



**Rheumatic Heart disease: Pilot Study for a Population-Based  
Evaluation of Prevalence and Cardiovascular Outcomes  
among Schoolchildren in Nepal**

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# Rheumatic Heart disease: Pilot Study for a Population-Based Evaluation of Prevalence and Cardiovascular Outcomes among Schoolchildren in Nepal

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## Abstract

**Objectives:** To evaluate a protocol for a population-based screening program targeting prevention of rheumatic heart disease (RHD) progression by early echocardiographic diagnosis of valvular lesions and early implementation of secondary prevention.

**Design:** Observational survey with subsequent prospective cohort study.

**Setting:** Private boarding school in the urban area of the Sunsari district situated on the foothills of the Lower Himalayan Range in Eastern Nepal.

**Participants:** 54 unselected school going Asian children 5-15 years of age, 24 girls and 30 boys.

**Primary outcome measures:** Borderline or definite RHD on screening echocardiography according to the criteria provided by the World Heart Federation. In a subsequent cohort study enrolling children with evidence of RHD, we will investigate clinical outcome under secondary antibiotic prevention and regular medical follow-up.

**Results:** Among the 54 children who were screened, clinical examination detected four children with soft systolic murmurs, two of which were found to have valvular lesions consistent with borderline RHD and were recommended secondary antibiotic prevention. The parents of one of the children opted against antibiotic prevention after consultation with an external cardiologist.

**Conclusions:** This pilot study shows that the methods outlined in the protocol can be translated into a large-scale population-based study. We learned that collaboration with teachers and parents will be of key importance in order to establish a sustainable program.

**Trial registration:** ClinicalTrials.gov Identifier: NCT01550068

Article Summary

Article focus:

- Pilot study for a population-based program targeting prevention of rheumatic heart disease (RHD) progression by early echocardiographic diagnosis of valvular lesions and early implementation of secondary prevention.

Key messages:

- The echocardiographic criteria for diagnosis of RHD provided by the World Heart Federation are a valuable instrument for population-based screening.
- Teachers educated on RHD were allies in our study and helped us to establish contact with both the children and their parents.
- Adequate information of the parents of children with evidence of silent RHD is of key importance for long-term adherence to secondary antibiotic prevention.

Strengths and limitations:

- The pilot study demonstrates feasibility of a large-scale population-based screening program for RHD by the use of portable echocardiography.
- Long-term follow-up will identify determinants of adherence to secondary prevention and show the impact of early implantation of secondary prevention on disease progression.

## Introduction

Rheumatic Heart Disease (RHD) is estimated to affect more than 15 million people worldwide and leads to 250,000 deaths every year. [1] More than 80% of the children younger than 15 years of age grow up in regions of the world where RHD is endemic. [2] A discrepancy of reported prevalence rates of RHD among schoolchildren in developing countries is particularly attributable to diverse sensitivities of echocardiographic and clinical screening, respectively. RHD consolidates a spectrum of different stages of clinically silent and clinically manifest stages of valvular degeneration culminating in congestive heart failure, increasing the risk of endocarditis, cerebrovascular events, and eventually leading to premature death of the effected working aged population in developing countries.

Acute rheumatic fever (ARF) ensues from an autoimmune reaction in response to group A  $\beta$ -hemolytic streptococcal pharyngitis and may result in RHD through the cumulative valvular damage of recurrent episodes of ARF. [2] Whereas overcrowding and poverty are major determinants of disease proliferation, limited access to healthcare resources renders primary prevention with prompt antibiotic treatment of streptococcal pharyngitis difficult to effectuate in large parts of endemic regions of the world. Secondary prevention among children with a documented history of ARF or evidence of RHD is achieved by regular oral or intravenous administration of penicillin continued until early adulthood.

The World Health Organization has recommended echocardiographic screening of RHD in high prevalence regions. [3] Early detection of subclinical RHD by use of echocardiography warrants timely implementation of secondary antibiotic prophylaxis and may prevent progression of valvular damage leading to congestive heart failure. We performed a pilot study in order to test the feasibility of a cross-sectional survey to assess prevalence of RHD according to the World Heart Federation criteria using echocardiography as compared to traditional cardiac auscultation. [4]

Aims and Objectives

The goal of the project consists in the prevention of RHD progression by early echocardiographic diagnosis of valvular lesions and early implementation of secondary prevention. We designed a study 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. [5] The objective of the pilot study of the cross-sectional survey was to evaluate the administrative and logistic feasibility of a full-scale population screening study, specifically pertaining to questionnaire design, and protocol adherence, and additionally to assess the recruitment of children with signs of RHD into a prospective cohort.

Methods

Study Design and Setting

The design of the study has been outlined in detail previously. [5] In summary, a cross-sectional survey of schoolchildren aged 5-15 years will be performed for clinically silent or manifest RHD in the Sunsari district of Eastern Nepal. The location in rural or urban areas, as well as public or private administration of the schools will be used as a surrogate to reflect the socio-economic demographic distribution of the population in Eastern Nepal. Children found to have signs consistent with RHD will be enrolled in a prospective cohort to be followed over the course of five years. The Sunsari district is situated on the foothills of the Lower Himalayan Range in Eastern Nepal and extends to the south of the city of Dharan, the third largest city in Nepal.

Study Population

For the pilot study of the cross-sectional survey, a private boarding school in the urban area of the Sunsari district was selected. A discussion with the principal of the school was performed in order to outline the aim of the project and obtain informed consent.

### *Data Collection*

Data on social background and past medical history was acquired in a standardized interview on the basis of a questionnaire. Demographic variables such as age, household characteristics, and socio-economic indicators were recorded along with a short medical history followed by physical examination documenting height, weight, and potential clinical signs of ARF. Screening for RHD was performed independently by cardiac auscultation to detect pathologic heart murmurs, as well as by portable echocardiography using the Samsung portable U6 echocardiographic machine to document morphologic and/or functional valvular lesions consistent with RHD by two different examiners.

All data was documented on paper case report forms which were subsequently transferred into an electronic database.

### *Definitions*

RHD was classified in accordance with the WHF criteria for individuals aged  $\leq 20$  years into definite and borderline. [4] Definite RHD was divided into four subcategories. Subcategory A is defined by pathological mitral regurgitation and at least two morphological features of RHD of the mitral valve, subcategory B is diagnosed in the presence of mitral stenosis with a mean gradient of  $\geq 4$  mmHg. Subcategory C is characterized 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 partitioned into three subcategories. Subcategory A is determined by the presence of at least two morphological features of RHD of the mitral valve without pathological mitral regurgitation or mitral stenosis, subcategories B and C are characterized 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 (i.e. valvular thickening) without any associated pathological stenosis or regurgitation (C and D, respectively) are classified as normal echocardiographic findings.

*Treatment*

The primary caregivers of children with evidence of RHD were contacted by the school principal and the cardiologist and were summoned for a thorough clinical and echocardiographic examination at B.P. Koirala institute of Health Sciences. During that outpatient visit, the indication for secondary antibiotic prevention was discussed and orientation for inclusion into a prospective registry was provided.

The study was conducted in compliance with the Declaration of Helsinki and was registered with clinical trials.gov (NCT01550068). The study was approved by the ethic committee of B.P. Koirala Institute of Health Sciences and was given an exempt status by the ethics committee at University of Bern, Switzerland (KEK-BE 018/12). The pilot study was supported by an unrestricted grant from the foundation “Coeur de la Tour” (<http://www.coeurdelatour.ch>) from Geneva, Switzerland.

*Sample Size Calculation*

Sample size was determined by practical aspects rather than estimations of prevalence rates. In order to adequately evaluate the questionnaires and assess the duration of a screening examination, we

considered a mixed cohort of school children across all age groups important. The localization of the school in an urban area of the lower-middle class with only limited access to electricity throughout the hours of the day simulated a challenge often encountered in more rural areas of Eastern Nepal. The screening examinations were timed and performed in a single afternoon.

### *Statistical Analysis*

Statistical analyses were performed using SPSS Statistics Version 17.0. Continuous variables are presented as mean  $\pm$  standard deviation (SD) and were compared by means of students t-test. Categorical data are expressed as frequency (percentages), and were compared using the chi-square test.

### **Results**

Fifty-four children from a private boarding school in urban Dharan ranging from 5 to 15 years of age were included into the pilot observational survey (Figure 1), which was performed by two cardiologists (TP, NS), a pediatrician, a general medicine resident, and a nurse. Screening examinations for this pilot study were performed in two dedicated rooms, one for physical examinations and another for echocardiography. Boys and girls were examined separately; cardiac auscultation of girls was performed by a female doctor or a male doctor in the presence of a female chaperone. School teachers took responsibility for the organization of completion of questionnaires and physical/echocardiographic examination. Baseline characteristics of the children belonging mostly to lower middle-class families are summarized in Table 1. Clinical auscultation revealed four children with soft systolic heart murmurs. None of the examined children had echocardiographic evidence of definite RHD. However, two children

were found to have borderline RHD, and two children had isolated thickening of the anterior mitral valve leaflet without pathological regurgitation, that did not meet the criteria for borderline RHD according to the WHF criteria ([Table 2](#)).

A 12 year-old asymptomatic boy with no history of ARF and a soft systolic heart murmur was found to have significant thickening of the anterior mitral valve leaflet (0.5 cm) associated with pathological mitral regurgitation and mild tricuspid regurgitation. Another asymptomatic 12 year-old boy with a soft systolic heart murmur had restricted posterior mitral valve leaflet motion with evidence of pathological mitral regurgitation and mild tricuspid regurgitation.

The parents of both children were oriented about the echocardiographic findings and the children were given an appointment to the outpatient clinic of B.P. Koirala Institute of Health Sciences for thorough echocardiographic examination, that did not reveal any additional relevant findings in either of the boys. Both children were started on secondary antibiotic prevention with intramuscular Penicillin every 3 weeks and will be followed prospectively.

One of the parents was seeking a second opinion from another cardiologist not involved in the study who recommended against antibiotic prevention in clinically silent RHD and decided to discontinue antibiotic prevention after few weeks.

Discussion

We report the results of a pilot study evaluating a clinical research protocol for an observational survey of RHD among school going children and cardiovascular outcome. In line with previous reports on prevalence rates of subclinical RHD from Southeast Asia published within the last decade, the extrapolated prevalence rate in our cohort amounted to 37 per 1000 children diagnosed with subclinical

RHD [6-8]. This pilot study represents an integral part for the final implementation of the protocol in a large population-based setting. The main findings can be summarized as follows:

1. Clinical and echocardiographic screening for RHD is feasible within 5-10 minutes per child. Active involvement of the teachers who are familiar with the children not only facilitates the organization but also anticipates distrust towards medical personnel from both children and teachers.
2. Adequate orientation of and collaboration with the parents after diagnosis of RHD in a child is of key importance to adherence to preventive antibiotic treatment. Accepting the diagnosis of subclinical RHD in an apparently healthy child is difficult for both the parents and the children and calls for continued support.
3. The WHF criteria are a helpful instrument in classifying subclinical valvular lesions consistent with RHD.

We learned from this pilot study, that focus group discussions with the teachers and the principal of the school in preparation for the screening examination are useful to establish the much needed collaboration with the teachers and to win the confidence of the children. Informed teachers were allies in our study not only in terms of facilitating the organization of the pilot study, but also with regard to the orientation of the parents of the two children diagnosed with clinically silent RHD. Moreover, completion of parts of the questionnaire asking for socio-economic background could be assisted by the teachers and would improve quality of the data. As a consequence we plan to extend the participation of the teachers in the collection of the baseline criteria in the main study.

With regard to scientific equipment, the indispensability of a battery-operated portable echocardiography machine emerged. In the city of Dharan, electricity is not supplied around the clock, and power cuts can be unpredictable and long. In order that the number of children being screened in a

day would not be limited by the battery lifetime of the portable echocardiography machine, a number of spare batteries will be needed.

In addition to the school teachers, the parents of the children will be the key players for successful completion of the program. Accepting disease in an asymptomatic child is difficult for every parent. Continued education during every clinical visit with adequate cultural sensitivity should reinforce adherence to treatment. Given the high illiteracy rate in Nepal, letters to the information brochures distributed to the parents will not achieve the targeted objective. In response to the need for education on RHD diagnosis and prevention, we are therefore preparing a documentary film that will be broadcasted on local television and in schools before the screening examinations begin.

The recently released WHF criteria for echocardiographic diagnosis of RHD proved helpful in the classification of valvular lesions potentially related to subclinical RHD and provides an adequate instrument for large population-based studies.

## Acknowledgement

Sina Pilgrim, MD; Kavita Shah, RN; Kishori Dhakal, RN

## Competing interests

None

## Funding

The study is supported by an unrestricted grant from the foundation “Coeur de la Tour”  
(<http://www.coeurdelatour.ch>) from Geneva, Switzerland.

## Data Sharing Statement

There is no additional data available

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## Figure Legends

**Figure 1:** Distribution of Age among Schoolchildren in Pilot Observational Survey

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Tables

Table 1. Pilot Study Baseline Characteristics

Baseline characteristics	n (%) or mean (SD)
Age (years)	9.6 (2.9)
Height in (cm)	127 (16)
Weight in (kg)	28 (12)
Male	30 (55.6)
Documented history of ARF	0 (0)
<i>Socio-economic status</i>	
Number of family members	4.9 (1.2)
Children	2.2 (0.9)
Adults	2.6 (1.0)
<i>Amenities at home</i>	
Household, Number of rooms	2.8 (1.6)
Family owns a car	1 (1.9)
Television at home	50 (92.6)
Internet connection at home	4 (7.7)
Family uses a cell phone	51 (94.4)

**Table 2. Pilot Screening Using the World Heart Federation (WHF) Criteria for Echocardiographic Diagnosis of Rheumatic Heart Disease**

WHF Criteria	n (per 1000)
<i>Definite Rheumatic Heart Disease (RHD)</i>	0 (0)
Subcategory A: RHD of the MV <sup>1</sup> with regurgitation	0 (0)
Subcategory B: RHD of the MV <sup>1</sup> with stenosis	0 (0)
Subcategory C: RHD of the AV <sup>2</sup>	0 (0)
Subcategory D: Multivalvular RHD	0 (0)
<i>Borderline Rheumatic Heart Disease (RHD)</i>	2 (37. 0)
Subcategory A: Morphological features of the MV <sup>1</sup>	2 (37. 0)
Subcategory B: MV <sup>1</sup> regurgitation	0 (0)
Subcategory C: AV <sup>2</sup> regurgitation	0 (0)
Normal*	52 (962.9)

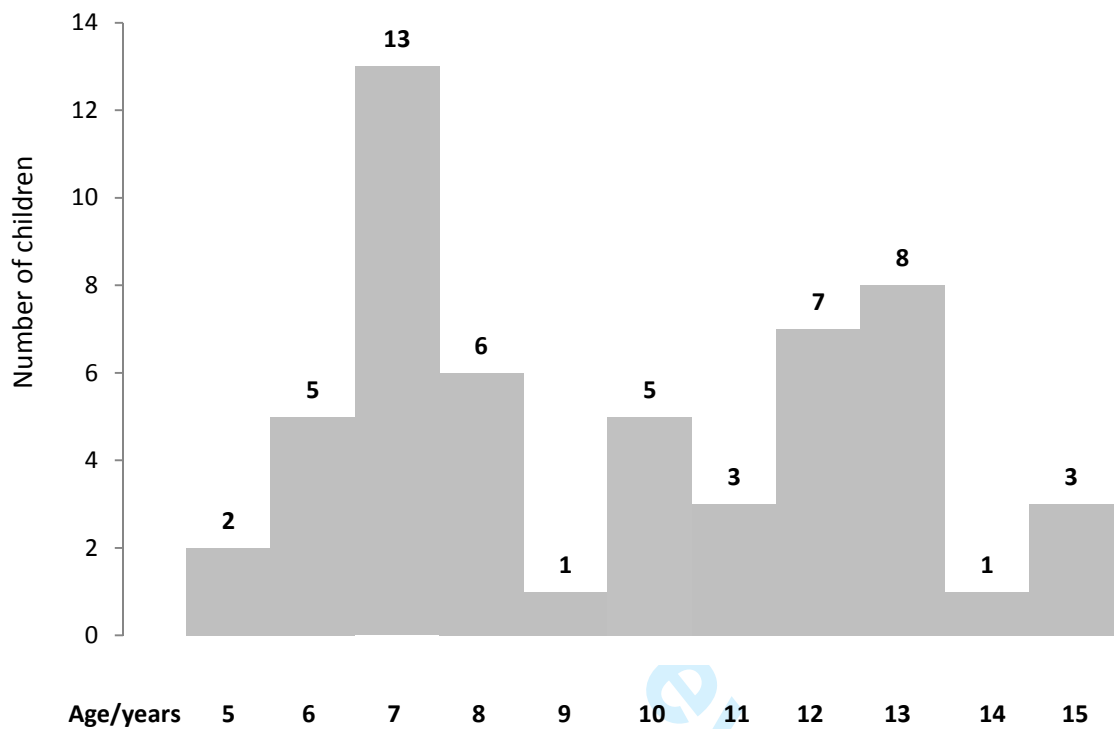
<sup>1</sup>MV=mitral valve

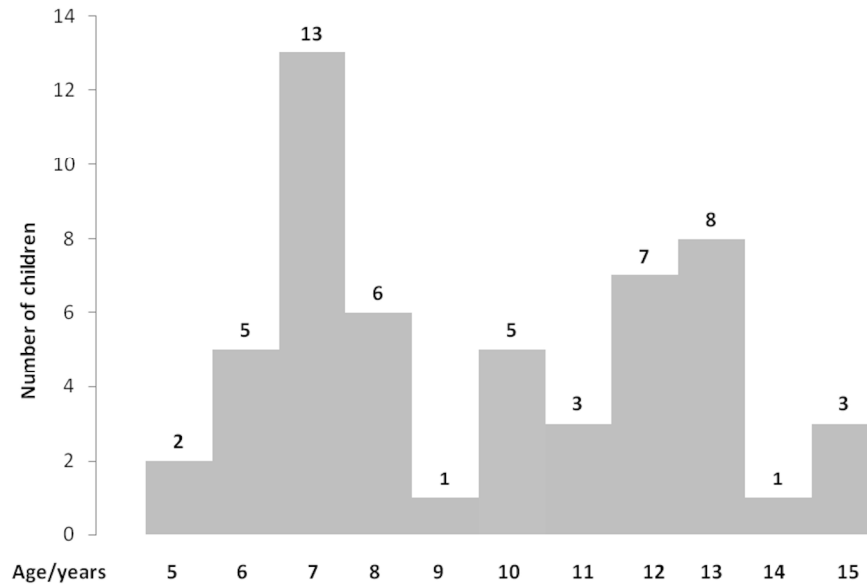
<sup>2</sup>AV=aortic valve

\*two children with anterior mitral leaflet thickening without pathological mitral regurgitation consistent

Figures

Figure 1. Distribution of Age among Schoolchildren in Pilot Observational Survey





STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6/7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7/8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8
		(b) Describe any methods used to examine subgroups and interactions	-
		(c) Explain how missing data were addressed	-
		(d) If applicable, describe analytical methods taking account of sampling strategy	-

		(e) Describe any sensitivity analyses	-
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	15
Outcome data	15*	Report numbers of outcome events or summary measures	16
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	-
		(b) Report category boundaries when continuous variables were categorized	-
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
<b>Discussion</b>			9/10
Key results	18	Summarise key results with reference to study objectives	9/10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	-
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	7

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

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## Abstract

**Objectives:** To evaluate a protocol for a population-based program targeting prevention of rheumatic heart disease (RHD) progression by early echocardiographic diagnosis of valvular lesions and timely implementation of secondary prevention.

**Design:** Observational survey with a subsequent prospective cohort study.

**Setting:** Private boarding school in the urban area of the Sunsari district situated on the foothills of the Lower Himalayan Range in Eastern Nepal.

**Participants:** Fifty-four unselected school going children 5-15 years of age, 24 girls and 30 boys.

**Primary outcome measure:** Logistic feasibility of a large-scale population-based screening study using the echocardiographic criteria formulated by the World Heart Federation, with longitudinal follow-up of children with definite or borderline RHD in a prospective cohort study.

**Results:** Standardized interview, physical examination and screening echocardiography were performed in a three-staged process and took approximately 6 minutes per child. Socio-economic status was assessed using surrogate markers such as the occupation of the primary caregiver, numbers of rooms at home, car, television, cell phone and internet connection. Physical examination was focused on cardiac auscultation and signs of acute rheumatic fever and targeted echocardiography was performed by an independent examiner without knowledge of the clinical findings. Two children with evidence of borderline RHD were re-examined at B.P. Koirala institute of Health Sciences and the indication for secondary antibiotic prevention was discussed with the parents and the children. At six months of follow-up, echocardiographic findings were stable in both children. Implementation of secondary antibiotic prevention was challenged by impaired awareness of subclinical RHD among parents and inadequate cooperation with family physicians.

**Conclusions:** This pilot study shows that the methods outlined in the protocol can be translated into a large-scale population-based study. We learned that education and collaboration with teachers, parents and family physicians/pediatricians will be of key importance in order to establish a sustainable program.

**Trial registration:** ClinicalTrials.gov Identifier: NCT01550068

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## Article Summary

### *Article focus:*

- Pilot study for a population-based program targeting prevention of rheumatic heart disease (RHD) progression by early echocardiographic diagnosis of valvular lesions and timely implementation of secondary prevention.

### *Key messages:*

- The echocardiographic criteria for diagnosis of RHD provided by the World Heart Federation are a valuable instrument for population-based screening.
- Adequate information of the parents of children with evidence of silent RHD and cooperation with the family physicians is of key importance for long-term adherence to secondary antibiotic prevention.

### *Strengths and limitations:*

- The pilot study demonstrates feasibility of a large-scale population-based screening program for RHD by the use of portable echocardiography, with a subsequent prospective cohort study.

Introduction

Rheumatic Heart Disease (RHD) is estimated to affect more than 15 million people worldwide and leads to 250,000 deaths every year. [1] More than 80% of the children younger than 15 years of age grow up in regions of the world where RHD is endemic. [2] A discrepancy of reported prevalence rates of RHD among schoolchildren in developing countries is particularly attributable to diverse sensitivities of echocardiographic and clinical screening, respectively. RHD consolidates a spectrum of different stages of clinically silent and clinically manifest valvular degeneration culminating in congestive heart failure, increasing the risk of endocarditis, cerebrovascular events, and eventually leading to premature death of the effected working age population in developing countries.

Acute rheumatic fever (ARF) ensues from an autoimmune reaction in response to group A  $\beta$ -hemolytic streptococcal pharyngitis and may result in RHD through the cumulative valvular damage of recurrent episodes of ARF. [2] Whereas overcrowding and poverty are major determinants of disease proliferation, limited access to healthcare resources renders primary prevention with prompt antibiotic treatment of streptococcal pharyngitis difficult to effectuate in large parts of endemic regions of the world. Secondary prevention among children with a documented history of ARF or evidence of RHD is achieved by regular oral or intravenous administration of penicillin continued until early adulthood.

The World Health Organization has recommended echocardiographic screening of RHD in high prevalence regions. [3] Early detection of subclinical RHD by use of echocardiography warrants timely implementation of secondary antibiotic prophylaxis and may prevent progression of valvular damage leading to congestive heart failure. We performed a pilot study in order to test the feasibility of a cross-sectional survey and a longitudinal cohort study to assess prevalence and clinical outcome of RHD according to the World Heart Federation criteria. [4]

## Aims and Objectives

The goal of the project consists in the prevention of RHD progression by early echocardiographic diagnosis of valvular lesions and timely implementation of secondary prevention. We designed a study 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. [5] The objective of the pilot study was to evaluate the administrative and logistic feasibility of a large-scale population-based screening study, specifically pertaining to questionnaire design and protocol adherence, and to assess the recruitment of children with signs of RHD into a prospective cohort with longitudinal follow-up.

## Methods

### *Study Design and Setting*

The design of the study has been outlined in detail previously. [5] In summary, a cross-sectional survey of schoolchildren aged 5-15 years will be performed for clinically silent or manifest RHD in the Sunsari district of Eastern Nepal. The location in rural or urban areas, as well as public or private administration of the schools will be used as a surrogate to reflect the socio-economic demographic distribution of the population in Eastern Nepal. Children found to have signs consistent with RHD will be enrolled in a prospective cohort to be followed over the course of five years. The Sunsari district is situated on the foothills of the Lower Himalayan Range in Eastern Nepal and extends to the south of the city of Dharan, the third largest city in Nepal.

*Study Population*

The selection of the school for the pilot study was driven by practical reasons and was not based on a pre-specified sampling procedure to obtain a representative study population. As a consequence, the cohort of the pilot study is not eligible for inclusion into the actual study cohort.

A small private boarding school in the urban area of the Sunsari district was selected. A discussion with the principal of the school was performed in order to outline the aim of the project and obtain informed consent. All children of this particular school underwent screening echocardiography.

*Data Collection*

Data acquisition was organized in a three-staged process by study nurses and physicians. School teachers organized the transfer of the children between the study nurses and physicians gathering demographic characteristics, performing physical examination, and conducting echocardiography, respectively. Data on social background and past medical history was acquired in a standardized interview on the basis of a questionnaire. Demographic variables such as age, household characteristics, and socio-economic indicators were recorded along with a short medical history followed by physical examination documenting height, weight, and potential clinical signs of ARF. Study nurses questioned the children about demographic characteristics, filled in the questionnaire, and measured height and weight. A first physician completed the medical history and executed physical examination including cardiac auscultation. A second independent physician performed screening echocardiography using the Samsung portable U6 echocardiography machine to document morphologic and/or functional valvular lesions consistent with RHD.

Parents of children with evidence of RHD were contacted by the physicians and oriented about the findings. The children and parents were subsequently invited for a thorough examination at B.P. Koirala

Institute of Health Sciences. Follow-up data of children with borderline or definite RHD was collected during a dedicated follow-up visit six months after screening.

All data was documented on dedicated paper case report forms which were subsequently transferred into an electronic database.

### *Definitions*

RHD was classified in accordance with the WHF criteria for individuals aged  $\leq 20$  years into definite and borderline. [4] Definite RHD was divided into four subcategories. Subcategory A is defined by pathological mitral regurgitation and at least two morphological features of RHD of the mitral valve, subcategory B is diagnosed in the presence of mitral stenosis with a mean gradient of  $\geq 4$  mmHg. Subcategory C is characterized 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 partitioned into three subcategories. Subcategory A is determined by the presence of at least two morphological features of RHD of the mitral valve without pathological mitral regurgitation or mitral stenosis, subcategories B and C are characterized 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 (i.e. valvular thickening) without any associated pathological stenosis or regurgitation (C and D, respectively) are classified as normal echocardiographic findings.

### *Ethics and Funding*

The study was conducted in compliance with the Declaration of Helsinki and was registered with clinical trials.gov (NCT01550068). The study was approved by the ethic committee of B.P. Koirala Institute of Health Sciences and was given an exempt status by the ethics committee at University of Bern, Switzerland (KEK-BE 018/12). The pilot study was supported by an unrestricted grant from the foundation “Coeur de la Tour” (<http://www.coeurdelatour.ch>) from Geneva, Switzerland.

*Sample Size Calculation*

Sample size was determined by practical aspects rather than estimations of prevalence rates. In order to adequately evaluate the questionnaires and assess the duration of a screening examination, we considered a mixed cohort of schoolchildren across all age groups important. We considerably selected a private school with a small number of students in order to allow screening of all children from the selected school in a single day. The localization of the school in an urban area of the lower-middle class with only limited access to electricity throughout the hours of the day simulated a challenge often encountered in more rural areas of Eastern Nepal. The screening examinations were timed and performed in a single afternoon.

*Statistical Analysis*

Statistical analyses were performed using SPSS Statistics Version 17.0. Continuous variables are presented as mean  $\pm$  standard deviation (SD). Categorical data are expressed as frequency (percentages).

**Results**

### *Observational Survey*

Fifty-four children from a private boarding school in the urban area of the Sunsari district ranging from 5 to 15 years of age were included into the pilot observational survey, which was performed by two cardiologists, a pediatrician, an internal medicine resident, and two nurses. Screening was scheduled for a single afternoon on a regular school day. Standardized interview, physical examination and screening echocardiography were performed in a three-staged process and took approximately 6 minutes per child. Screening examinations for this pilot study were performed in two dedicated rooms, one for interview and physical examinations and another one for echocardiography. Boys and girls were examined separately; cardiac auscultation of girls was performed by a female doctor or a male doctor in the presence of a female chaperone. Teachers ensured the efficient realization of the screening process and engaged children waiting to be examined.

Socio-economic status was evaluated using specific questions addressing surrogate markers such as the occupation of the primary caregiver, numbers of rooms at home, car, television, cell phone and internet connection. These questions were readily answered by the majority of the children irrespective of age. Most of the children were belonging to lower middle-class families, where the primary caregiver was a manual worker, five family members were living in three rooms, owned a television and cell phone, but had no car and no internet connection at home ([Figure 1](#)). In turn, questions pertaining to a documented history of a previous attack of rheumatic fever had to be addressed using approximative closed questions about regular medication intake, hospitalizations or prolonged disease in the past, and joint pain. No verification with parents or medical documentation was performed.

Physical examination documented height and weight, and was focused on cardiac auscultation and signs of acute rheumatic fever. Mean age was  $9.6 \pm 2.6$  years, and 56% of the children were boys. Cardiac auscultation revealed four children with soft systolic heart murmurs.

Targeted echocardiography was performed by an independent examiner without knowledge of the clinical findings. While none of the children had echocardiographic evidence of definite RHD, two children were found to have borderline RHD, and two children had isolated thickening of the anterior mitral valve leaflet without pathological regurgitation, that did not meet the criteria for borderline RHD according to the WHF criteria. A 12 year-old asymptomatic boy with no history of ARF and a soft systolic heart murmur was found to have significant thickening of the anterior mitral valve leaflet associated with pathological mitral regurgitation and mild tricuspid regurgitation. Another asymptomatic 12 year-old boy with a soft systolic heart murmur had restricted posterior mitral valve leaflet motion with evidence of pathological mitral regurgitation and mild tricuspid regurgitation. During a subsequent outpatient visit at B.P. Koirala institute of Health Sciences, the indication for secondary antibiotic prevention was discussed with the parents and the children, and orientation for inclusion into a prospective registry was provided.

Barriers to implementation of the observational survey included limited electricity supply around the clock and unpredictable power cuts rendering a battery-operated portable echocardiography machine indispensable.

The selection process of schools that adequately reflect the demographic distribution of the target area was outlined previously and was not assessed in the present pilot study. [5]

*Longitudinal Follow-up*

Both children with evidence of borderline RHD are being prospectively followed and were invited for a clinical and echocardiographic follow-up examination at six months after screening. None of the children

had experienced an adverse event and echocardiographic findings were stable as compared to baseline in both kids.

Secondary antibiotic prevention was discontinued in both children within the first six months of follow-up. The family physicians who had not been involved in the initial decision for initiation of prevention had recommended against prolonged antibiotic treatment in the absence of pathological heart murmurs and no documented attacks of rheumatic fever.

Implementation of secondary antibiotic prevention was challenged by impaired understanding of subclinical RHD among parents and family physicians/pediatricians. Limited public awareness and education, as well as inadequate collaboration with family physicians emerged as barriers to compliance with secondary prevention.

## Discussion

We report the results of a pilot study evaluating a research protocol for an observational survey of RHD among school going children and a subsequent prospective cohort study of children with evidence of rheumatic valvular lesions. This pilot study represents an integral part for the final implementation of the protocol in a large population-based setting. The main findings can be summarized as follows:

1. Clinical and echocardiographic screening of RHD is feasible within 5-10 minutes per child. Active involvement of the teachers who are familiar with the children not only facilitates the organization but also anticipates distrust towards medical personnel from both children and teachers.
2. Adequate orientation of and collaboration with the parents after diagnosis of RHD in a child is of key importance to adherence to preventive antibiotic treatment. Accepting the diagnosis of

subclinical RHD in an apparently healthy child is difficult for both the parents and the children and calls for continued support.

3. Collaboration with family physicians and pediatricians is important to improve adherence to secondary prevention for clinically silent RHD. Inconsistent information causes insecurity and decreases the motivation for compliance with regular antibiotic prevention.
4. The WHF criteria are a helpful instrument to classify subclinical valvular lesions consistent with RHD.

We learned from this pilot study, that collaboration with teachers, parents, and family physicians/pediatricians is indispensable to perform efficient screening, improve compliance with secondary prevention and ascertain clinical follow-up.

Informed teachers were allies in our study not only in terms of facilitating the organization of the pilot study, but also with regard to the orientation of the parents of the two children diagnosed with clinically silent RHD. Moreover, completion of parts of the questionnaire asking for socio-economic background could be assisted by the teachers and would improve quality of the data. As a consequence we plan to extend the participation of the teachers in the collection of the baseline criteria in the main study.

In addition to the school teachers, the parents of the children will be the key players for successful completion of the program. Accepting disease in an asymptomatic child is difficult for every parent. Continued education during every clinical visit with adequate cultural sensitivity should reinforce adherence to treatment. Given the high illiteracy rate in Nepal, letters to the information brochures distributed to the parents will not achieve the targeted objective. In response to the need for education on RHD diagnosis and prevention, we are therefore preparing a documentary film that will be broadcasted on local television and in schools before the screening examinations begin.

Collaboration with family physicians and pediatricians will be central to improve long-term adherence to secondary antibiotic prevention for silent RHD. Inconsistent information will cause insecurity among parents and children and decrease the motivation for compliance with regular antibiotic prevention. Continuing education will be provided to family physicians in the area in order to enhance collaboration and coordinate recommendations on secondary prevention.

Previous studies using primary screening echocardiography performed in endemic regions in Southeast Asia [6, 7, 8], the Western Pacific [9, 10], Africa [6, 11] and Central America [12] reported prevalence rates of RHD among children ranging from 20.4 per 1000 to 55.2 per 1000 children most of which using the 2006 World Health Organization criteria (WHO). In contrast to the WHO criteria combining both, clinical and echocardiographic findings, the WHF criteria are based on echocardiographic criteria only, and have been applied for the present pilot study [3, 4]. Studies documenting echocardiographic follow-up reported stable disease or even regression of valvular lesions in three quarters of the children, but were mainly limited by a short duration of follow and a small sample size [7, 8, 12].

The recently released WHF criteria for echocardiographic diagnosis of RHD proved helpful in the classification of valvular lesions potentially related to subclinical RHD and provide an adequate instrument for large population-based studies.

**Acknowledgement**

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**Competing interests**

None

**Funding**

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(<http://www.coeurdelatour.ch>) from Geneva, Switzerland.

**Data Sharing Statement**

There is no additional data available

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Figure Legends

The manuscript contains no figures.

## Tables

**Table 1. Pilot Study Baseline Characteristics**

Baseline characteristics	n (%) or mean (SD)
Age (years)	9.6 (2.9)
Height in (cm)	127 (16)
Weight in (kg)	28 (12)
Male	30 (55.6)
Documented history of ARF	0 (0)
<i>Socio-economic status</i>	
Number of family members	4.9 (1.2)
Children	2.2 (0.9)
Adults	2.6 (1.0)
<i>Amenities at home</i>	
Household, Number of rooms	2.8 (1.6)
Family owns a car	1 (1.9)
Television at home	50 (92.6)
Internet connection at home	4 (7.7)
Family uses a cell phone	51 (94.4)

# Rheumatic Heart disease: Pilot Study for a Population-Based Evaluation of Prevalence and Cardiovascular Outcomes among Schoolchildren in Nepal

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<sup>‡</sup>Department of Internal Medicine and Cardiology, B.P. Koirala Institute of Health Sciences, Dharan, Nepal; <sup>\*</sup>Department of Cardiology, Swiss Cardiovascular Center Bern, Bern University Hospital, Bern, Switzerland; <sup>†</sup>Clinical Trials Unit, Department of Social and Preventive Medicine, Bern University, Bern, Switzerland; <sup>°</sup>Hôpital de la Tour, Geneva, Switzerland

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## Abstract

**Objectives:** To evaluate a protocol for a population-based program targeting prevention of rheumatic heart disease (RHD) progression by early echocardiographic diagnosis of valvular lesions and timely implementation of secondary prevention.

**Design:** Observational survey with a subsequent prospective cohort study.

**Setting:** Private boarding school in the urban area of the Sunsari district situated on the foothills of the Lower Himalayan Range in Eastern Nepal.

**Participants:** Fifty-four unselected school going children 5-15 years of age, 24 girls and 30 boys.

**Primary outcome measure:** Logistic feasibility of a large-scale population-based screening study using the echocardiographic criteria formulated by the World Heart Federation, with longitudinal follow-up of children with definite or borderline RHD in a prospective cohort study.

**Results:** Standardized interview, physical examination and screening echocardiography were performed in a three-staged process and took approximately 6 minutes per child. Socio-economic status was assessed using surrogate markers such as the occupation of the primary caregiver, numbers of rooms at home, car, television, cell phone and internet connection. Physical examination was focused on cardiac auscultation and signs of acute rheumatic fever and targeted echocardiography was performed by an independent examiner without knowledge of the clinical findings. Two children with evidence of borderline RHD were re-examined at B.P. Koirala institute of Health Sciences and the indication for secondary antibiotic prevention was discussed with the parents and the children. At six months of follow-up, echocardiographic findings were stable in both children. Implementation of secondary antibiotic prevention was challenged by impaired awareness of subclinical RHD among parents and inadequate cooperation with family physicians.

**Conclusions:** This pilot study shows that the methods outlined in the protocol can be translated into a large-scale population-based study. We learned that education and collaboration with teachers, parents and family physicians/pediatricians will be of key importance in order to establish a sustainable program.

**Trial registration:** ClinicalTrials.gov Identifier: NCT01550068

For peer review only

## Article Summary

### *Article focus:*

- Pilot study for a population-based program targeting prevention of rheumatic heart disease (RHD) progression by early echocardiographic diagnosis of valvular lesions and timely implementation of secondary prevention.

### *Key messages:*

- The echocardiographic criteria for diagnosis of RHD provided by the World Heart Federation are a valuable instrument for population-based screening.
- Adequate information of the parents of children with evidence of silent RHD and cooperation with the family physicians is of key importance for long-term adherence to secondary antibiotic prevention.

### *Strengths and limitations:*

- The pilot study demonstrates feasibility of a large-scale population-based screening program for RHD by the use of portable echocardiography, with a subsequent prospective cohort study.

Introduction

Rheumatic Heart Disease (RHD) is estimated to affect more than 15 million people worldwide and leads to 250,000 deaths every year. [1] More than 80% of the children younger than 15 years of age grow up in regions of the world where RHD is endemic. [2] A discrepancy of reported prevalence rates of RHD among schoolchildren in developing countries is particularly attributable to diverse sensitivities of echocardiographic and clinical screening, respectively. RHD consolidates a spectrum of different stages of clinically silent and clinically manifest valvular degeneration culminating in congestive heart failure, increasing the risk of endocarditis, cerebrovascular events, and eventually leading to premature death of the effected working age population in developing countries.

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The World Health Organization has recommended echocardiographic screening of RHD in high prevalence regions. [3] Early detection of subclinical RHD by use of echocardiography warrants timely implementation of secondary antibiotic prophylaxis and may prevent progression of valvular damage leading to congestive heart failure. We performed a pilot study in order to test the feasibility of a cross-sectional survey and a longitudinal cohort study to assess prevalence and clinical outcome of RHD according to the World Heart Federation criteria. [4]

## Aims and Objectives

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3. Collaboration with family physicians and pediatricians is important to improve adherence to secondary prevention for clinically silent RHD. Inconsistent information causes insecurity and decreases the motivation for compliance with regular antibiotic prevention.

4. The WHF criteria are a helpful instrument to classify subclinical valvular lesions consistent with RHD.

We learned from this pilot study, that collaboration with teachers, parents, and family physicians/pediatricians is indispensable to perform efficient screening, improve compliance with secondary prevention and ascertain clinical follow-up.

Informed teachers were allies in our study not only in terms of facilitating the organization of the pilot study, but also with regard to the orientation of the parents of the two children diagnosed with clinically silent RHD. Moreover, completion of parts of the questionnaire asking for socio-economic background could be assisted by the teachers and would improve quality of the data. As a consequence we plan to extend the participation of the teachers in the collection of the baseline criteria in the main study.

In addition to the school teachers, the parents of the children will be the key players for successful completion of the program. Accepting disease in an asymptomatic child is difficult for every parent. Continued education during every clinical visit with adequate cultural sensitivity should reinforce adherence to treatment. Given the high illiteracy rate in Nepal, letters to the information brochures distributed to the parents will not achieve the targeted objective. In response to the need for education on RHD diagnosis and prevention, we are therefore preparing a documentary film that will be broadcasted on local television and in schools before the screening examinations begin.

Collaboration with family physicians and pediatricians will be central to improve long-term adherence to secondary antibiotic prevention for silent RHD. Inconsistent information will cause insecurity among parents and children and decrease the motivation for compliance with regular antibiotic prevention. Continuing education will be provided to family physicians in the area in order to enhance collaboration and coordinate recommendations on secondary prevention.

Previous studies using primary screening echocardiography performed in endemic regions in Southeast Asia [6, 7, 8], the Western Pacific [9, 10], Africa [6, 11] and Central America [12] reported prevalence rates of RHD among children ranging from 20.4 per 1000 to 55.2 per 1000 children most of which using the 2006 World Health Organization criteria (WHO). In contrast to the WHO criteria combining both, clinical and echocardiographic findings, the WHF criteria are based on echocardiographic criteria only, and have been applied for the present pilot study [3, 4]. Studies documenting echocardiographic follow-up reported stable disease or even regression of valvular lesions in three quarters of the children, but were mainly limited by a short duration of follow and a small sample size [7, 8, 12].

The recently released WHF criteria for echocardiographic diagnosis of RHD proved helpful in the classification of valvular lesions potentially related to subclinical RHD and provide an adequate instrument for large population-based studies.

**Acknowledgement**

Sina Pilgrim, MD; Kavita Shah, RN; Kishori Dhakal, RN

**Competing interests**

None

**Funding**

The study is supported by an unrestricted grant from the foundation “Coeur de la Tour”  
(<http://www.coeurdelatour.ch>) from Geneva, Switzerland.

**Data Sharing Statement**

There is no additional data available

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Figure Legends

The manuscript contains no figures.

## Tables

**Table 1. Pilot Study Baseline Characteristics**

Baseline characteristics	n (%) or mean (SD)
Age (years)	9.6 (2.9)
Height in (cm)	127 (16)
Weight in (kg)	28 (12)
Male	30 (55.6)
Documented history of ARF	0 (0)
<i>Socio-economic status</i>	
Number of family members	4.9 (1.2)
Children	2.2 (0.9)
Adults	2.6 (1.0)
<i>Amenities at home</i>	
Household, Number of rooms	2.8 (1.6)
Family owns a car	1 (1.9)
Television at home	50 (92.6)
Internet connection at home	4 (7.7)
Family uses a cell phone	51 (94.4)

Rebuttal Letter

*bmjopen-2012-001616*

Rheumatic Heart disease: Pilot Study for a Population-Based Evaluation of Prevalence and Cardiovascular Outcomes among Schoolchildren in Nepal

**Reviewer #1: Eloi Marijon**

We thank reviewer Dr Marijon for the careful review and helpful suggestions and answer the raised issues below:

**Comment#1:** Difficult to report a screening of a so restricted population (N=54!!!), with 2 positive cases....and the Authors claimed that they can conclude that such a prevalence is similar than prevalence rates reported previously in the region of the world!! I would be very please to review the article after the end of the whole study (and not only the pilot study as reported here).

**Reply#1:** We agree with the reviewer that the present pilot study is not powered to generate data on prevalence rates. Reliable evaluation of disease prevalence in a given geographical region depends on both number of subjects screened and selection of appropriate clusters representing the population in that area. Sample size calculation for evaluation of disease prevalence in our study has been outlined previously (Pilgrim T et al. Protocol for a population-based study of rheumatic heart disease prevalence and cardiovascular outcomes among schoolchildren in Nepal. BMJ Open 2012; 2(3):e001320). In contrast, the present pilot study was rather intended to assess the administrative and logistic feasibility of a large-scale population-based screening study, specifically pertaining to questionnaire design, and protocol adherence, and additionally to assess the recruitment of children with signs of RHD into a prospective cohort.

In order to streamline the key message of our manuscript, we deleted the following sentence in the discussion section of the revised version of the manuscript:

In line with previous reports on prevalence rates of subclinical RHD from Southeast Asia published within the last decade, the extrapolated prevalence rate in our cohort amounted to 37 per 1000 children diagnosed with subclinical RHD [6-8].

**Comment#2:** Similarly to the point discussed above, we cannot conclude anything from these results. The only interest of this paper is to consider the new echo criteria recommended by WHF.

**Reply#2:** We agree with the reviewer that the observations from the pilot study do not extend our knowledge on rheumatic heart disease. However, we think that the methods of the pilot study were adequate to evaluate the feasibility of a full-scale study as outlined in the section "aims and objectives", and that the conclusion formulated in the abstract is in line with the objective. We are convinced that the pilot study improved the logistic organization of the full-scale study.

**Reviewer #2: Andrea Z Beaton**

We thank reviewer Dr Beaton for the careful review and helpful suggestions and answer the raised issues below:

This is a pilot study to assess the feasibility of implementing an RHD screening and secondary prophylaxis program in primary schools in Nepal. While this is clearly stated in the Objectives section of the abstract - it becomes muddled as the reader progresses through the paper. In particular - the results section focuses on disease prevalence (which the study is not powered to obtain and is not the stated objective of the study.)

**Comment#1:** Perhaps the problem starts in the abstract where the primary outcomes measure is:

"Borderline or definite RHD on screening echocardiography according to the criteria provided by the World Heart Federation" which does not match the final conclusion that a large scale study is feasible.

**Reply#1:** We agree with the comment of the reviewer that the primary outcome measure formulated in the abstract does not match the objective and the conclusion. In order to correct this inconsistency, we changed the “primary outcome measure” in the abstract section in the revision version of the manuscript as follows:

*“Primary outcome measure: Logistic feasibility of a large-scale population-based screening study using the echocardiographic criteria formulated by the World Heart Federation, with longitudinal follow-up of children with definite or borderline RHD in a prospective cohort study.”*

Furthermore, we revised the results section of the manuscript focusing more on feasibility of the study.

**Comment#2:** In the methods section it would be useful to the reader if more details were provided on how the 54 children were selected - randomly, randomly according to age, etc.

**Reply#2:** We thank the reviewer for making us aware of this unclarity. The private boarding school that was selected for screening is a very small school with 54 students only. We considerably selected this school to avoid randomization of individual students from different classes. Instead, all children of the school underwent screening echocardiography. Accordingly, the following sentence has been added to the section methods/study population of the revised version of the manuscript:

*“All children of this particular school underwent screening echocardiography.”*

Furthermore, we included the following statement to the methods/sample size calculation section of the revised version of the manuscript.

*“We considerably selected a private school with a small number of students in order to allow screening of all children from the selected school in a single day.”*

**Comment#3:** Again - here the main outcome measure is not clearly defined. The stated goal is feasibility - with likely qualitative results anticipated. The given results focus on disease prevalence - and extrapolate a prevalence number per/1000 from a very small subset of patients. The authors point (feasibility) is a good one, and would be better served by focusing on this in the results section.

**Reply#3:** We agree with the reviewer's suggestion to focus on applicability of the study design in the results section rather than quantitative data. The focus of the results section has been revised according to the objective of the pilot study.

**Comment#4:** The limitation of very small sample size (which could hugely over- or underestimate true disease prevalence should be stated.

**Reply#4:** In view of the very small sample size, we renounced to extrapolate a prevalence rate and deleted the following sentence in the revised version of the manuscript.

~~In line with previous reports on prevalence rates of subclinical RHD from Southeast Asia published within the last decade, the extrapolated prevalence rate in our cohort amounted to 37 per 1000 children diagnosed with subclinical RHD [6-8].~~

**Comment#5:** See above - need results section to focus on barriers to implementation, etc. Now covered mostly in the discussion section.

**Reply#5:** We agree that parts of the discussion section rather address results. Therefore we re-structured the results and the discussion section and included two paragraphs focusing on barriers to implementation of the study in the results section of the revised version of the manuscript. We included the following paragraphs to the results section/observational survey and longitudinal follow-up, respectively.

*"Barriers to implementation of the observational survey included limited electricity supply around the clock and unpredictable power cuts rendering a battery-operated portable echocardiography machine indispensable."*

*"Implementation of secondary antibiotic prevention was challenged by impaired understanding of subclinical RHD among parents and family physicians/pediatricians. Limited public awareness and*

education, as well as inadequate collaboration with family physicians emerged as barriers to compliance with secondary prevention.”

**Comment#6:** No previous evidence is presented in the discussion section. There are many articles discussing large scale screening programs - in particular, Authors should refer to: Saxena, 2011, Heart. RHEUMATIC study, which looks at screening and follow-up in over 6,000 children in India.

**Reply#6:** We agree with the reviewer that previous studies of similar design have to be discussed in the discussion section of the manuscript. For this reason we implemented the following paragraph into the discussion section of the revised version of the manuscript.

*“Previous studies using primary screening echocardiography performed in endemic regions in Southeast Asia [6, 7, 8], the Western Pacific [9, 10], Africa [6, 11] and Central America [12] reported prevalence rates of RHD among children ranging from 20.4 per 1000 to 55.2 per 1000 children most of which using the 2006 World Health Organization criteria (WHO). In contrast to the WHO criteria combining both, clinical and echocardiographic findings, the WHF criteria are based on echocardiographic criteria only, and have been applied for the present pilot study [3, 4]. Studies documenting echocardiographic follow-up reported stable disease or even regression of valvular lesions in three quarters of the children, but were mainly limited by a short duration of follow and a small sample size [7, 8, 12].”*

**Comment#7:** I think the message here gets lost in some of the other goals/objectives. As stated above: Perhaps the problem starts in the abstract where the primary outcomes measure is: "Borderline or definite RHD on screening echocardiography according to the criteria provided by the World Heart Federation" which does not match the final conclusion that a large scale study is feasible. The objective and the primary outcome measure should match in their goals. If the study is to assess feasibility of implementation, the primary outcomes measure should not be disease prevalence.

**Reply#7:** We agree with the comment of the reviewer that the primary outcome measure formulated in the abstract does not match the objective and the conclusion. In order to correct this

inconsistency, we changed the “primary outcome measure” in the abstract section in the revision version of the manuscript as follows:

**“Primary outcome measure:** *Logistic feasibility of a large-scale population-based screening study using the echocardiographic criteria formulated by the World Heart Federation, with longitudinal follow-up of children with definite or borderline RHD in a prospective cohort study.*”

Furthermore, the results section of the revised version of the manuscript has been completely revised.

**Comment#8:** Rheumatic heart disease imposes an enormous global burden of disease and is a major cause of morbidity and mortality in developing nations. Echocardiography has been shown to detect 3-5 times more disease than clinical exam alone; the recently published 2012 World Heart Federation guidelines now provide a framework for consistent echocardiographic diagnosis and disease reporting. This study addresses an important consideration - the feasibility of implementing large-scale screening efforts.

The major problem I see with this study is in its focus. The reader is expecting to hear about feasibility and the primary outcomes measure is prevalence. I think reworking the article to make it more focused (other data will be more appropriately reported in the prospective cohort that will come after the pilot study) will greatly improve its message.

**Replyt#8:** We thank the reviewer for her comment and agree that the focus of the previous version of the manuscript was inadequate for the objective of the pilot study. We restructured the entire results and the methods section focusing on feasibility rather than prevalence in the revised version of the manuscript.

**Reviewer #3: Ana Olga Mocumbi**

We thank reviewer Dr Mocumbi for the careful review and helpful suggestions and answer the raised issues below:

**Comment#1:** Reference 5 is not available.

**Reply#1:** We regret that reference 5 might not have been available at the time of review of the present pilot study. Below please find the reference that can now be accessed online:

*Pilgrim T, Kalesan B, Karki P, Basnet A, Meier B, Urban P, Shrestha NR. Protocol for a population-based study of rheumatic heart disease prevalence and cardiovascular outcomes among schoolchildren in Nepal. BMJ Open. 2012;2(3). pii: e001320.*

**Comment#2:** Regarding the study design the authors state that the study was observational but it included intervention (early secondary prevention) which results are important for the implementation phase but do not seem to be the objective at this stage. However, some results of follow are given (although the follow up time is not specified). Please clarify this issue.

**Reply#2:** We thank the reviewer for this comment and included standardized follow-up at six months into the revised version of the manuscript addressing repeat echocardiography and compliance with secondary prevention.

*“Longitudinal Follow-up*

*Both children with evidence of borderline RHD are being prospectively followed and were invited for a clinical and echocardiographic follow-up examination at six months after screening. None of the children had experienced an adverse event and echocardiographic findings were stable as compared to baseline in both kids.*

*Secondary antibiotic prevention was discontinued in both children within the first six months of follow-up. The family physicians who had not been involved in the initial decision for initiation of prevention had recommended against prolonged antibiotic treatment in the absence of pathological heart murmurs and no documented attacks of rheumatic fever.*

Implementation of secondary antibiotic prevention was challenged by impaired understanding of subclinical RHD among parents and family physicians/pediatricians. Limited public awareness and education, as well as inadequate collaboration with family physicians emerged as barriers to compliance with secondary prevention."

**Comment#3:** Specific queries: Being a feasibility study for the component of assessment of prevalence there is also need to rephrase "In a subsequent cohort study...". This seems to refer to the actual protocol as there is no data on follow up of the studied children. Could the authors comment on this?

**Reply#3:** We thank the reviewer for this comment and realized that the subsequent cohort study has to be implemented into the current manuscript of the pilot study in order to be consistent with the actual protocol. For this reason, we adapted the objectives, adapted the methods, and included the paragraph copied above to the results section of the manuscript.

**Comment#4:** "Unselected" children studied in this pilot study refer to children who are not eligible for the actual survey. This needs to be clarified in the text.

**Reply#4:** We agree that the cohort of the pilot study is not eligible for inclusion into the actual survey, since the selection of the school was driven by practical reasons rather than based on the sampling procedure outlined in the study protocol. Accordingly, we added the following sentence to the section methods/study population:

*"The selection of the school for the pilot study was driven by practical reasons and was not based on a pre-specified sampling procedure to obtain a representative study population. As consequence, the cohort of the pilot study is not eligible for inclusion into the actual study cohort."*

**Comment#5:** It is stated that "long term follow up will identify determinants of adherence and show impact of secondary prophylaxis". This seems to refer to the implementation phase as follow up of

the children diagnosed does not seem to be part of this pilot study; either clarification or rephrasing of the text is needed.

**Reply#5:** We agree that the statement in question does not belong into the article summary of the present pilot study. Therefore, we deleted this bullet point in the summary section.

**Comment#6:** Methods, Results and Discussion: Methods section needs review to concentrate on the study design and population of the feasibility study. (We did not have access to reference 5). This section should include several aspects that are included only in Discussion, such as time spent to perform an echo, role of teachers and design of focus group discussions, etc ... which are included as "findings".

**Reply#6:** We agree that several aspects addressed in the discussion section should be introduced in the methods section. We therefore added the following sentences to the section methods/data collection:

*"Data acquisition was organized in a three-staged process by study nurses and physicians and took approximately 6 minutes per child. School teachers organized the transfer of the children between the study nurses and physicians gathering demographic characteristics, performing physical examination, and conducting echocardiography, respectively. Data on social background and past medical history was acquired in a standardized interview on the basis of a questionnaire. Demographic variables such as age, household characteristics, and socio-economic indicators were recorded along with a short medical history followed by physical examination documenting height, weight, and potential clinical signs of ARF. Study nurses questioned the children about demographic characteristics, filled in the questionnaire, and measured height and weight. A first physician completed the medical history and executed physical examination including cardiac auscultation. A second independent physician performed screening echocardiography using the Samsung portable U6 echocardiography machine to document morphologic and/or functional valvular lesions consistent with RHD. "*

**Comment#7:** The paragraph that states the compliance of ethics rules should probably be separated from the section "Treatment".

**Reply#7:** We agree that the paragraph addressing compliance with ethic rules is not in context with the section "treatment" and separated the two paragraphs accordingly. We now created a separate paragraph under the title "Ethics and Funding."

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6/7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7/8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8
		(b) Describe any methods used to examine subgroups and interactions	-
		(c) Explain how missing data were addressed	-
		(d) If applicable, describe analytical methods taking account of sampling strategy	-

		(e) Describe any sensitivity analyses	-
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	15
Outcome data	15*	Report numbers of outcome events or summary measures	16
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	-
		(b) Report category boundaries when continuous variables were categorized	-
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
<b>Discussion</b>			9/10
Key results	18	Summarise key results with reference to study objectives	9/10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	-
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	7

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

For peer review only



**Rheumatic Heart disease: Pilot Study for a Population-Based  
Evaluation of Prevalence and Cardiovascular Outcomes  
among Schoolchildren in Nepal**

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<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	Epidemiology, Infectious diseases, Public health, Rheumatology
Keywords:	CARDIOLOGY, Cardiac Epidemiology < CARDIOLOGY, Echocardiography < CARDIOLOGY, Valvular heart disease < CARDIOLOGY

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# Rheumatic Heart disease: Pilot Study for a Population-Based Evaluation of Prevalence and Cardiovascular Outcomes among Schoolchildren in Nepal

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ClinicalTrials.gov Identifier: NCT01550068

Keywords: rheumatic heart disease, screening, schoolchildren

Word Count: 3576

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## Abstract

**Objectives:** To evaluate a protocol for a population-based program targeting prevention of rheumatic heart disease (RHD) progression by early echocardiographic diagnosis of valvular lesions and timely implementation of secondary prevention.

**Design:** Observational survey with a subsequent prospective cohort study.

**Setting:** Private boarding school in the urban area of the Sunsari district situated on the foothills of the Lower Himalayan Range in Eastern Nepal.

**Participants:** Fifty-four unselected school going children 5-15 years of age, 24 girls and 30 boys.

**Primary outcome measure:** Logistic feasibility of a large-scale population-based screening study using the echocardiographic criteria formulated by the World Heart Federation, with longitudinal follow-up of children with definite or borderline RHD in a prospective cohort study.

**Results:** Standardized interview, physical examination and screening echocardiography were performed in a three-staged process and took approximately 6 minutes per child. Socio-economic status was assessed using surrogate markers such as the occupation of the primary caregiver, numbers of rooms at home, car, television, cell phone and internet connection. Physical examination was focused on cardiac auscultation and signs of acute rheumatic fever and targeted echocardiography was performed by an independent examiner without knowledge of the clinical findings. Two children with evidence of borderline RHD were re-examined at B.P. Koirala institute of Health Sciences and the indication for secondary antibiotic prevention was discussed with the parents and the children. At six months of follow-up, echocardiographic findings were stable in both children. Implementation of secondary antibiotic prevention was challenged by impaired awareness of subclinical RHD among parents and inadequate cooperation with family physicians.

**Conclusions:** This pilot study shows that the methods outlined in the protocol can be translated into a large-scale population-based study. We learned that education and collaboration with teachers, parents and family physicians/pediatricians will be of key importance in order to establish a sustainable program.

**Trial registration:** ClinicalTrials.gov Identifier: NCT01550068

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## Article Summary

### *Article focus:*

- Pilot study for a population-based program targeting prevention of rheumatic heart disease (RHD) progression by early echocardiographic diagnosis of valvular lesions and timely implementation of secondary prevention.

### *Key messages:*

- The echocardiographic criteria for diagnosis of RHD provided by the World Heart Federation are a valuable instrument for population-based screening.
- Adequate information of the parents of children with evidence of silent RHD and cooperation with the family physicians is of key importance for long-term adherence to secondary antibiotic prevention.

### *Strengths and limitations:*

- The pilot study demonstrates feasibility of a large-scale population-based screening program for RHD by the use of portable echocardiography, with a subsequent prospective cohort study.

Introduction

Rheumatic Heart Disease (RHD) is estimated to affect more than 15 million people worldwide and leads to 250,000 deaths every year. [1] More than 80% of the children younger than 15 years of age grow up in regions of the world where RHD is endemic. [2] A discrepancy of reported prevalence rates of RHD among schoolchildren in developing countries is particularly attributable to diverse sensitivities of echocardiographic and clinical screening, respectively. RHD consolidates a spectrum of different stages of clinically silent and clinically manifest valvular degeneration culminating in congestive heart failure, increasing the risk of endocarditis, cerebrovascular events, and eventually leading to premature death of the effected working age population in developing countries.

Acute rheumatic fever (ARF) ensues from an autoimmune reaction in response to group A  $\beta$ -hemolytic streptococcal pharyngitis and may result in RHD through the cumulative valvular damage of recurrent episodes of ARF. [2] Whereas overcrowding and poverty are major determinants of disease proliferation, limited access to healthcare resources renders primary prevention with prompt antibiotic treatment of streptococcal pharyngitis difficult to effectuate in large parts of endemic regions of the world. Secondary prevention among children with a documented history of ARF or evidence of RHD is achieved by regular oral or intravenous administration of penicillin continued until early adulthood.

The World Health Organization has recommended echocardiographic screening of RHD in high prevalence regions. [3] Early detection of subclinical RHD by use of echocardiography warrants timely implementation of secondary antibiotic prophylaxis and may prevent progression of valvular damage leading to congestive heart failure. We performed a pilot study in order to test the feasibility of a cross-sectional survey and a longitudinal cohort study to assess prevalence and clinical outcome of RHD according to the World Heart Federation criteria. [4]

## Aims and Objectives

The goal of the project consists in the prevention of RHD progression by early echocardiographic diagnosis of valvular lesions and timely implementation of secondary prevention. We designed a study 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. [5] The objective of the pilot study was to evaluate the administrative and logistic feasibility of a large-scale population-based screening study, specifically pertaining to questionnaire design and protocol adherence, and to assess the recruitment of children with signs of RHD into a prospective cohort with longitudinal follow-up.

## Methods

### *Study Design and Setting*

The design of the study has been outlined in detail previously. [5] In summary, a cross-sectional survey of schoolchildren aged 5-15 years will be performed for clinically silent or manifest RHD in the Sunsari district of Eastern Nepal. The location in rural or urban areas, as well as public or private administration of the schools will be used as a surrogate to reflect the socio-economic demographic distribution of the population in Eastern Nepal. Children found to have signs consistent with RHD will be enrolled in a prospective cohort to be followed over the course of five years. The Sunsari district is situated on the foothills of the Lower Himalayan Range in Eastern Nepal and extends to the south of the city of Dharan, the third largest city in Nepal.

*Study Population*

The selection of the school for the pilot study was driven by practical reasons and was not based on a pre-specified sampling procedure to obtain a representative study population. As a consequence, the cohort of the pilot study is not eligible for inclusion into the actual study cohort.

A small private boarding school in the urban area of the Sunsari district was selected. A discussion with the principal of the school was performed in order to outline the aim of the project and obtain informed consent. All children of this particular school underwent screening echocardiography.

*Data Collection*

Data acquisition was organized in a three-staged process by study nurses and physicians. School teachers organized the transfer of the children between the study nurses and physicians gathering demographic characteristics, performing physical examination, and conducting echocardiography, respectively. Data on social background and past medical history was acquired in a standardized interview on the basis of a questionnaire. Demographic variables such as age, household characteristics, and socio-economic indicators were recorded along with a short medical history followed by physical examination documenting height, weight, and potential clinical signs of ARF. Study nurses questioned the children about demographic characteristics, filled in the questionnaire, and measured height and weight. A first physician completed the medical history and executed physical examination including cardiac auscultation. A second independent physician performed screening echocardiography using the Samsung portable U6 echocardiography machine to document morphologic and/or functional valvular lesions consistent with RHD.

Parents of children with evidence of RHD were contacted by the physicians and oriented about the findings. The children and parents were subsequently invited for a thorough examination at B.P. Koirala

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All data was documented on dedicated paper case report forms which were subsequently transferred into an electronic database.

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RHD was classified in accordance with the WHF criteria for individuals aged  $\leq 20$  years into definite and borderline. [4] Definite RHD was divided into four subcategories. Subcategory A is defined by pathological mitral regurgitation and at least two morphological features of RHD of the mitral valve, subcategory B is diagnosed in the presence of mitral stenosis with a mean gradient of  $\geq 4$  mmHg. Subcategory C is characterized 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 partitioned into three subcategories. Subcategory A is determined by the presence of at least two morphological features of RHD of the mitral valve without pathological mitral regurgitation or mitral stenosis, subcategories B and C are characterized 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 (i.e. valvular thickening) without any associated pathological stenosis or regurgitation (C and D, respectively) are classified as normal echocardiographic findings.

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*Statistical Analysis*

Statistical analyses were performed using SPSS Statistics Version 17.0. Continuous variables are presented as mean ± standard deviation (SD). Categorical data are expressed as frequency (percentages).

**Results**

### *Observational Survey*

Fifty-four children from a private boarding school in the urban area of the Sunsari district ranging from 5 to 15 years of age were included into the pilot observational survey, which was performed by two cardiologists, a pediatrician, an internal medicine resident, and two nurses. Screening was scheduled for a single afternoon on a regular school day. Standardized interview, physical examination and screening echocardiography were performed in a three-staged process and took all together approximately 6 minutes per child. Screening examinations for this pilot study were performed in two dedicated rooms, one for interview and physical examinations and another one for echocardiography. Boys and girls were examined separately; cardiac auscultation of girls was performed by a female doctor or a male doctor in the presence of a female chaperone. Teachers ensured the efficient realization of the screening process and engaged children waiting to be examined.

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Physical examination documented height and weight, and was focused on cardiac auscultation and signs of acute rheumatic fever. Mean age was  $9.6 \pm 2.6$  years, and 56% of the children were boys. Cardiac auscultation revealed four children with soft systolic heart murmurs.

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Barriers to implementation of the observational survey included limited electricity supply around the clock and unpredictable power cuts rendering a battery-operated portable echocardiography machine indispensable.

The selection process of schools that adequately reflect the demographic distribution of the target area was outlined previously and was not assessed in the present pilot study. [5]

*Longitudinal Follow-up*

Both children with evidence of borderline RHD are being prospectively followed and were invited for a clinical and echocardiographic follow-up examination at six months after screening. None of the children

had experienced an adverse event and echocardiographic findings were stable as compared to baseline in both kids.

Secondary antibiotic prevention was discontinued in both children within the first six months of follow-up. The family physicians who had not been involved in the initial decision for initiation of prevention had recommended against prolonged antibiotic treatment in the absence of pathological heart murmurs and no documented attacks of rheumatic fever.

Implementation of secondary antibiotic prevention was challenged by impaired understanding of subclinical RHD among parents and family physicians/pediatricians. Limited public awareness and education, as well as inadequate collaboration with family physicians emerged as barriers to compliance with secondary prevention.

## Discussion

We report the results of a pilot study evaluating a research protocol for an observational survey of RHD among school going children and a subsequent prospective cohort study of children with evidence of rheumatic valvular lesions. This pilot study represents an integral part for the final implementation of the protocol in a large population-based setting. The main findings can be summarized as follows:

1. Clinical and echocardiographic screening of RHD is feasible within 5-10 minutes per child. Active involvement of the teachers who are familiar with the children not only facilitates the organization but also anticipates distrust towards medical personnel from both children and teachers.
2. Adequate orientation of and collaboration with the parents after diagnosis of RHD in a child is of key importance to adherence to preventive antibiotic treatment. Accepting the diagnosis of

subclinical RHD in an apparently healthy child is difficult for both the parents and the children and calls for continued support.

3. Collaboration with family physicians and pediatricians is important to improve adherence to secondary prevention for clinically silent RHD. Inconsistent information causes insecurity and decreases the motivation for compliance with regular antibiotic prevention.
4. The WHF criteria are a helpful instrument to classify subclinical valvular lesions consistent with RHD.

We learned from this pilot study, that collaboration with teachers, parents, and family physicians/pediatricians is indispensable to perform efficient screening, improve compliance with secondary prevention and ascertain clinical follow-up.

Informed teachers were allies in our study not only in terms of facilitating the organization of the pilot study, but also with regard to the orientation of the parents of the two children diagnosed with clinically silent RHD. Moreover, completion of parts of the questionnaire asking for socio-economic background could be assisted by the teachers and would improve quality of the data. As a consequence we plan to extend the participation of the teachers in the collection of the baseline criteria in the main study.

In addition to the school teachers, the parents of the children will be the key players for successful completion of the program. Accepting disease in an asymptomatic child is difficult for every parent. Continued education during every clinical visit with adequate cultural sensitivity should reinforce adherence to treatment. Given the high illiteracy rate in Nepal, letters to the information brochures distributed to the parents will not achieve the targeted objective. In response to the need for education on RHD diagnosis and prevention, we are therefore preparing a documentary film that will be broadcasted on local television and in schools before the screening examinations begin.

Collaboration with family physicians and pediatricians will be central to improve long-term adherence to secondary antibiotic prevention for silent RHD. Inconsistent information will cause insecurity among parents and children and decrease the motivation for compliance with regular antibiotic prevention. Continuing education will be provided to family physicians in the area in order to enhance collaboration and coordinate recommendations on secondary prevention.

Previous studies using primary screening echocardiography performed in endemic regions in Southeast Asia [6, 7, 8], the Western Pacific [9, 10], Africa [6, 11] and Central America [12] reported prevalence rates of RHD among children ranging from 20.4 per 1000 to 55.2 per 1000 children most of which using the 2006 World Health Organization criteria (WHO). In contrast to the WHO criteria combining both, clinical and echocardiographic findings, the WHF criteria are based on echocardiographic criteria only, and have been applied for the present pilot study [3, 4]. Studies documenting echocardiographic follow-up reported stable disease or even regression of valvular lesions in three quarters of the children, but were mainly limited by a short duration of follow and a small sample size [7, 8, 12].

The recently released WHF criteria for echocardiographic diagnosis of RHD proved helpful in the classification of valvular lesions potentially related to subclinical RHD and provide an adequate instrument for large population-based studies.

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**Competing interests**

None

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**Data Sharing Statement**

There is no additional data available

**Contributorship Statement**

NS: substantial contribution to conception and design, drafting the article and final approval of the version to be published.  
BK: substantial contribution to conception and design, drafting the article and final approval of the version to be published.  
PK: substantial contribution to conception and design, revising the content of the draft and final approval of the version to be published.  
KS: substantial contribution to conception and design, revising the content of the draft and final approval of the version to be published.  
AB: substantial contribution to conception and design, revising the content of the draft and final approval of the version to be published.  
PU: substantial contribution to conception and design, revising the content of the draft and final approval of the version to be published.

TP: substantial contribution to conception and design, drafting the article and final approval of the version to be published.

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Figure Legends

The manuscript contains no figures.

## Tables

**Table 1. Pilot Study Baseline Characteristics**

Baseline characteristics	n (%) or mean (SD)
Age (years)	9.6 (2.9)
Height in (cm)	127 (16)
Weight in (kg)	28 (12)
Male	30 (55.6)
Documented history of ARF	0 (0)
<i>Socio-economic status</i>	
Number of family members	4.9 (1.2)
Children	2.2 (0.9)
Adults	2.6 (1.0)
<i>Amenities at home</i>	
Household, Number of rooms	2.8 (1.6)
Family owns a car	1 (1.9)
Television at home	50 (92.6)
Internet connection at home	4 (7.7)
Family uses a cell phone	51 (94.4)

# Rheumatic Heart disease: Pilot Study for a Population-Based Evaluation of Prevalence and Cardiovascular Outcomes among Schoolchildren in Nepal

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<sup>‡</sup>Department of Internal Medicine and Cardiology, B.P. Koirala Institute of Health Sciences, Dharan, Nepal; <sup>\*</sup>Department of Cardiology, Swiss Cardiovascular Center Bern, Bern University Hospital, Bern, Switzerland; <sup>†</sup>Clinical Trials Unit, Department of Social and Preventive Medicine, Bern University, Bern, Switzerland; <sup>°</sup>Hôpital de la Tour, Geneva, Switzerland

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## Abstract

**Objectives:** To evaluate a protocol for a population-based program targeting prevention of rheumatic heart disease (RHD) progression by early echocardiographic diagnosis of valvular lesions and timely implementation of secondary prevention.

**Design:** Observational survey with a subsequent prospective cohort study.

**Setting:** Private boarding school in the urban area of the Sunsari district situated on the foothills of the Lower Himalayan Range in Eastern Nepal.

**Participants:** Fifty-four unselected school going children 5-15 years of age, 24 girls and 30 boys.

**Primary outcome measure:** Logistic feasibility of a large-scale population-based screening study using the echocardiographic criteria formulated by the World Heart Federation, with longitudinal follow-up of children with definite or borderline RHD in a prospective cohort study.

**Results:** Standardized interview, physical examination and screening echocardiography were performed in a three-staged process and took approximately 6 minutes per child. Socio-economic status was assessed using surrogate markers such as the occupation of the primary caregiver, numbers of rooms at home, car, television, cell phone and internet connection. Physical examination was focused on cardiac auscultation and signs of acute rheumatic fever and targeted echocardiography was performed by an independent examiner without knowledge of the clinical findings. Two children with evidence of borderline RHD were re-examined at B.P. Koirala institute of Health Sciences and the indication for secondary antibiotic prevention was discussed with the parents and the children. At six months of follow-up, echocardiographic findings were stable in both children. Implementation of secondary antibiotic prevention was challenged by impaired awareness of subclinical RHD among parents and inadequate cooperation with family physicians.

**Conclusions:** This pilot study shows that the methods outlined in the protocol can be translated into a large-scale population-based study. We learned that education and collaboration with teachers, parents and family physicians/pediatricians will be of key importance in order to establish a sustainable program.

**Trial registration:** ClinicalTrials.gov Identifier: NCT01550068

For peer review only

## Article Summary

### *Article focus:*

- Pilot study for a population-based program targeting prevention of rheumatic heart disease (RHD) progression by early echocardiographic diagnosis of valvular lesions and timely implementation of secondary prevention.

### *Key messages:*

- The echocardiographic criteria for diagnosis of RHD provided by the World Heart Federation are a valuable instrument for population-based screening.
- Adequate information of the parents of children with evidence of silent RHD and cooperation with the family physicians is of key importance for long-term adherence to secondary antibiotic prevention.

### *Strengths and limitations:*

- The pilot study demonstrates feasibility of a large-scale population-based screening program for RHD by the use of portable echocardiography, with a subsequent prospective cohort study.

Introduction

Rheumatic Heart Disease (RHD) is estimated to affect more than 15 million people worldwide and leads to 250,000 deaths every year. [1] More than 80% of the children younger than 15 years of age grow up in regions of the world where RHD is endemic. [2] A discrepancy of reported prevalence rates of RHD among schoolchildren in developing countries is particularly attributable to diverse sensitivities of echocardiographic and clinical screening, respectively. RHD consolidates a spectrum of different stages of clinically silent and clinically manifest valvular degeneration culminating in congestive heart failure, increasing the risk of endocarditis, cerebrovascular events, and eventually leading to premature death of the effected working age population in developing countries.

Acute rheumatic fever (ARF) ensues from an autoimmune reaction in response to group A  $\beta$ -hemolytic streptococcal pharyngitis and may result in RHD through the cumulative valvular damage of recurrent episodes of ARF. [2] Whereas overcrowding and poverty are major determinants of disease proliferation, limited access to healthcare resources renders primary prevention with prompt antibiotic treatment of streptococcal pharyngitis difficult to effectuate in large parts of endemic regions of the world. Secondary prevention among children with a documented history of ARF or evidence of RHD is achieved by regular oral or intravenous administration of penicillin continued until early adulthood.

The World Health Organization has recommended echocardiographic screening of RHD in high prevalence regions. [3] Early detection of subclinical RHD by use of echocardiography warrants timely implementation of secondary antibiotic prophylaxis and may prevent progression of valvular damage leading to congestive heart failure. We performed a pilot study in order to test the feasibility of a cross-sectional survey and a longitudinal cohort study to assess prevalence and clinical outcome of RHD according to the World Heart Federation criteria. [4]

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## Discussion

We report the results of a pilot study evaluating a research protocol for an observational survey of RHD among school going children and a subsequent prospective cohort study of children with evidence of rheumatic valvular lesions. This pilot study represents an integral part for the final implementation of the protocol in a large population-based setting. The main findings can be summarized as follows:

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4. The WHF criteria are a helpful instrument to classify subclinical valvular lesions consistent with RHD.

We learned from this pilot study, that collaboration with teachers, parents, and family physicians/pediatricians is indispensable to perform efficient screening, improve compliance with secondary prevention and ascertain clinical follow-up.

Informed teachers were allies in our study not only in terms of facilitating the organization of the pilot study, but also with regard to the orientation of the parents of the two children diagnosed with clinically silent RHD. Moreover, completion of parts of the questionnaire asking for socio-economic background could be assisted by the teachers and would improve quality of the data. As a consequence we plan to extend the participation of the teachers in the collection of the baseline criteria in the main study.

In addition to the school teachers, the parents of the children will be the key players for successful completion of the program. Accepting disease in an asymptomatic child is difficult for every parent. Continued education during every clinical visit with adequate cultural sensitivity should reinforce adherence to treatment. Given the high illiteracy rate in Nepal, letters to the information brochures distributed to the parents will not achieve the targeted objective. In response to the need for education on RHD diagnosis and prevention, we are therefore preparing a documentary film that will be broadcasted on local television and in schools before the screening examinations begin.

Collaboration with family physicians and pediatricians will be central to improve long-term adherence to secondary antibiotic prevention for silent RHD. Inconsistent information will cause insecurity among parents and children and decrease the motivation for compliance with regular antibiotic prevention. Continuing education will be provided to family physicians in the area in order to enhance collaboration and coordinate recommendations on secondary prevention.

Previous studies using primary screening echocardiography performed in endemic regions in Southeast Asia [6, 7, 8], the Western Pacific [9, 10], Africa [6, 11] and Central America [12] reported prevalence rates of RHD among children ranging from 20.4 per 1000 to 55.2 per 1000 children most of which using the 2006 World Health Organization criteria (WHO). In contrast to the WHO criteria combining both, clinical and echocardiographic findings, the WHF criteria are based on echocardiographic criteria only, and have been applied for the present pilot study [3, 4]. Studies documenting echocardiographic follow-up reported stable disease or even regression of valvular lesions in three quarters of the children, but were mainly limited by a short duration of follow and a small sample size [7, 8, 12].

The recently released WHF criteria for echocardiographic diagnosis of RHD proved helpful in the classification of valvular lesions potentially related to subclinical RHD and provide an adequate instrument for large population-based studies.

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Sina Pilgrim, MD; Kavita Shah, RN; Kishori Dhakal, RN

**Competing interests**

None

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**Data Sharing Statement**

There is no additional data available

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Figure Legends

The manuscript contains no figures.

## Tables

**Table 1. Pilot Study Baseline Characteristics**

Baseline characteristics	n (%) or mean (SD)
Age (years)	9.6 (2.9)
Height in (cm)	127 (16)
Weight in (kg)	28 (12)
Male	30 (55.6)
Documented history of ARF	0 (0)
<i>Socio-economic status</i>	
Number of family members	4.9 (1.2)
Children	2.2 (0.9)
Adults	2.6 (1.0)
<i>Amenities at home</i>	
Household, Number of rooms	2.8 (1.6)
Family owns a car	1 (1.9)
Television at home	50 (92.6)
Internet connection at home	4 (7.7)
Family uses a cell phone	51 (94.4)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6/7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7/8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8
		(b) Describe any methods used to examine subgroups and interactions	-
		(c) Explain how missing data were addressed	-
		(d) If applicable, describe analytical methods taking account of sampling strategy	-

		(e) Describe any sensitivity analyses	-
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	15
Outcome data	15*	Report numbers of outcome events or summary measures	16
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	-
		(b) Report category boundaries when continuous variables were categorized	-
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
<b>Discussion</b>			9/10
Key results	18	Summarise key results with reference to study objectives	9/10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	-
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	7

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

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