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Protocol for a population-based study of rheumatic heart disease prevalence and cardiovascular outcomes among schoolchildren in Nepal

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ABSTRACT

Introduction: Rheumatic heart disease (RHD) remains a major contributor to morbidity and mortality in developing countries. The reported prevalence rates of RHD are highly variable and mainly attributable to differences in the sensitivity of either clinical screening to detect advanced heart disease or echocardiographic evaluation where disease is diagnosed earlier across a continuous spectrum. The clinical significance of diagnosis of subclinical RHD by echocardiographic screening and early implementation of secondary prevention has not been clearly established.

Methods and analysis: The authors designed a cross-sectional survey to determine the prevalence of RHD in children from private and public schools between the age of 5 and 15 years in urban and rural areas of Eastern Nepal using both cardiac auscultation and echocardiographic evaluation. Children with RHD will be treated with secondary prevention and enrolled in a prospective cohort study. The authors will compare the prevalence rates by cardiac auscultation and echocardiography, determine risk factors associated with diagnosis and progression of RHD, investigate social and economic barriers for receiving adequate cardiac care and assess clinical outcomes with regular medical surveillance as a function of stage of disease at the time of diagnosis. Prospective clinical studies investigating the impact of secondary prevention for subclinical RHD on long-term clinical outcome will be of central relevance for future health resource utilisation in developing countries.

Ethics and dissemination: The study was considered ethically uncritical and was given an exempt status by the ethics committee at University of Bern, Switzerland. The study has been submitted to the National Nepal Health Research Council and was registered with http://www.ClinicalTrials.gov (NCT01550068). The study findings will be reported in peer-reviewed publications.

ClinicalTrials.gov Identifier: NCT01550068.

ARTICLE SUMMARY

Article focus

- Study protocol of a population-based evaluation of the prevalence rate of RHD among schoolchildren in Eastern Nepal, with a subsequent prospective longitudinal cohort study assessing long-term clinical outcome of children undergoing secondary prevention for borderline and definite RHD according to the World Heart Federation criteria.

Key messages

- RHD remains a major contributor to morbidity and mortality in developing countries.
- Echocardiographic screening allows diagnosis of RHD at an earlier stage across a continuous spectrum as compared with cardiac auscultation.
- The clinical significance of diagnosis of subclinical RHD by echocardiographic screening and early implementation of secondary prevention has not been clearly established.

Strengths and limitations of this study

- The protocol describes a comprehensive approach to implement echocardiographic screening in a high prevalence region as recommended by the WHO and outlines a robust analysis plan to investigate clinical outcome with secondary prevention for subclinical RHD.
- Since access to education is a marker of socioeconomic status, restriction of screening to school going children is subjected to selection bias likely to underestimate the real disease burden related to RHD in Eastern Nepal.
- Cultural sensitivity with education programmes and focus group discussions will anticipate the potential social stigma of a diagnosis with a heart condition during childhood and increase public awareness.

INTRODUCTION

Rheumatic fever complicated by rheumatic heart disease (RHD) remains a major contributor to morbidity and premature

death among the socioeconomically underprivileged working age population of developing countries.[1] RHD results from an autoimmune response due to molecular mimicry between the M-protein on the group A β-haemolytic streptococci cell membrane and cardiac myosin eventually leading to valvular damage.[2] High prevalence rates of acute rheumatic fever (ARF) and RHD have been reported from different geographic regions around the world such as Southeast Asia, the Western Pacific and Africa that share demographic characteristics determined by poverty and limited access to healthcare resources.[3] The burden of RHD is likely to escalate in these countries due to increasing urbanisation and overcrowding.

Prevalence rates of RHD from screening studies in Southeast Asian countries range from 0.7 to 22 per 1000 children using traditional cardiac auscultation and from 20 to 51 per 1000 children using echocardiography.[4–11] A considerable variation in prevalence rates reflects the substantially higher sensitivity of echocardiographic screening as compared with cardiac auscultation due to diagnosis across a continuous spectrum of disease as opposed to presence or absence of a heart murmur using cardiac auscultation. Echocardiographic screening for RHD has been recommended by the WHO in high prevalence regions,[12] and the recently released criteria for echocardiographic diagnosis of RHD by the World Heart Federation warrant consistent reporting and facilitate the evaluation of progression of minor echocardiographic lesions over time.[13] The diagnosis of RHD at an earlier clinically silent stage by the detection of morphological and functional valvular lesions without a corresponding heart murmur challenges our current concept of prevention and treatment.

Medical management of ARF and RHD largely depends upon preventive measures comprising reduction of overcrowding, prompt antibiotic treatment of streptococcal pharyngitis and secondary prevention achieved by regular oral or intramuscular administration of penicillin continued until early adulthood among children with a documented history of ARF or evidence of RHD. Even though preventive measures with penicillin are inexpensive and efficient, this strategy is difficult to effectuate in developing countries with limited access to healthcare resources. Enrolment of patients with ARF and RHD in a registry with close follow-up has been demonstrated to reduce the cardiovascular sequelae associated with disease progression.[14]

Effective measures to reduce the global burden of RHD represent an ongoing challenge involving reduction in overcrowding, improving hygiene, increasing public awareness and facilitating access to healthcare. In the absence of fundamental socioeconomic changes improving primordial prevention, systematic screening for RHD based on public and private education represents the most comprehensive approach and aims at a reduction of the late complications of RHD by early implementation of secondary prevention. Current research has been predominantly focused on assessing prevalence rates using passive survey systems without subsequent enrolment in registries or offering longitudinal follow-up. In order to assess the determinants of disease and its progression along with short- and long-term clinical outcomes, we plan to include all cases of RHD in a cohort study to be treated according to their disease stage at diagnosis and followed up for at least 5 years.

AIMS AND OBJECTIVES

The objective of this study is to investigate the prevalence rate of definite and borderline RHD among children in Eastern Nepal and to assess long-term clinical outcome of children undergoing secondary antibiotic prevention for RHD. More specifically, we aim to (a) compare the prevalence rates by cardiac auscultation and echocardiography, (b) determine risk factors associated with diagnosis and progression of RHD, (c) investigate social and economic barriers for receiving adequate cardiac care and (d) assess clinical outcomes as a function of stage of disease at the time of diagnosis with regular medical surveillance.

METHODS

Study design and setting

A cross-sectional survey of schoolchildren in the Sunsari district of Eastern Nepal will be performed to identify children with RHD, and those with evidence of disease will subsequently be enrolled in a prospective longitudinal cohort study for a period of 5 years. The Sunsari district situated on the foothills of the Lower Himalayan Range in Eastern Nepal involves 52 villages with a total population of around 630 000 inhabitants. Dharan is the largest city in the Sunsari district and the third largest city in the country.

Cross-sectional survey

We will perform clinical and echocardiographic screening of children aged 5–15 years from public and private schools in urban and rural areas in Eastern Nepal. A multistage sampling procedure will be used to select the study sample. In order to ensure a representative target population, the location and administration of the schools will be used as a surrogate to reflect the socioeconomic demographic distribution of the population in Eastern Nepal. Since approximately 80% of the population in Nepal lives in rural areas,[15] we will include three rural and one urban area in Eastern Nepal and enrol one-third of the patients from the urban area from private schools.

Prospective cohort study

All children with documented history of ARF and/or echocardiographic evidence of RHD will be reexamined in regular time intervals, at 6 months, at 1 year and yearly thereafter up to at least 5 years, in the context of a prospective cohort study. Both children and their primary care givers will be educated in order to ensure compliance with secondary prevention and regular

follow-up. A standardised questionnaire will address clinical symptoms, compliance to treatment and assess prespecified clinical end points. Echocardiographic follow-up will be performed yearly up to 5 years at B.P. Koirala Institute of Health Sciences (BPKIHS).

Study population

For the cross-sectional survey, all parents of the schoolchildren will be informed by a letter distributed to the children outlining the project details and indicating a contact address for queries. Since close to half of the adult population in Nepal is illiterate,[15] focus group discussions with the healthcare providers, school principals, local healthcare workers and parents will be offered to understand and establish initiatives to win the confidence of the communities. A written informed consent form of the principal of each of the selected schools will be obtained. Schoolchildren of parents that do not actively withdraw consent for screening will be examined. Inclusion criteria for the observational survey will be as follows: (1) age 5–15 years, (2) written informed consent for participation in the screening study by the school principal and (3) passive consent from the parent/primary care giver of the children. Given the observational design of the study, no formal exclusion criteria apply. Children will be enrolled in the prospective registry in the presence of a documented history of ARF or echocardiographic evidence of definite or borderline RHD and written informed consent given by the children and/or their parents/primary care givers.

Data collection

A questionnaire customised to the age of the children will acquire data on social background and past medical history in a standardised interview. Demographic variables such as age, household characteristics and socioeconomic indicators will be recorded along with a short medical history followed by physical examination documenting height, weight and potential clinical signs of ARF. Screening for RHD will be performed independently by cardiac auscultation to detect pathologic heart murmurs, as well as by echocardiography to document morphologic and/or functional valvular lesions consistent with RHD. All data will be recorded in a dedicated web-based database.

Treatment

All patients enrolled in the RHD cohort will be treated with a standard antibiotic regimen for secondary prevention consisting of intramuscular administration of weight-adjusted penicillin G benzathine every 3–4 weeks or daily oral administration of penicillin V for the entire duration of follow-up. Patients allergic to penicillin will be treated with daily oral administration of azithromycin.[16]

Definitions

ARF will be defined by the modified Jones criteria.[17] Echocardiographic diagnosis will classify RHD according to the World Heart Federation criteria for individuals aged ≤20 years into definite and borderline. Definite RHD is further subdivided into four subcategories. Subcategory A is pathological mitral regurgitation and at least two morphological features of RHD of the mitral valve and subcategory B is the presence of mitral stenosis with a mean gradient of ≥4 mm Hg. Subcategory C is defined by pathological aortic regurgitation in combination with at least two morphological features of RHD of the aortic valve and subcategory D is determined by borderline disease of both the aortic valve and the mitral valve. Borderline RHD is subdivided into three subcategories. Subcategory A is the presence of at least two morphological features of RHD of the mitral valve without pathological mitral regurgitation or mitral stenosis and subcategories B and C are determined by pathological mitral regurgitation or pathological aortic regurgitation, respectively. Physiological mitral regurgitation (A), physiological aortic regurgitation (B) and an isolated morphological feature of RHD of the mitral or aortic valve (ie, valvular thickening) without any associated pathological stenosis or regurgitation (C and D, respectively) will be classified as normal echocardiographic findings.[13]

A patient will be defined as adherent to secondary prevention if he/she receives at least 80% of the prescribed intramuscular antibiotic administration captured from hospital records. In patients receiving oral antibiotics, adherence will be assessed by self-report and by pill counts at every follow-up visit. Other treatment adherence end points will be frequency of follow-up appointments and follow-up status.

Quality of life (QOL) will be assessed using PedsQL generic core and cardiac module scales. PedsQL addresses the child's perspectives across the widest possible age range. The generic module scale encompass physical functioning (eight items), emotional functioning (five items), social functioning (five items) and school functioning (five items). The PedsQL cardiac module has five scales related to symptoms (seven items), perceived physical appearance (three items), treatment anxiety (four items), cognitive problems (five items) and communication (three items).[18]

Outcomes and treatment effect

Clinical outcomes such as all-cause mortality, stroke, endocarditis, hospitalisation for congestive heart failure, valvular surgery, mitral balloon valvuloplasty and recurrence of rheumatic fever will be recorded among patients with RHD enrolled in the longitudinal cohort study. Additionally, we will obtain time-varying covariates like socioeconomic parameters, adherence to treatment and information on QOL.

We anticipate that compliance with secondary prevention will be one of the major challenges, which in turn requires continued education. We plan to ensure compliance by means of face-to-face education by the research coordinator at each visit to both the child and the care giver, making them aware of the risk of

recurrence of rheumatic fever and the potential consequences of progression of RHD. Visit reminders by mail and if necessary by personal visits will also be used to ensure adequate compliance.

Primary care givers will be educated to detect symptoms and signs of potential allergic reactions of antibiotic treatment such as a skin rash, hives, swollen lips/tongue and wheezing and will be provided with an emergency medical contact number. In case of drug-related adverse side effects such as diarrhoea, nausea, pain/swelling/infection at the site of injection, we will recommend to switch the antibiotic administration from intramuscular to oral or vice versa as a first step. If children/care givers refuse regular antibiotic intake despite counselling, they will have the option to retract their decision at any given point in time. With their consent, these children will remain in the registry in order to provide care and treatment in case of potential late complications as a consequence of disease progression. In the event of children being diagnosed at an advanced stage with significant valvular heart disease leading to congestive heart failure, we will assure optimal interdisciplinary medical treatment.

Quality assurance

All data will be checked for completeness and plausibility before being entered into a web-based data entry system. Positive screening results will be verified in the cardiology outpatient clinic of BPKIHS by complete echocardiographic examination. Quality assurance of the data will be ensured in a two-tiered fashion. First of all, the web-based data entry system will not allow for entering implausible values and text fields will be minimal and restricted to specification of 'other'. The second tier will be automated monthly reports which generates denominator along with the total frequencies. When missing data are identified, the research coordinator will identify the field by means of querying and will try to obtain the values from records or if necessary back to the participant within 1 month of last contact. The database will be backed up every week for further security on to a dedicated data server. Biannual reports will be submitted to the foundation 'Coeur de la Tour' in Geneva, Switzerland. The study will be conducted in compliance with the Declaration of Helsinki.

The study was registered with ClinicalTrials.gov (NCT01550068) and was given an exempt status by the ethics committee at University of Bern, Switzerland (KEK-BE 018/12). The study protocol has been submitted to the National Nepal Health Research Council. The study is supported by an unrestricted grant from the foundation 'Coeur de la Tour' (http://www.coeurdelatour.ch) from Geneva, Switzerland.

Statistical considerations

Sample size

Sample size calculations were based on reported prevalence rates of RHD using cardiac auscultation in schoolchildren in Southeast Asian countries.[4–11] We calculated a sample size of 9500 schoolchildren between the ages of 5 and 15 years with a type I error of 0.05 and a power of 90% for an expected diagnosis rate of 2 per 1000. The lower end of the prevalence estimates was chosen in order to obtain a sufficient sample size in the subsequent cohort study and to be able to provide optimal treatment to a maximum number of affected children. We will include one urban and three rural areas from the different parts of the target area (Sunsari district), thus including 2500 participants in each area. One-third of the patients from the urban area will be enrolled from private schools.

Data analysis plan

In the cross-sectional study, age- and sex-specific prevalence rates for RHD will be calculated by sociodemographic covariates. The design effect of the cluster sampling strategy will then be calculated using the variations of prevalence rates among the different clusters.[19] A multiplication factor equal to the square root of the design effect will be used to construct the 95% CIs for the prevalence estimates to avoid erroneously narrow CIs. Prevalence rates with 95% CI will be calculated separately for the two screening methods. Multivariable analysis will be performed for assessing the socioeconomic factors for RHD. Among children with RHD, the socioeconomic barriers to receive adequate medical care will be assessed by using a multivariate logistic regression model. Furthermore, the association of RHD with age, gender, socioeconomic status and urban–rural residence will be evaluated with univariate and multivariate analyses.

Cohort baseline characteristics and procedural variables will be presented as counts and percentages for dichotomous variables and as mean and SD for continuous variables. Factor analysis of the scales in QOL will be performed using appropriate rotations, and index scores of the constructs will be computed if not more than 25% of the items are missing. Adherence to treatment will be measured as a dichotomous variable and QOL scores as mean (SD)/median (IQR) will be presented for each follow-up time interval. We will present and compare the baseline and procedural characteristics by the stages of disease progression at baseline using χ^2 tests or analyses of variance. Comparisons of the baseline characteristics of the study subjects among the disease stages at baseline will be performed using linear or logistic regression. For the specific clinical end point, compliance and QOL univariable and multivariable Cox proportional hazard regression models will be used to calculate HRs with 95% CI among the stages of disease at baseline. We will construct Kaplan–Meier curves for the time to the development of clinical end point by stage of disease at baseline, treating death as a competing risk.

DISCUSSION

This protocol outlines the rationale and design for a multiphase study including a cross-sectional survey comparing two different screening methods for RHD

quantifying the amount of disease, followed by a cohort study addressing the impact of early implementation of secondary prevention.

The net primary school attendance rate in Nepal amounts to 86% and 82% for boys and girls, respectively.[15] This study assesses the prevalence of RHD only to children of families who can afford education, thus pointing out selection bias. Since access to education is a marker of socioeconomic status which at the same time represents a major determinant of susceptibility to ARF and RHD, restriction of screening to school going children is therefore likely to underestimate the real disease burden related to RHD.

We anticipate certain challenges during the course of the study. Primarily, screening per se might expose the children and their families to anxiety related to potential positive screening results requiring long-term medical management. Additionally, we acknowledge the social stigma of being diagnosed with a heart disease especially among girls in these communities. An information letter distributed to the parents prior to screening, focus group discussions and education programmes will condense clear and simple messages to allay fears regarding RHD and its subsequent management. Adequate knowledge and cultural sensitivity not to offend or harm the children and the parents' perception will be of prime importance and will be adhered to during the entire course of the project.

Even though the population attributable risk of RHD is expected to be high, false-positive screening results may occur. In order to reduce false-positive findings, all echocardiographic clips with borderline or definite RHD will be assessed from two independent cardiologists. Moreover, screening in a large population of schoolchildren might yield in exceptional cases important incidental clinical findings unrelated to RHD but yet relevant for future prognosis (ie, bicuspid aortic valve, atrial septal defect). Parents will be informed about such findings and advised on how to proceed for best medical management. If the parents or caretakers give their consent, the children will be invited for follow-up at BPKIHS for further investigation. First medical contact due to incidental findings relevant for future prognosis will be reimbursed.

Prospective clinical studies investigating the impact of secondary prevention for subclinical RHD on long-term clinical outcome will be of central relevance for future health resource utilisation in developing countries.

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Competing interests None.

Ethics approval Ethics approval was provided by Ethics Committee at University of Bern, Switzerland (KEK-BE 018/12).

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Data sharing statement There are no additional data available.

REFERENCES

1. Carapetis JR, Currie BJ, Mathews JD. Cumulative incidence of rheumatic fever in an endemic region: a guide to the susceptibility of the population? *Epidemiol Infect* 2000;124:239–44.
2. Carapetis JR, McDonald M, Wilson NJ. Acute rheumatic fever. *Lancet* 2005;366:155–68.
3. Seckeler MD, Hoke TR. The worldwide epidemiology of acute rheumatic fever and rheumatic heart disease. *Clin Epidemiol* 2011;3:67–87.
4. Marijon E, Ou P, Celermajer DS, *et al*. Prevalence of rheumatic heart disease detected by echocardiographic screening. *N Engl J Med* 2007;357:470–6.
5. Bhaya M, Panwar S, Beniwal R, *et al*. High prevalence of rheumatic heart disease detected by echocardiography in school children. *Echocardiography* 2009;27:448–53.
6. Saxena A, Ramakrishnan S, Roy A, *et al*. Prevalence and outcome of subclinical rheumatic heart disease in India: the RHEUMATIC (Rheumatic Heart Echo Utilization and Monitoring Actuarial Trends in Indian Children) study. *Heart* 2011;97:2018–22.
7. Sadiq M, Islam K, Abid R, *et al*. Prevalence of rheumatic heart disease in school children in urban Lahore. *Heart* 2009;95:353–7.
8. Bahadur KC, Sharma D, Shrestha MP, *et al*. Prevalence of rheumatic and congenital heart disease in schoolchildren of Kathmandu valley in Nepal. *Indian Heart J* 2003;5:615–18.
9. Jose VJ, Gomathi M. Declining prevalence of rheumatic heart disease in rural schoolchildren in India: 2001–2002. *Indian Heart J* 2003;55:158–60.
10. Ahmed J, Mostafa Zaman M, Monzur Hassan MM. Prevalence of rheumatic fever and rheumatic heart disease in rural Bangladesh. *Trop Doct* 2005;35:160–1.
11. Periwal KL, Gupta BK, Panwar RB, *et al*. Prevalence of rheumatic heart disease in school children in Bikaner: an echocardiographic study. *J Assoc Physicians India* 2006;54:279–82.
12. Carapetis J, Parr J, Cherian T. *Standardization of Epidemiologic Protocols for Surveillance of Post-Streptococcal Sequelae: Acute Rheumatic Fever, Rheumatic Heart Disease and Acute Post-Streptococcal Glomerulonephritis*. Department of Health and Human Services, National Institutes of Health, 2010. http://www.niaid.nih.gov/topics/strepThroat/Documents/groupasequelae.pdf
13. Remenyi B, Wilson N, Steer A, *et al*. World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease—an evidence-based guideline. *Nat Rev Cardiol* 2012;9:297–309.
14. Pelajo CF, Lopez-Benitez JM, Torres JM, *et al*. Adherence to secondary prophylaxis and disease recurrence in 536 Brazilian children with rheumatic fever. *Pediatr Rheumatol Online J* 2010;8:22.
15. UNICEF. *Statistics 2005–2010*. http://www.unicef.org/infobycountry/nepal_nepal_statistics.html (accessed 16 Apr 2012).
16. Gerber MA, Baltimore RS, Eaton CB, *et al*. Prevention of rheumatic fever and diagnosis of acute streptococcal pharyngitis. A scientific statement from the American Association of Rheumatic fever,

Endocarditis, and Kawasaki Disease Committee of the Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation* 2009;119:1541–51.
17. Anon. Guidelines for the diagnosis of rheumatic fever. Jones Criteria, 1992 update. Special Writing Group of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young of the American Heart Association. *JAMA* 1992;268:2069–73.
18. Uzark K, Jones K, Slusher J, *et al*. Quality of life in children with heart disease as perceived by children and parents. *Pediatrics* 2008;121: e1060–7.
19. Bennett S, Woods T, Liyanage WM, *et al*. A simplified general method for cluster-sample survey of health in developing countries. *World Health Stat Q* 1991;44:98–106.

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Notes