BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (http://bmjopen.bmj.com/site/about/resources/checklist.pdf) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

**ARTICLE DETAILS**

| TITLE (PROVISIONAL) | A modeling study of the ability to diagnose Acute Rheumatic Fever at Different Levels of the Ugandan Healthcare System |
|---------------------|---------------------------------------------------------------------------------------------------------------|
| AUTHORS             | Ndagire, Emma; Ollberding, Nicholas; Sarnacki, Rachel; Meghna, Murali; Pulle, Jafesi; Atala, Jenifer; Agaba, Collins; Kansiime, Rosemary; Bowen, Asha; Longenecker, Chris T.; Oyella, Linda; Rwebemba, Joselyn; Okello, Emmy; Parks, Tom; Zang, Huaiyu; Carapetis, Jonathan; Sable, Craig; Beaton, Andrea |

**VERSION 1 – REVIEW**

| REVIEWER           | Paez, Arsenio |
|--------------------|---------------|
|                    | Northeastern University Bouve College of Health Sciences |
| REVIEW RETURNED    | 15-May-2021   |

**GENERAL COMMENTS**

Dear Authors, this is a very interesting paper with important conclusions and recommendations! It also draws much needed attention to ARF in Uganda and other LMICs. However, the paper requires editing and some key information is needed, particularly information about the study from which your data came. It should be described and cited, as the data being analyzed comes from that study. The methods of that study can have a considerable impact on your findings, and this comes up to some degree in your limitation. This is major aspect of your methods that is currently missing, and is needed in the paper. Please see my attached file for questions, queries and suggested edits. Also, use of the appropriate reporting guidelines would greatly enhance the paper.

Page 5

Lines 7-12: This sentence can do with a bit of editing for clarity. I would suggest making it into sentences.

Line 20: Suggest beginning a new sentence with “early detection....”

Line 26: What is mean by “health seeking behaviors?” It would be very helpful to clarify this for the reader.

Line 43: If there is enough room (word count, etc) would be very helpful to either give a brief description of Jones’ criteria or add them as a table/figure.

Lines 52-54: I’m not certain when I read this section if you mean you are investigating the Jones criteria in Uganda or alternative methods. Could do with a bit of rewording to make clear what your aims and hypotheses are here. What are your aims, objectives and hypotheses? I would suggest being explicit about these.
Page 6:

Line 24: What was the study? It should be described and cited, as the data being analysed comes from that study. The methods of that study can have a considerable impact on your findings, and this comes up to some degree in your limitation. This is major aspect of your methods that is currently missing, and is needed in the paper. Line 31: What kind of expert?

Page 7

Lines 8-10: Can you cite this or give more information, and cite that? This is rather vague as written and more information would be very helpful. Page 11

Line 44: What is meant by broad healthcare strengthening? I suggest rewording this for greater clarity.

Lines 46-51: This is an important section but a very long sentence. It would be much clearer as two or three sentences, and needs a bit of grammatical editing and rewording (ex ongoing and ongoing). Not only artificial intelligence but also machine learning could make very important contributions to these developments.

Page 12

Lines 5-13: Just a comment: this a powerful statement and very important one. It would have been a good one to have included in your abstract in some way.

Limitations section: This brings back the issue about not having cited or described the study this data came from. Without that information, it is also impossible for the reader to have a sense of what was done, how, and how that may influence the results.

REVIEWER

Marino, Achille
Gaetano Pini-CTO

REVIEW RETURNED

24-Jun-2021

GENERAL COMMENTS

The paper is mainly well written and clear. Nowadays, acute rheumatic fever is reemerging as interesting topic in pediatric rheumatology, the globalization and the stream of people coming from high risk countries makes the incidence of the disease growing; therefore prompt diagnosis and early prophylaxis are crucial in order to avoid severe complications.

Trying to obtain an early and easy diagnosis of acute rheumatic fever, especially in low resources setting is very interesting and attractive. I agree with the exclusion of the patients that had fulminating carditis or chorea. There are only some critical issues that should be better explained:
- Please add the long form of the abbreviations in the abstract
- Please argument the reason why you excluded “possible ARF” patients.
- Do you use the terms “Tier” and “model” as synonyms? Please clarify it.
- Both results and discussion are not clear, stats should be just part of results and should be clearly presented. Is not possible to make diagnosis in tier 1? Is necessary to have always an echocardiography? Please explain. Besides reporting available
Reviewer comments

Reviewer: 1
Dr. Arsenio Paez, Northeastern University Bouve College of Health Sciences, University of Oxford
Department of Primary Care Health Sciences

Comments to the Author:

Dear Authors, this is a very interesting paper with important conclusions and recommendations! It also draws much needed attention to ARF in Uganda and other LMICs. However, the paper requires editing and some key information is needed, particularly information about the study from which your data came. It should be described and cited, as the data being analyzed comes from that study. The methods of that study can have a considerable impact on your findings, and this comes up to some degree in your limitation. This is major aspect of your methods that is currently missing, and is needed in the paper. Please see my attached file for questions, queries and suggested edits. Also, use of the appropriate reporting guidelines would greatly enhance the paper.

Thank you!

The study from which the data came has been described and cited (P.4 lines 7-23)

Page 5
Lines 7-12: This sentence can do with a bit of editing for clarity. I would suggest making it into sentences.

Thanks for the suggestion. We have broken the above sentence into two. (Page 3 lines 3-5)

Line 20: Suggest beginning a new sentence with "early detection ............."

Thank you for the suggestion. This has been done. (Page 3 line 9-10)

Line 26: What is mean by "health seeking behaviors?" It would be very helpful to clarify this for the reader.

Health seeking behavior is defined as any action or inaction undertaken by individuals who perceive themselves to have a health problem or be ill for the purpose of finding an appropriate remedy (Olenja J 2004). Hence by poor health seeing behavior, we mean that the majority of the population takes no action to receive appropriate treatment for acute rheumatic fever. This mainly caused by lack of awareness of the disease. This has been clarified (Page 3 lines 12-13).

Line 43: If there is enough room (word count, etc) would be very helpful to either give a brief description of Jones’ criteria or add them as a table/figure.

Thank you for this suggestion. We have cited these criteria (Page 3 line 20) and added them as supplemental material.

Lines 52-54: I’m not certain when I read this section if you mean you are investigating the Jones criteria in Uganda or alternative methods. Could do with a bit of rewording to make clear what your aims and hypotheses are here. What are your aims, objectives and hypotheses? I would suggest being explicit about these.

We are investigating the possibility of diagnosing acute rheumatic fever in a setting where it is difficult to apply the full Jones criteria. Most of the items specified in the Jones criteria such as echocardiography, electrocardiography, and acute phase reactants are not commonly available in low resource settings. For example, can a health worker at a community health center diagnose a patient with acute rheumatic fever using history and clinical examination alone since that is what is available? We have re-written the objective of the study and made it clearer. (Page 3 lines 25-26)

Page 6:
Line 24: What was the study? It should be described and cited, as the data being analysed
comes from that study. The methods of that study can have a considerable impact on your findings, and this comes up to some degree in your limitation. This is major aspect of your methods that is currently missing, and is needed in the paper.

Data used in derivation of the models was obtained from a data base of a large epidemiologic study on acute rheumatic fever conducted in three districts of Uganda. The details of this study have been included in the methods section and the study has been cited. (Page 4 lines 7-23)

Line 31: What kind of expert?

By expert, we meant a cardiologist. This has been specified (Page 4 line 11)

Page 7
Lines 8-10: Can you cite this or give more information, and cite that? This is rather vague as written and more information would be very helpful. Thanks for the suggestion. We have cited this. (Page 5 line 3)

Page 11
Line 44: What is meant by broad healthcare strengthening? I suggest rewording this for greater clarity.

Broad healthcare strengthening in this context means improvement in a variety of health care services for example availability of ultrasound scan can be used for provision of both cardiac and obstetric services. This has been made clear. (Page 9 lines 21-24)

Lines 46-51: This is an important section but a very long sentence. It would be much clearer as two or three sentences, and needs a bit of grammatical editing and rewording (ex ongoing and ongoing). Not only artificial intelligence but also machine learning could make very important contributions to these developments.

Thanks for this suggestion. The statement has been broken into two sentences. (Page 9, lines 21-24)

Page 12
Lines 5-13: Just a comment- this a powerful statement and very important one. It would have been a good one to have included in your abstract in some way.

Thank you.

Limitations section: This brings back the issue about not having cited or described the study this data came from. Without that information, it is also impossible for the reader to have a sense of what was done, how, and how that may influence the results.

The study from which the data came has been described in the methods section and has been cited. (Page 4 lines 7-23)

Reviewer: 2
Dr. Achille Marino, Gaetano Pini-CTO
Comments to the Author:
The paper is mainly well written and clear. Nowadays, acute rheumatic fever is reemerging as interesting topic in pediatric rheumatology, the globalization and the stream of people coming from high risk countries makes the incidence of the disease growing; therefore prompt diagnosis and early prophylaxis are crucial in order to avoid severe complications.

Trying to obtain an early and easy diagnosis of acute rheumatic fever, especially in low resources setting is very interesting and attractive. I agree with the exclusion of the patients that had fulminant carditis or chorea. There are only some critical issues that should be better explained:
- Please add the long form of the abbreviations in the abstract

Thank you. The long forms of the abbreviations have been added in the abstract (P.1 line 2, line 17)
- Please argument the reason why you excluded “possible ARF” patients.

We excluded patients with possible ARF because they are a non- specific phenotype. This was included in the methods section (P.4 line 22-23)
- Do you use the terms “Tier” and “model” as synonyms? Please clarify it.
A model was generated for each tier of the health system. This has been clarified throughout the manuscript.

- Both results and discussion are not clear, stats should be just part of results and should be clearly presented.

Thank you for your comment. We have carefully reviewed the results and discussion for clarity and to ensure no new results are presented in the discussion section (Pages 8-10).

Is not possible to make diagnosis in tier 1?

According to our results, a model based on tier 1 predictors alone (i.e. from history and physical exam alone) has low sensitivity. This means that although one can make a diagnosis using these predictors, they will miss making the diagnosis in very many patients.

Is necessary to have always an echocardiography? Please explain.

Based on findings from this study, demonstration of carditis on echocardiography contributed to the highest model performance. This suggests the need to include echocardiography in diagnosis of ARF and supports the inclusion of echocardiogram in the Jone's criteria.

Besides reporting available literature, results should be commented in the discussion; moreover add your conclusions.

We have commented about our results in the discussion section and clearly stated our conclusions and recommendations. (P.10 line 19-24).

Editor(s)' Comments to Author:
- Please include the study design in the title. Thank you. This has been added (Title page)
- Along with your revised manuscript, please include a copy of the STROBE checklist indicating the page/line numbers of your manuscript where the relevant information can be found (https://strobe-statement.org/index.php?id=strobe-home)

Thank you for this suggestion. Is it Ok if we include the TRIPOD checklist for predictive model development instead since our study was a predictive modeling study? We have attached this.

-Please include figure legends at the end of your main manuscript.

These have been included (P.18)
Response to reviewer 1 comments

Page 9: Line 24/25 (or 52) Could you please clarify this sentence? “Investment in echocardiography and ultrasound in general, also has broad healthcare strengthening, such as the example of integrated cardiac and obstetrical ultrasound piloted in two communities in rural Uganda. I am not certain what is meant by "healthcare strengthening." Does this mean that it supports and improves healthcare?

Thank you. We have clarified what we meant by healthcare strengthening in this context. We have removed the term health care strengthening and replaced it with “improve and support health service delivery”. The above sentence reads as below:

“Investment in echocardiography and ultrasound in general could improve and support health care delivery such as the example of integrated cardiac and obstetrical ultrasound piloted in two communities in rural Uganda.” Lines 24-25, page 9.

Page 10 Line 1-2: This is a bit redundant: “obstetrical ultrasound piloted in two communities in rural Uganda16.” Suggest removing one “ongoing.”

Thank you. We have removed one “ongoing.” Lines 1-2, page 10.

Page 10 Line 2-3. This is an excellent point! We can see how this has influenced the ability to diagnose diabetic retinopathy in India, for example. If you could add a sentence more about how AI might be of use in the context of your findings, that would be very helpful for the reader.

Supplementary figure 1: This may need a higher resolution copy of the figure. It was a bit pixelated when I downloaded the pdf.

Thank you for this suggestion. We have added a sentence on how AI may be used in the context of our findings. AI combined with point of care ultrasound scan could be used by frontline health workers to improve diagnosis of acute rheumatic fever within the community. Lines 2-5, page 10.
Supplementary figure 1: This may need a higher resolution copy of the figure. It was a bit pixelated when I downloaded the pdf.

Thank you. We have included a higher resolution copy of this figure.