and does not cross-react with heart myosin. *Microb. Pathog.*, 1994, **17**, 111–120.
38. Kapur, V., Maffei, J. T., Greer, R. S., Li, L. L., Adams, G. J. and Musser, J. M., Vaccination with streptococcal extracellular cysteine protease (interleukin-1 beta convertase) protects mice against challenge with heterologous group A streptococci. *Microb. Pathog.*, 1994, **16**, 443–450.
39. Yokoyama, Y. and Harabuchi, Y., Intranasal immunization with lipoteichoic acid and cholera toxin evokes specific pharyngeal IgA and systemic IgG responses and inhibits streptococcal adherence to pharyngeal epithelial cells in mice. *Int. J. Pediatr. Otorhinolaryngol.*, 2002, **63**, 235.
40. Dey, N. *et al.*, High diversity of group A streptococcal emm types in an Indian community: the need to tailor multivalent vaccines. *Clin. Infect. Dis.*, 2005, **40**, 46–51.