Evaluating efficiency and equity of prevention and control strategies for rheumatic fever and rheumatic heart disease in India: an extended cost-effectiveness analysis

Jyoti Dixit, Shankar Prinja, Gaurav Jyani, Pankaj Bahuguna, Ankur Gupta, Rajesh Vijayvergiya, Rajesh Kumar

Summary

Background There is a dearth of evidence on the cost-effectiveness of a combination of population-based primary, secondary, and tertiary prevention and control strategies for rheumatic fever and rheumatic heart disease. The present analysis evaluated the cost-effectiveness and distributional effect of primary, secondary, and tertiary interventions and their combinations for the prevention and control of rheumatic fever and rheumatic heart disease in India.

Methods A Markov model was constructed to estimate the lifetime costs and consequences among a hypothetical cohort of 5-year-old healthy children. Both health system costs and out-of-pocket expenditure (OOPE) were included. OOPE and health-related quality-of-life were assessed by interviewing 702 patients enrolled in a population-based rheumatic fever and rheumatic heart disease registry in India. Health consequences were measured in terms of life-years and quality-adjusted life-years (QALY) gained. Furthermore, an extended cost-effectiveness analysis was undertaken to assess the costs and outcomes across different wealth quartiles. All future costs and consequences were discounted at an annual rate of 3%.

Findings A combination of secondary and tertiary prevention strategies, which had an incremental cost of ₹23 051 (US$30) per QALY gained, was the most cost-effective strategy for the prevention and control of rheumatic fever and rheumatic heart disease in India. The number of rheumatic heart disease cases prevented among the population belonging to the poorest quartile (four cases per 1000) was four times higher than the richest quartile (one per 1000). Similarly, the reduction in OOPE after the intervention was higher among the poorest income group (29·8%) than among the richest income group (27·0%).

Interpretation The combined secondary and tertiary prevention and control strategy is the most cost-effective option for the management of rheumatic fever and rheumatic heart disease in India, and the benefits of public spending are likely to be accrued much more by those in the lowest income groups. The quantification of non-health gains provides strong evidence for informing policy decisions by efficient resource allocation on rheumatic fever and rheumatic heart disease prevention and control in India.

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Introduction

Rheumatic fever and rheumatic heart disease are neglected public health problems.[1] Rheumatic heart disease is the most commonly acquired heart disease in those younger than 25 years.[2] According to WHO, at least 15·6 million people have rheumatic heart disease, of which two thirds are children aged between 5 years and 15 years.[1] Of the 0·5 million individuals who acquire rheumatic fever every year, 300 000 go on to develop rheumatic heart disease during their lifetime.[1] 233 000 annual deaths are directly attributable to rheumatic fever or rheumatic heart disease, of which 95% occur in low-income countries.[3] In India, the prevalence of rheumatic heart disease has been reported to be in the range of 0·12–4·54 per 1000 children aged 5–15 years.[4] The number of rheumatic heart disease cases in India could range from 0·44 to 3·37 million.[5] Since these estimates are based on conservative assumptions, the true disease burden is likely to be substantially higher.

A range of primary, secondary, and tertiary prevention strategies is available,[6] which can be used in isolation or in different combinations (appendix p 8). Since these interventions have different effects on the prevention of disease onset, disease progression, mortality, or quality of life, a composite measure such as quality-adjusted life-years (QALY) becomes more appropriate to compare the outcomes.[7] The cost of various rheumatic fever and rheumatic heart disease prevention and control strategies also varies significantly; hence, a full economic evaluation becomes the most appropriate design to generate evidence for decision making. Since the disease is concentrated among poorer groups, any prevention approach is likely to have equity implications.

See **Online** for appendix

Research in context

Evidence before this study

We searched PubMed for English-language studies published since the commencement of the database up to June 15, 2022, that estimated the cost-effectiveness of prevention and control strategies for rheumatic fever and rheumatic heart disease in India. All economic evaluations reporting directly measurable outcomes such as disease cases averted, deaths averted, life-years gained, or constructed metrics such as quality-adjusted life-years (QALYs) gained and disability-adjusted life-years (DALYs) averted were included in the review. We combined disease-related terms such as "group A streptococcus" OR "group A streptococcal" OR "streptococcus pyogenes" OR "group A streptococcus" OR "group A streptococcal" OR "streptococcus pyogenes" OR "group-A streptococcal pharyngitis" OR "GAS pharyngitis" OR "pharyngitis" OR "rheumatic fever" OR "rheumatic heart disease" OR "stroke" AND ("rheumatic fever" OR "rheumatic heart disease") OR "endocarditis" AND ("rheumatic fever" OR "rheumatic heart disease") with health economic terms such as "cost-effectiveness" OR "cost effectiveness" OR "incremental cost-effectiveness ratio" OR "ICER" OR "cost-benefit" OR "cost benefit" OR "cost-utility" OR "cost utility" OR "health economics" OR "economics" OR "economic evaluation" OR "quality adjusted life year" OR "QALY" OR "disability adjusted life year" OR "DALY". The initial search using the keywords identified 321 articles from the database. A total of 44 economic evaluations were found for group A streptococcus pharyngitis, rheumatic fever, and rheumatic heart disease. The majority (93%) of the studies were conducted in countries categorised as high income or upper middle income. Only three studies were found from low-income and middle-income economies or less (two studies from Africa and one study from India). Two studies (from Africa and India) compared all the three prevention strategies, primary, secondary, and tertiary, in isolation. However, none of the studies compared a combination of either of these population-based control strategies so far. There is a heterogeneity of evidence across different studies. Although some previous evaluations have reported primary prevention as the most cost-effective option, other studies from sites endemic for rheumatic heart disease have suggested echocardiographic screening with lifelong secondary prophylaxis as a low-cost tool and perhaps a cost-effective strategy. Hence, there is no clear consensus on the cost-effectiveness of prevention strategies for rheumatic fever and rheumatic heart disease. Moreover, the generalisability of these studies to India is difficult since findings are sensitive to local input variables. Furthermore, no study has evaluated the distributional effect of primary, secondary, or tertiary interventions and their combinations for the prevention and control of rheumatic fever and rheumatic heart disease. This absence of information becomes important in the case of rheumatic fever and rheumatic heart disease because these diseases have a strong association with income status, and the cost of treatment is a factor in limiting access to care in low-income and middle-income countries.

Added value of this study

The findings of our study provide important evidence on the cost-effectiveness and distributional effect of primary, secondary, and tertiary interventions and their combinations for the prevention and control of rheumatic fever and rheumatic heart disease in India. Our study is a valuable addition to the existing international evidence available on this topic, because no previous studies have compared a combination of either of these population-based prevention and control strategies. We found that adding primary prevention leads to a 29% reduction in rheumatic fever cases. The highest reduction in the number of clinical rheumatic heart disease (54%) and severe rheumatic heart disease cases (76%) was observed when primary, secondary, and tertiary interventions were scaled up compared with all other interventions. The combined secondary and tertiary prevention strategy was the most cost-effective strategy, with an incremental cost of ₹23 051 (US$30) per QALY gained. The number of rheumatic heart disease cases prevented with combined secondary and tertiary interventions among the poorest 25% of the population (four cases per 1000) was four times higher than the richest quartile (one per 1000 cases). Similarly, the relative reduction in out-of-pocket expenditure with the combined secondary and tertiary prevention strategy was the highest among the poorest income group (29·8%), followed by poor (29·5%), middle (28·8%), and rich (27·0%) quartiles. The numbers of patients incurring catastrophic health expenditures (23·1%) and impoverishing health expenditures (7·9%) were higher in the poorest quartile than the richest quartile wherein only 0·3% incurred catastrophic health expenditures and none were impoverished. The combined secondary and tertiary intervention was the most cost-effective strategy across all population subgroups stratified by the level of wealth, with the highest efficiency among the least wealthy.

Implications of all the available evidence

Rheumatic fever and rheumatic heart disease are diseases of world's poorest communities, and they have long been neglected by global and national health efforts. Our study offers compelling evidence for the integration of rheumatic fever and rheumatic heart disease prevention and control into national programmes, on efficiency, equity, and financial risk protection grounds. We recommend the expansion of the coverage for secondary and tertiary care interventions. However, the study findings are sensitive to local input variables on costs, quality of life, and disease burden, and thus cannot be generalisable to other low-income and middle-income countries.

As a result, an extended cost-effectiveness analysis (ECEA), which evaluates the distributional outcomes and costs in addition to the average population estimates of efficiency, becomes more valuable for decision making.[8]

Most of the economic evaluations conducted so far have concentrated on interventions for the prevention of rheumatic fever.[9,10] However, rheumatic heart disease has more important long-term consequences, owing to the high costs associated with a usually lifelong secondary prophylaxis for the prevention of rheumatic fever recurrence, and associated with the medical management and surgical interventions required to manage the complications of rheumatic heart disease.[6] Some previous evaluations have reported primary prevention as the most cost-effective option.[10–12] However, some studies on endemic sites in rheumatic heart disease have suggested that echocardiographic screening with lifelong secondary prophylaxis is a cost-effective strategy when compared with primary prevention.[13,14] Therefore, there is no clear consensus on the cost-effectiveness of prevention and control strategies for rheumatic fever and rheumatic heart disease. Moreover, the generalisability of these studies to the Indian population is difficult, because findings are sensitive to local epidemiological and cost variables.

In the Indian context, there is only one study that has evaluated the cost–benefit ratio of primary, secondary, and tertiary strategies.[11] The authors reported primary prevention (the treatment of culture-positive group A streptococcal pharyngitis cases) to be the most cost-effective option. However, there were several methodological limitations to this study. Firstly, there was no description of how the social cost of children who dropped out of school was computed. Secondly, the social costs of those who dropped out of school who developed rheumatic heart disease were only included in secondary and tertiary prevention alone scenarios, assuming the 100% effectiveness of primary prevention, which is unrealistic. This assumption of 100% effectiveness by Soudarsanane and colleagues[11] is overoptimistic and underestimates the medical, indirect, and social costs of those who develop rheumatic heart disease in primary prevention strategies, leading to the gross underestimation of cost of primary prevention.[11] Thirdly, the unit costs of various services were obtained from older published literature and adjusted for inflation. Lastly, there was no quantification of the improvement in quality of life, which offers the potential to improve patient care and clinical outcomes. Considering these gaps in the literature, we assessed the cost-effectiveness of primary, secondary, and tertiary prevention strategies in isolation and in different combinations in India. In addition, we ascertained the distributional effect of interventions on health consequences and out-of-pocket expenditure (OOPE) across population subgroups stratified by level of wealth.

Methods

Evaluation approach

A Markov cohort model was used to estimate lifetime health outcomes and resulting costs among a cohort of 1000 healthy children for seven intervention scenarios—namely, primary prevention; secondary prevention; tertiary prevention; primary and secondary prevention; secondary and tertiary prevention; primary and tertiary prevention; and primary, secondary, and tertiary prevention. In each intervention scenario, the coverage of the intervention was assumed to be 70%. Each of these interventions was compared against a routine care scenario that comprised a mix of interventions at their real-world coverage.[15] A detailed description of the scenarios considered in the present model is presented in the appendix (p 9).

This model consists of ten mutually exclusive disease states (appendix p 3). Costs and utilities were assigned to each health state and then were aggregated. The model was run on an annual cycle length. The health outcomes were measured in terms of QALYs using a societal perspective (both health system and patient perspectives). Indirect expenditure due to the wage loss of patients or their caregivers was not included in the analysis in accordance with Indian health technology assessment guidelines.[7] Future costs and outcomes were discounted at the standard rate of 3% per year. Guidelines of Consolidated Health Economic Evaluation Reporting Standards were used for reporting these outcomes.[16] The study was approved by the Institutional Ethics Committee of the Post Graduate Institute of Medical Education and Research in Chandigarh, India (reference number NK/4348/PhD/4608).

Health states: definitions, care, and costs

The model started with a cohort of 1000 children aged 5 years who appeared to be healthy , without group A streptococcal pharyngitis, rheumatic fever, or rheumatic heart disease, because the incidence of rheumatic fever before the age of 5 years is low compared with in those older than 5 years.[17,18] An average of 7 episodes of sore throat were assumed to occur per year among children aged 5–15 years.[19] A probability of 0·024 for group A streptococcal pharyngitis per episode of sore throat was assumed among children aged 5–15 years.[15,20] The possibilities of developing three commonly observed complications were considered: congestive heart failure, stroke, and infective endocarditis. The operational definitions of health states obtained from published literature are given in the appendix (pp 5–6).[21]

Intervention costs

Health system cost and OOPE incurred by patients were estimated separately for primary, secondary, and tertiary prevention strategies. A detailed description of the costs included in each scenario is summarised in the appendix (p 4). To estimate the cost of treatment, actual

care-seeking patterns were used by level of care provision in public health-care facilities (primary health centres, community health centres, district hospitals, and tertiary hospitals) on the basis of an analysis of data collected from 702 patients enrolled in a rheumatic fever and rheumatic heart disease registry.[15] The patients in the registry were at different stages of disease and had different treatment profiles, with an average follow-up of 10 years.[15]

Cost of primary prevention

The health system costs per outpatient consultation at primary health centres, community health centres, and district hospitals were obtained from National Health System Cost Database (appendix pp 14–15).[22] The primary data on the cost of throat swab cultures were collected using a mixed micro-costing approach[23] (appendix p 7). The culture testing was assumed to be available only in the district hospital and all throat swabs were assumed to be transported to district hospital for the diagnosis of group A streptococcal pharyngitis. A standardised tool used for economic costing studies of health facilities in India was used to collect data from a district hospital situated in Mohali, India.[22,24,25] The service delivery cost consisted of the opportunity cost of human resource time in sample collection and its testing; capital cost consisted of the cost incurred for building space, medical equipment, and furniture; and the cost incurred on consumables and overheads included electricity, water, and maintenance. In addition, OOPE incurred by the patients with group A streptococcal pharyngitis on antibiotic treatment was elicited from published literature.[26] Costs were converted to US$ using a conversion rate of 1 US$ being equivalent to ₹76.[27]

Cost of secondary prevention

The health system cost of secondary prevention included the cost of outpatient consultation at different levels of care providers and the cost of diagnostics including throat swab culture, white blood cell count, erythrocyte sedimentation rate, anti-streptolysin O titre, electrocardiography (ECG), chest radiograph, and echocardiography. The health system cost was ascertained by collecting data on resources consumed for the provision of cardiac care services in a large tertiary care public hospital using a mixed micro-costing approach.[24,25] The health system costs of outpatient consultation and echocardiography were assessed at a tertiary hospital, and the health system cost of an ECG was estimated at both a tertiary hospital and a district hospital because an ECG is provided at both centres in the real world. The cost of other diagnostic services (erythrocyte sedimentation rate, white blood cell, anti-streptolysin O titre, and chest radiograph) were obtained from previously conducted studies in similar settings.[24,25] The OOPE included monthly expenditure on secondary prophylaxis (consultation fees, drugs, consumables, etc), laboratory investigations and diagnostic tests, and direct non-medical expenditure including travelling, food, boarding, lodging, and informal payment. The data on OOPE was collected by interviewing 106 patients with rheumatic fever (on secondary prevention) who were enrolled in a population-based registry situated in the two districts of Punjab-Ropar and Mohali, and the union territory Chandigarh, using a structured interview schedule as part of a cross-sectional survey undertaken in 2016.[15]

Cost of tertiary prevention

The cost of tertiary prevention included health system cost and OOPEs for outpatient consultation, diagnostic tests, hospitalisation, and surgery. The health system cost of outpatient consultation was assessed in both cardiology and cardiothoracic vascular surgery departments.[28] The cost of cardiac care services such as outpatient consultation, diagnostic tests (chest radiograph, echocardiography, and ECG), hospitalisation (with or without intensive care), valve replacement surgery (single, double, or triple), and balloon valvotomy were estimated and included in the analysis. OOPEs incurred by patients with rheumatic heart disease were obtained by interviewing 283 patients with rheumatic heart disease with complications and 313 patients with rheumatic heart disease without complications. All these patients were part of the rheumatic fever and rheumatic heart disease registry. The OOPE were estimated in terms of monthly expenditure on illness borne by patients with rheumatic heart disease (stratified by with and without rheumatic heart disease-associated complications), expenditure incurred per episode of hospitalisation, valve replacement surgery (stratified according to the number of valves and type of valve: either mechanical or bioprosthetic), and balloon valvotomy. The monthly OOPE included medicines, laboratory investigations, diagnostic tests, anticoagulants, and follow-up care.

Valuation of consequences

For each treatment strategy, the effectiveness indicator was measured in terms of the number of life-years and QALYs gained. A systematic review and meta-analysis for the assessment of burden of group A streptococcal pharyngitis, rheumatic fever, and rheumatic heart disease in India was conducted.[29] The effectiveness of primary, secondary, and tertiary prevention was obtained from published literature.[30–32] The sensitivity and specificity of throat swab culture and echocardiography tests were also obtained from published studies.[33–35] The coverage at current or counterfactual scenarios was considered to be 10%. The coverage rate of 10% was supported by stakeholder consultation, which included clinicians, researchers, and policy decision makers at the state and national level. We assumed that the coverage of services in the intervention scenario would be scaled up to 70% from 10%, which was based on the observed service use

of 74·6% among patients in the registry.[15] This assumed coverage is also supported by the reported coverage of other services in national health programmes and care-seeking behaviour. A situational analysis published by Save the Children in 2019 based on data from National Family Health Survey showed that nearly 72·7% of respondents sought treatment for respiratory infections at health facilities in India.[26] Furthermore, many national programmes in India have a coverage rate of more than 70%. For instance, approximately 95% of patients with tuberculosis were put on treatment according to the India tuberculosis report 2022 by the Ministry of Health and Family Welfare, Government of India. The treatment success rate among patients with tuberculosis in the public sector is 83% and in the private sector is 82% in India.[36] Another example is from the National AIDS and sexually transmitted disease control programme 2021 in India, which found that 83% of patients diagnosed with HIV are on antiretroviral therapy.[37]

The rates of progression of disease between different health states were ascertained from the published literature.[38,39] Because the published estimates of disease progression were available in the form of rates, these were then converted into annual transition probabilities with the appropriate methods.[40] Age-specific all-cause mortality rates were obtained from the Indian sample registration system life table.[41] The utility values were identified for each health state in the model. To measure the health-related quality of life of the patients, the EuroQoL five dimensions tool, comprising the EQ-5D-5L descriptive system and EQ-VAS,[42,43] was used to interview 702 patients with rheumatic fever or rheumatic heart disease who were seeking different treatments.[44] We used a reference population value set from Thailand to compute the health-related quality-of-life index value of individual health states, given the absence of a reference population value set from India. This method is in accordance with the recommendations made in the draft Indian reference case, developed by the Health Technology Assessment in India for conducting health technology assessments in India.

Statistical analysis

An incremental cost per QALY gained was estimated for each intervention scenario. Additionally, an ECEA was undertaken for assessing the costs and outcomes across different income groups. For the ECEA, three input variables, namely the risk of rheumatic fever among patients with group A streptococcal pharyngitis, OOPE, and health-related quality of life, were varied across four income quartiles (rich, middle, poor, and poorest). The variation in the risk of rheumatic fever according to socioeconomic status was obtained from published literature.[45,46] The primary data collected from 702 patients enrolled in the rheumatic fever and rheumatic heart disease registry were stratified into quartiles: poorest, poor, middle, and rich, based on per-person monthly consumption expenditure. The stratified data were then analysed to compute utility scores as well as OOPE for each health state for each respective income quartile. The outcomes of ECEA were quantified in terms of the number of cases and deaths averted, reduction in OOPE, and number of patients incurring catastrophic and impoverishing health expenditures across income quartiles with alternative intervention scenarios. The input variables used in ECEA are detailed in the appendix (pp 16–18). The conceptual framework of the methods used in ECEA is depicted in figure 1. The mathematical model was developed in Microsoft Excel version 2019.

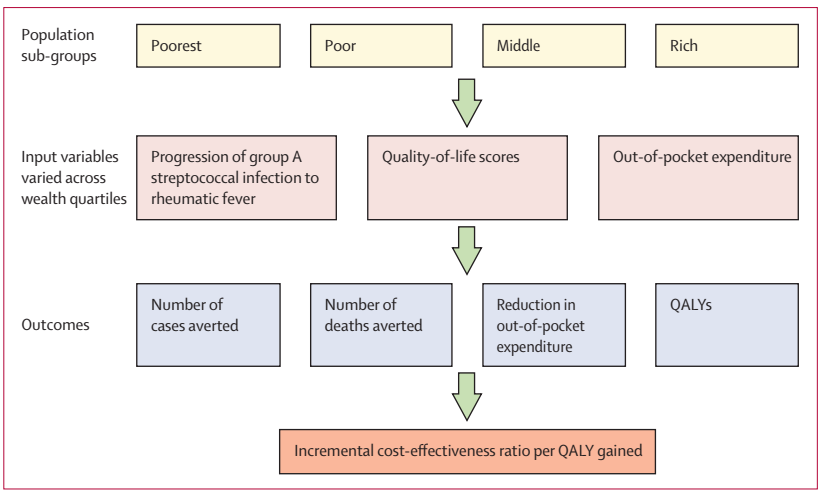

Figure 1: **Conceptual framework of the extended cost-effectiveness analysis**
QALY=quality-adjusted life-years.

Sensitivity analysis

The effect of uncertainty in the variable values used in eight scenarios (seven intervention and one routine care scenario) on the overall incremental cost-effectiveness ratio (ICER) was assessed with a probabilistic sensitivity analysis. We varied estimates on clinical variables such as transition probabilities; mortality rates; clinical effectiveness (relative risk) of primary, secondary, and tertiary prevention and control strategies; diagnostic accuracy in terms of sensitivity and specificity of throat swab culture test and echocardiography; health-care service use patterns; and costs and utility scores in the probabilistic sensitivity analysis. The discount rate was varied from 3% to 5%. We applied different distributions for each of these input variables. We used β distribution for clinical variables and utility scores, γ distribution for costs, and uniform distribution for diagnostic accuracy and health-care service use patterns. The actual value of the SE or upper and lower bounds were used to create a distribution around the point estimate of a variable. Wherever the upper and lower bounds were not provided, a variation of 50% on either side of the base value was used for cost variables, and a variation of 20% was used for clinical variables. The median value of ICER with the

	Costs in ₹ (US$)	Incremental cost in ₹ (US$)	Effect (QALYs)	Incremental effect	Incremental cost-effectiveness ratio (cost per QALY)
Secondary prevention	₹10 695 525 ($140 730)	..	28 811·3	..	..
Secondary and tertiary	₹10 758 143 ($141 544)	₹62 618 ($834)	28 814·0	2·7	₹23 051 ($30)
Primary, secondary, and tertiary	₹59 987 672 ($789 311)	₹49 229 529 ($647 757)	28 823·0	9·0	₹5 411 599 ($71 205)
Routine care	₹11 725 084 ($154 277)	..	28 804·2	..	Dominated
Tertiary	₹12 217 558 ($160 757)	..	28 809·0	..	Dominated
Primary	₹60 675 308 ($798 359)	..	28 816·8	..	Dominated
Primary and tertiary	₹60 710 609 ($798 823)	..	28 820·1	..	Dominated
Primary and secondary	₹59 967 995 ($789 052)	..	28 821·2	..	Extendedly dominated

QALY=quality-adjusted life-years.

Table 1: **Costs, outcomes, and cost-effectiveness of various strategies for the prevention and control of rheumatic fever and rheumatic heart disease in India**

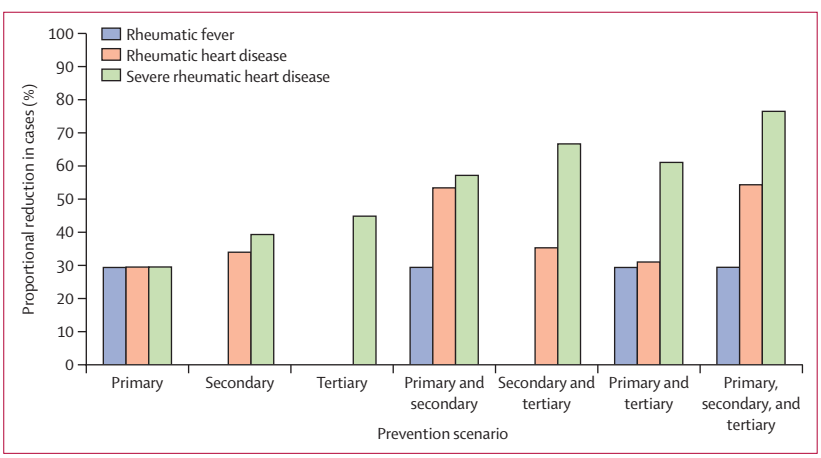

Figure 2: **Reduction in rheumatic fever, rheumatic heart disease, and severe rheumatic heart disease cases relative to routine care**

2·5th and 97·5th percentiles was calculated with 999 Monte Carlo simulations. The probability of the prevention strategies to be cost-effective at a willingness-to-pay threshold equal to per-person gross domestic product (GDP) was also estimated using a societal perspective. As of 2022, the per-person GDP of India is estimated to be ₹146 890 (equivalent to US$1928).[47] In addition to this, univariate sensitivity analysis was undertaken by varying coverage rates from 20–70% to assess the effect of the coverage rate on cost-effectiveness of the most efficient intervention.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The present model estimated the mean prevalence of group A streptococcal pharyngitis among children aged 5–15 years to be 26·3%. Furthermore, the prevalence of rheumatic fever and rheumatic heart disease among children aged 5–14 years was estimated to be 1·43 per 1000 population. The lifetime risk of developing rheumatic heart disease among patients with rheumatic fever was 56% in the counter-factual routine care scenario. Overall, the lifetime societal cost (health system and patient costs) for implementing secondary intervention was the lowest compared with all other interventions (₹10 695 525 [$140 730]) followed by a combination of secondary and tertiary interventions (₹10 758 143 [$141 544]). The lifetime cost was highest when combined primary and tertiary interventions were implemented (₹60 710 609 [$798 823]), followed by primary intervention alone (₹60 675 308 [$798 359]; table 1). We estimated that adding primary prevention alone to routine care leads to a 29% reduction in rheumatic fever cases. The highest reduction in the number of clinical rheumatic heart disease cases (54%) and severe rheumatic heart disease cases (76%) were when primary, secondary, and tertiary interventions were scaled up compared with the routine care scenario (figure 2; appendix p 27).

The highest number of life-years (28 833 life-years) was gained with the combination of primary, secondary, and tertiary interventions followed by primary and secondary interventions combined (28 832 life-years), primary and tertiary interventions combined (28 831 life-years), primary interventions (28 830 life-years), and combined secondary and tertiary preventions intervention (28 827 life-years). Similarly, the number of QALYs gained was highest in combined primary, secondary, and tertiary interventions (28 823·0 QALYs) followed by primary and secondary interventions (28 821·2 QALYs), primary and tertiary interventions (28 820·1 QALYs), primary interventions (28 816·8 QALYs), and combined secondary and tertiary interventions (28 814·0 QALYs) as shown in table 1.

We found that three interventions—namely, combined secondary and tertiary interventions, secondary intervention alone, and a combination of primary,

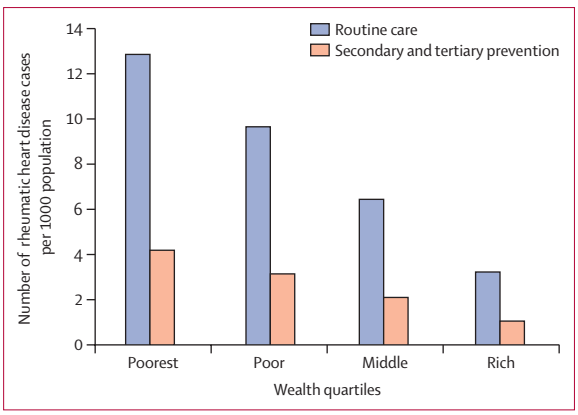

Figure 3: **Number of rheumatic heart disease cases per 1000 population in routine care and combined secondary and tertiary scenarios across different wealth quartiles**

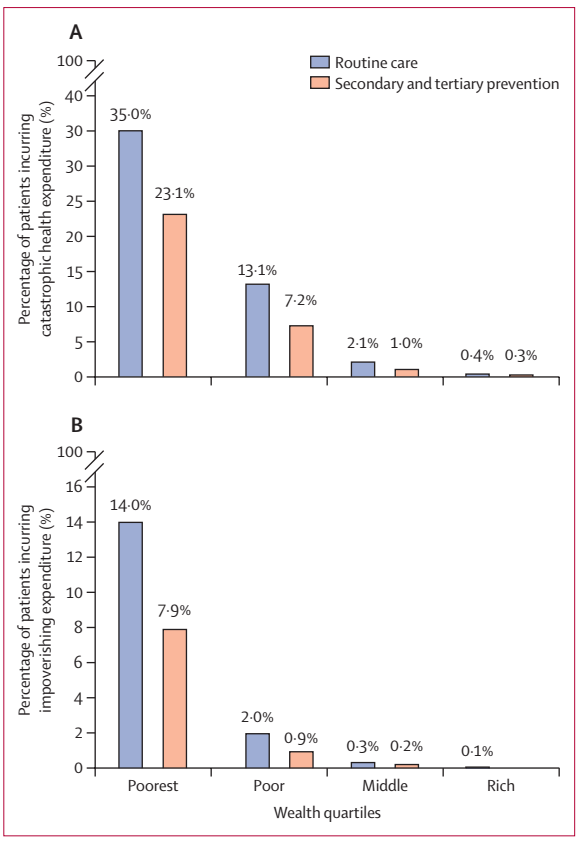

Figure 4: **Percentage of patients incurring catastrophic (A) and impoverishing (B) health expenditure in the routine care scenario versus the combined secondary and tertiary intervention scenario**

secondary, and tertiary interventions—were the most cost-effective of all other interventions. The ICER of the combined primary, secondary, and tertiary intervention (₹5 411 599 [$71 205]) is 37 times the per-person GDP of India. Among the three remaining strategies, a combination of secondary and tertiary prevention, with an incremental cost of ₹23 051 ($30) per QALY gained, was the most cost-effective strategy (table 1).

The number of rheumatic heart disease cases prevented with combined secondary and tertiary interventions among the poorest 25% of the population (four per 1000 cases) was four times higher than among the richest quartile (one per 1000 cases; figure 3). Similarly, the relative reduction in OOPE with the combined secondary and tertiary prevention strategy was highest among the poorest income group (29·8%), followed by poor (29·5%), middle (28·8%), and rich (27·0%) quartiles, as shown in the appendix (p 28). The number of patients incurring catastrophic health expenditures (23·1%) and impoverishing health expenditures (7·9%) was higher in the poorest quartile than the richest quartile, wherein only 0·3% were found to incur catastrophic health expenditures and none incurred impoverishing health expenditures (figure 4).

The incremental cost per QALY gained with implementation of combined secondary and tertiary interventions among the poorest quartile was ₹22 902 ($301) and among the richest quartile was ₹32 657 ($428; table 2). The combined secondary and tertiary intervention was the most cost-effective strategy across all population subgroups stratified by the level of wealth, and was more cost-effective among the poorest quartile compared with all other wealth quartiles. At the current willingness-to-pay threshold at a one-time per-person GDP of ₹146 890 ($1928) in India, the combined secondary and tertiary intervention had 100% probability to be cost-effective (appendix p 29). Furthermore, a univariate analysis also suggested that by varying the coverage rate from 20–60%, a combination of secondary and tertiary prevention scenarios was the most cost-effective strategy, with an incremental cost of ₹60 450 ($795) at 20% coverage, ₹38 644 ($508) at 30% coverage, ₹31 142 ($409) at 40% coverage, ₹27 226 ($358) at 50% coverage, and ₹24 763 ($325) at 60% coverage per QALY gained, which is substantially less than the current willingness-to-pay threshold of the one-time per-person GDP of India.

Discussion

To the best of our knowledge, this is the first evaluation of the efficiency and distributional consequences of primary, secondary, and tertiary interventions, and their combinations, for the prevention and control of rheumatic fever and rheumatic heart disease in India. We found substantial potential for reduction in rheumatic fever and rheumatic heart disease cases and deaths with the scale-up in the coverage of prevention and control strategies. Among the seven intervention scenarios we explored, we found that a combined secondary and tertiary prevention scenario was the most cost-effective strategy for the prevention and control of rheumatic fever and rheumatic heart disease in India. The benefits in terms of number of cases and deaths averted were estimated to be highest among the poorest 25% of the population. Hence, the combination of secondary and

	Total	Poorest	Poor	Middle	Rich
Secondary	..	..	..	..	..
Secondary and tertiary	23 050 ($303)	22 902 ($301)	22 596 ($297)	25 663 ($ 338)	32 657 ($428)
Primary, secondary, and tertiary	5 411 599 ($71 205)	2 909 610 ($38 284)	3 961 345 ($52 123)	5 523 536 ($72 678)	8 920 477 ($117 375)
Routine care	D	D	D	D	D
Tertiary	D	D	D	D	D
Primary	D	D	D	D	D
Primary and tertiary	D	D	D	D	D
Primary and secondary	ED	ED	ED	ED	ED

Dominated intervention is defined as an intervention with higher costs and fewer health benefits than alternative interventions. This is an undesirable strategy and should not be recommended. Extendedly dominated is defined as an intervention with an incremental cost-effectiveness ratio higher than the incremental cost-effectiveness ratio of the next, more effective, alternative intervention (ie, the given treatment is dominated by the combination of two alternatives and should not be used to calculate appropriate incremental cost-effectiveness ratios). This is also an undesirable strategy. D=dominated strategies. ED=extendedly dominated strategies.

Table 2: **Incremental cost (in ₹ [US$]) per quality-adjusted life-years gained across income quintiles in various strategies for prevention and control of rheumatic fever and rheumatic heart disease in India**

tertiary interventions scaled up at a 70% coverage rate is recommended from both the efficiency and equity viewpoint. Finally, our estimates of catastrophic expenditures across socioeconomic groups factor in the current financing and use patterns. The extent of the benefit of intervention scenarios for those who are poor is likely to increase with the expansion in coverage of the publicly financed health insurance scheme that is Ayushman Bharat Pradhan Mantri Jan Arogya Yojana, and the strengthening of the public sector for delivery of primary, secondary, and tertiary care services through a programme such as the Health & Wellness Centres and the Ayushman Bharat Infrastructure Mission.[48]

The findings of our modelled analyses are in concurrence with the existing evidence from the literature. We estimated the prevalence of rheumatic heart disease among children aged 5–14 years to be 1·43 per 1000, which is in concurrence with previous studies reporting the prevalence in the range of 0·5–6·4 per 1000 children aged 5–14 years.[49–51] Furthermore, the lifetime risk of developing rheumatic heart disease among patients with rheumatic fever in a routine care scenario was 56%, which is similar to the lifetime risk of 50–75% as given in published literature.[10] The mean prevalence of group A streptococcal pharyngitis among children aged 5–15 years in the present model was 26·3%, which is again consistent with a systematic review and meta-analysis (24·1%).[52] Moreover, the model shows an overall life expectancy of 65·8 years, which is in line with the life expectancy of 66·1 years at 5 years of age, reported by the Sample Registration System (2014–18).[41]

There is scarce information on the cost-effectiveness of rheumatic fever and rheumatic heart disease interventions. There are a few studies that have investigated the cost-effectiveness of various methods of introducing primary prevention, whereas others have studied the cost-effectiveness of echocardiography as a diagnostic tool for active case-finding along with secondary prevention.[10,13,53] Among the studies evaluating primary prevention, a study by Manji and colleagues[13] in 2013 had compared the echocardiography and long-term antibiotic prophylaxis among patients with evidence of early rheumatic heart disease with two scenarios of primary prevention: throat swab culture testing and antibiotic treatment to only patients who were culture positive, and antibiotic prophylaxis to all patients with pharyngitis. This study reported that the maximum benefits in terms of QALYs were seen with antibiotic prophylaxis to all patients. However, the ICER of this strategy was much higher than the WHO threshold. Furthermore, antibiotic prophylaxis in patients who were throat swab culture test positive was more costly and less effective. Therefore, echocardiography along with long-term antibiotic prophylaxis was considered as the cost-effective option for prevention of rheumatic fever and rheumatic heart disease, which is consistent with our study findings. We also found high costs associated with the implementation of primary prevention.

Only one analysis, which was undertaken for the original Disease Control Priorities in Developing Countries project in 1993, explicitly studied the policy question of how to choose between prevention and surgical treatment. On the basis of this analysis, Watkins and colleagues[12] did a comparative analysis of different interventions (primary, secondary, and tertiary) for rheumatic fever and rheumatic heart disease prevention and control. The study reported that the scaling up of primary prevention strategies was a cost-saving approach, whereas the secondary prevention strategy was cost-effective.[12] However, that study modelled primary prevention alone as a hypothetical scenario wherein no costs of secondary and tertiary prevention were incorporated, which does not seem realistic.

There is only one study that has compared the cost-effectiveness of primary, secondary, and tertiary interventions in India for the prevention and control of rheumatic fever and rheumatic heart disease.[11] However, this study has several method limitations in terms of the valuation of costs in different scenarios, especially in the case of primary prevention. Additionally, the study falls

short of explicitly stating several assumptions. The assumption of 100% effectiveness of primary prevention is unrealistic. A meta-analysis of studies evaluating the effectiveness of primary prevention strategies reported a reduction of 68% in the incidence of rheumatic fever cases.[30] Considering a real-world coverage of 70%, and the sensitivity and specificity of diagnostic tests, our modelled analyses estimates that primary intervention prevents 29% of rheumatic fever cases. Finally, the unit costs of various services, even after inflation adjustment, are much lower than those in our study.

Rheumatic fever, and consequential rheumatic heart disease, are diseases of the world's poorest communities, which have long been neglected by global and national health systems. WHO recommends the establishment of a national rheumatic fever and rheumatic heart disease prevention programme in countries where rheumatic fever and rheumatic heart disease are substantial health problems.[6] However, the fiscal burden of managing rheumatic fever and rheumatic heart disease is often cited as a constraint. For example, in Africa, the direct medical cost of managing one patient with rheumatic heart disease for 6 years was estimated to be US$17 375 in 1987, increasing to $31 661 in the same year with surgical procedures.[54,55] In Nigeria, it was estimated that the cost of treating one patient with rheumatic fever was equivalent to the cost of preventing 5·4 cases of rheumatic fever.[56] The findings of our study offer compelling rationale for integration of rheumatic fever and rheumatic heart disease prevention and control into universal health coverage on both efficiency and equity grounds. Some of the services such as valve replacement surgery and balloon valvotomy for patients with rheumatic heart disease are already included in health benefit packages of India's national insurance scheme, Ayushman Bharat Pradhan Mantri Jan Arogya Yojana.[48] However, more needs to be done to ensure that the scheme coverage is extended to all patients with rheumatic fever and rheumatic heart disease. Furthermore, for the effective implementation of secondary prevention, the provision of injections of benzathine penicillin to all patients with rheumatic fever and rheumatic heart disease should be ensured at primary and secondary health-care facilities.

It should also be noted that there are many successful examples of the scaling up of public health programmes in India, such as for tuberculosis and HIV.[36,37] Furthermore, government-financed health insurance schemes such as Ayushman Bharat Pradhan Mantri Jan Arogya Yojana have led to a comprehensive coverage of secondary and tertiary care by reducing financial barriers to accessing care. Although the health and wellness centres aim to deliver an expanded range of services at the primary care level, Ayushman Bharat Pradhan Mantri Jan Arogya Yojana focuses on providing secondary and tertiary care services to the 40% of the population with the lowest income. Hence, the scaling-up of secondary and tertiary interventions to 70% would be feasible in the Indian health system. Furthermore, we undertook a univariate sensitivity analysis using lower coverage rates (ranging from 20–60%) for intervention scenarios. A combination of secondary and tertiary prevention scenarios was the most cost-effective strategy, with an incremental cost ranging from ₹24763 ($325) at 60% coverage to ₹60 450 ($795) at 20% coverage per QALY gained. Hence, the scaling of combined secondary and tertiary interventions as a practical policy in tackling rheumatic fever and rheumatic heart disease can be recommended for India.

There are several key strengths to our study. First, the synergy between interventions was evaluated by considering all possible combinations of the primary, secondary, and tertiary interventions. The majority of previous economic evaluations considered the choice only between primary, secondary, and tertiary in isolation, which is unrealistic.[11–13] Second, we relied on locally available robust data for our model. For example, the estimates of cost are derived from the National Health System Cost Database, or based on recent locally conducted studies.[23] Similarly, the valuation of quality of life and OOPE is based on real-world data collected from registry patients with long follow-up. Third, we improved the valuation of consequences by considering the sensitivity and specificity of the diagnostic tests. Finally, the evidence has been provided for decision makers from efficiency, equity, and financial risk protection points of view.

There are six notable limitations to this analysis. First, the specific complications of rheumatic heart disease surgery such as valve failure and the repeat of valve replacement surgery were not incorporated because of the absence of sound epidemiological data. Second, some variables, such as transition probabilities, utility scores, and OOPE estimates, were obtained from single sources (some of these might not be nationally representative) or were assigned on the basis of conservative assumptions.[38,39] However, the key results are robust to these assumptions, as shown by the sensitivity analyses. Third, the time-dependency of the transition between an attack of rheumatic fever and its progression to rheumatic heart disease is acknowledged, but existing literature restricts the ability to reliably model this dependency on a population basis. Fourth, we did not evaluate two scenarios, namely primary prevention using clinical diagnostic criteria and vaccination against disease, because of the absence of data on effectiveness and cost. These scenarios are recommended as future research areas once better data are available. Fifth, we assumed the same coverage rates for primary, secondary, and tertiary interventions across socioeconomic subgroups, which might not be equal. However, we made this assumption considering that most interventions from the government, which aim to reduce financial hardship and improve access to care, are particularly targeted to the poorer sections of the society. For example, the national flagship insurance programme Ayushman Bharat Pradhan Mantri

Jan Arogya Yojana provides the coverage of secondary and tertiary care treatment to the 40% poorest socioeconomic strata of society. Furthermore, a study by Selvaraj and colleagues[57] in 2021 reported that the difference in health-care use rates between individuals who were low-income and high-income had significantly declined from 2004 to 2018. Another study by Prinja and colleagues[58] also found that individuals with low incomes use public hospitals at a higher rate than individuals with high incomes, potentially suggesting equitable use. Hence, we assume that the current government initiatives aiming to reduce financial hardship and improve access to health care are likely to bridge the differences in disparity in service use between individuals with a high income and a low income. Nonetheless, we recommend this to be considered for future research work. Lastly, we used a Markov model for the present analysis, which has a memoryless feature because it assumes that the probability of a given transition in the model is independent of the nature or timing of earlier transitions. This model cannot distinguish the origin of the patients in the state at a given timepoint and treats them as homogeneous. Therefore, Markov models might be unsuitable for capturing the key aspects of some prognoses. To overcome this feature, we have added additional health states to account for the variations, which made our model more complex.

To conclude, a combined secondary and tertiary intervention is the most cost-effective and equitable strategy for the prevention and control of rheumatic fever and rheumatic heart disease in India. The incorporation of equity and considerations of financial risk protection into the economic evaluation in this study is a crucial methodological advancement that is relevant to the universal health coverage movement and its goals. Moreover, this inclusion leads to reductions in OOPE, especially for those who are poor. As a result, national programmes should be strengthened and reoriented on the basis of the evidence.

Contributors

SP, RK, and JD conceptualised the study, curated the data, did the investigations, produced the methods, were responsible for project administration, and provided resources and software. JD did the formal analysis. SP and RK acquired the funding. SP, RK, and PB supervised the study. SP, RK, JD, PB, GJ, AG, and RV validated the data. SP, RK, JD, PB, GJ, AG, and RV visualised the data. JD wrote the original draft. JD, SP, GJ, PB, AG, RV, and RK reviewed and edited the paper. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

The datasets and analysis will be available upon request. The study investigators retain ownership of their data. Any requests for access to data should be made directly to study investigator (shankarprinja@gmail.com).

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