PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Rheumatic Heart disease: Pilot Study for a Population-Based Evaluation of Prevalence and Cardiovascular Outcomes among Schoolchildren in Nepal
AUTHORS	Pilgrim, Thomas ; Shrestha, Nikesh; Kalesan, Bindu; Karki, Prahlad; Sherpa, Kunjang; Basnet, Anil; Urban, Philip

VERSION 1 - REVIEW

REVIEWER	Dr. Eloi Marijon INSERM United Kingdom
REVIEW RETURNED	29-Jun-2012

THE STUDY	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)
RESULTS & CONCLUSIONS	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

REVIEWER	Andrea Z Beaton Cardiology Fellow - Research and Advanced Imaging Children's National Medical Center Washington DC, USA I have no competing interests in the data reported in this article.
REVIEW RETURNED	16-Jul-2012

THE STUDY	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.) 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 Word Heart Federation" which does not match the final conclusion that a large scale study is feasible.

	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. 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. The limitation of very small sample size (which could hugely over- or underestimate true disease prevalence should be stated.
RESULTS & CONCLUSIONS	need results section to focus on barriers to implementation, etc. Now covered mostly in the discussion section. **Credible with the exception of the prevalence rate reported in the discussion - cannot accurately determine prevalence/1000 from 54 subjects. This number could be very misleading. *Again the conclusions are great - and very important, except for the prevalence number. 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. 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 Word 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.
GENERAL COMMENTS	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.

REVIEWER	Ana Olga Mocumbi MD PhD FESC Instituto Nacional de Saúde Universidade Eduardo Mondlane, Mozambique

	I have no conflict of interest to declare.
REVIEW RETURNED	02-Aug-2012

THE STUDY	Reference 5 is not available.
RESULTS & CONCLUSIONS	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.
GENERAL COMMENTS	The article submitted describes a pilot phase of an important large-scale study and draws attention to several important aspects to be taken into account in preparing such studies. There is some overlap in the manuscript regarding the description of the pilot and the actual study. I think that some changes to it are needed to help the readers understand the manuscript. I would therefore appreciate authors comments on the issues listed below-. General comment: 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. 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? “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. 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. 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”. The paragraph that states the compliance of ethics rules should probably be separated from the section “Treatment”.

VERSION 1 – AUTHOR RESPONSE

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 Word 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 implentetd 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 Word 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.

Replyt#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.”

VERSION 2 – REVIEW

REVIEWER	Ana Olga Mocumbi Cardiologist National Health Institute, Mozambique Division of Chronic Diseases I declare having no conflict of interest.
REVIEW RETURNED	11-Sep-2012

RESULTS & CONCLUSIONS	The authors report needing 6 minutes for each children: it is not clear if it is for the 3 steps of the study procedures or for echo only.

VERSION 2 – AUTHOR RESPONSE

Reviewer #3: **Ana Olga Mocumbi**

We thank reviewer Dr Mocumbi for the careful review of our revised manuscript and answer the raised issue below:

I think that the changes made by the authors improved the quality of the manuscript and would recommend it for acceptance, as the issues raised by the reviewers were tackled appropriately by the authors.

Comment#1: I would just appreciate if the authors could clarify if 6 minutes is the time spent for each echocardiography or for the three steps of the study

Replyt#1: We thank the reviewer for her comment. Six minutes was the time spent per child for all three steps of the study. We changed the sentence of the revised version of the manuscript accordingly:

"Standardized interview, physical examination and screening echocardiography were performed in a three-staged process and took all together approximately 6 minutes per child."