Author's response to reviews

Title: Antibiotics are prescribed inappropriately to adult pharyngitis patients and McIsaac modification of Centor score is the answer to reduce unnecessary antibiotic prescriptions in low socio-economic areas.

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Author's response to reviews: see over
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Dr. J Appleford-Cook
Editor
BMC Pulmonary Medicine

Dear Dr. Appleford-Cook,

Thank for reviewing our article entitled "Antibiotics are prescribed inappropriately to adult pharyngitis patients and McIsaac modification of Centor score is the answer to reduce unnecessary antibiotic prescriptions in low socio-economic areas". (Manuscript ID: 1570981650733247).

We appreciate the feedback that we received from your reviewers and have made changes to our manuscript accordingly. Please see below our point by point response to the comments. Our revised manuscript has been uploaded into your online system.

Editorial requests:

1. Please include the name of the ethical committee which granted approval for your study. Done. See Methods, Study Setting.

2. Please state explicitly if participants provided written informed consent. Done. See Methods, Study Setting.

3. Competing interests - Please include a 'Competing interests' section between the Conclusions and Authors' contributions. If there are none to declare, please write 'The authors declare that they have no competing interests'. Done.

4. Please include an Authors' contributions section before the Acknowledgements and Reference list. Done

Reviewer 1

1. The Centor/McIsaac score should range from 0-4. I would assume that some patients would have none of the 4 indicators. In our initial paper we did not add the data from "0". We had recruited 30 patients with score 0 and we have now added the data of those patients in the results and methods section. As a result, the tables and percentages have changed.
2. This paper suggests two major problems - overuse of antibiotics in patients having a very low probability of bacterial pharyngitis AND use of the wrong antibiotics. The Centor/McIsaac score can help with problem #1, but not problem #2. We agree with the reviewer that there are two distinct problems. We have added to the text around the second problem in our discussion section by highlighting how educational programs and guidelines need to be devised and disseminated.

3. My suggestions - focus on a discussion of how the clinical prediction rule could decrease antibiotic use dramatically, and also how you need an educational program to emphasize which antibiotics to use for empiric management of pharyngitis. Your point about using the prediction rule when one cannot afford rapid testing is important and needs even more emphasis. Thank you for your comment. As suggested by you, we have added this to our discussion.

4. I would minimize any discussion of validation on your population because your prevalence is too low to have adequate statistics. You clearly show a trend, but the confidence intervals would be too large to make meaningful conclusions. We have minimized this, as suggested.

5. On a purely personal note, in this patient population I am not certain why you choose the McIsaac modification. The original score works equally well as recently shown in the Archives of Internal Medicine. Thank you. You are correct, we could have chosen the original score.

Reviewer 2

1. The WHO reference they quote (reference #6) is adequate, but perhaps the authors should consider also quoting the more recent WHO Technical Report Series on streptococcal infections and rheumatic fever published in 2004 (TRS #923) which is addressed to the control of streptococcal infections and their sequelae. Thank you for this suggestion, we have added this reference. See Introduction, paragraph 1 after “as well as prevent the complication of GABHS pharyngitis particularly rheumatic fever and rheumatic heart disease”.

2. The authors appear to equate the presence of group A streptococci in the upper respiratory tract with "infection." We have added the word infection along with GABHS whenever we refer to infection.

3. They do not mention the issue of the streptococcal carrier state and how it
should be clinically approached. This should be addressed. **We have not added this - as the paper’s focus is not on carrier state and adding this to the introduction is lengthening the manuscript.**

4. The authors suggest a sensitivity of 80% for rapid antigen detection tests. As the authors are aware, some tests do not meet that standard, and others are reported to have >90%. Can the text be modified? **We have modified the text in the introduction to state, “Although WHO technical report states that there is less possibility of false-positive results with RADT, it should be noted that different kits of RADTs vary with respect to their sensitivity which ranges from 31–95%. Hence RADT cannot be used as a substitute to standard blood agar cultures (WHO technical report series # 923, 2001).”**

5. The authors state that they have approval of the ethics committee. Perhaps I have overlooked it, but was individual consent (written or oral) obtained from each enrolled subject? **Done. See comments from Editor.**

6. Again, I may have overlooked it, but is there an adequate description of how these subjects were selected? Was it random selection? If not, how can the methods of selection be justified? **We have added the description of how subjects were recruited under Methods, Patient recruitment.**

7. Evidence in the literature indicates that the peak of streptococcal infections is in children between the ages of 5 and 15 years. Yet the authors have included the age range 14 years to 65 years. One might question this age range because it would seem that the streptococcal experience of a 14 year old school child is quite different from a 60 or 65 year old adult. **We agree with the reviewer, however the focus of our study was adult pharyngitis and not pediatric. Note that also the McIsaac modified Centor score is already giving a benefit of 1+ point to patients aged less than 14 years that’s why we included the of 14 and over. A repeat study using the pediatric population would be interesting to conduct.**

8. Am I correct in assuming that the blood agar plates used sheep blood? If so, it should be stated. Many places in developing countries use outdated human blood and, as the authors are aware, this is inappropriate for this purpose. **Done.**

9. The bacitracin discs (it should be noted that these are special discs)) represent only a presumptive test for determining whether these are group A strains. Were any additional techniques used to confirm the serogroup, and if
not, why not? No additional techniques were used to confirm the serogroup because they are not routinely conducted in low resource settings such as ours. We wanted to use routine procedures as much as possible. This gives further importance to the use of Centor scoring.

10. Minor point but one that should be addressed: Several times throughout the manuscript the authors equate isolation of the streptococcus with infection. This is inaccurate. We have tried to correct this but if we have missed some, please let us know.

11. The fact that, at least in this reported sample, only 5% of those treated were culture positive is interesting and important to point out. We have pointed this out in the first paragraph of the discussion.

12. One of the recommendations that they make relates to the fact that clinicians in "low socioeconomic countries" need further education about this matter. From the literature clinicians in other settings also need education!! Yes this is true! However, since our results are generalizable to low socioeconomic countries, we have left this in.

13. It was of interest that among the antibiotics given, benzathine penicillin G was not mentioned. Is it not used? Why not? This also raises the question of whether compliance was checked in those subjects given oral antibiotics. That is a factor that must be considered. The WHO does recommend benzathine penicillin G. We did not see benzathine penicillin being used and have commented on this in the discussion.

14. I would like to see a similar study done in this population, but in children. Thank you. Indeed, our future studies should be directed to do this in children since the major prevalence of this infection in that population.

Reviewer 3

This is an interesting study on an important topic. The overprescription of antibiotics for URIs, and use of broad-spectrum antibiotics when a narrow spectrum is appropriate. The context however is also important and not clear, and the question and interpretation seem to confuse primary treatment and goals of secondary prevention.

1. The main reason to treat GAS is to prevent rheumatic fever. The prevalence of rheumatic fever in industrialized countries has declined dramatically over time,
but the disease remains a global health problem in developing countries. It is a
disease that is more common in impoverished areas. The guidelines for
treatment are based on industrialized regions, and except outbreaks in Salt
Lake City, Utah, for most of the US this is not an issue, and in the
Scandinavian countries not treating any GAS is probably also fine because the
lack of rheumatic fever. However, in developing countries rheumatic fever is a
problem and epidemiologic surveys using echo indicate prevalence of
rheumatic heart disease is significantly underestimated. Rheumatic fever
depends on the strain of GAS and host factors. The CDC principles and
western guidelines are based on prevalence of GAS (and rheumatic fever) and
are most relevant for the industrialized countries, immunocompetent adults,
without history of rheumatic fever or heart disease. It is not clear to me what
the prevalence of rheumatic heart disease in Pakistan, and this is an important
consideration in developing and discussing an appropriate strategy. It is not
clear what treating guidelines are available or used in Pakistan, thus to
compare or expect a Pakistani physician to read a paper that is in English and
a guideline for practice in another country is not clear. The rationale should be
provided. In addition this data is from tertiary care hospital, thus the reliability
and accuracy of these estimates for Pakistan in general is not clear as this is a
selected population. **We have added information in the discussion section on prevalence of RF in Pakistan.**

2. With regards to treatment, primary treatment allows for the benefit of
symptoms improvement, patients feel better 12-24 hours sooner, with abx
assuming all patients are given antipyretics and other pain medications. To
achieve this benefit, patients need to be treated early in the course of their
illness and at the time of MD assessment, before culture results are known.
For secondary prevention, that is to treat to prevent RHD, one can wait for
culture results. The current paper seems to confuse or fails to clarify these
issues as it pertains to the definition of appropriate use of abx. **We disagree
with this comment. We have used the standard definition for treatment of
pharyngitis – treatment of patients with presumed infection with abx – to
eradicate infection and prevent Rheumatic Fever. Our primary outcome
was eradication of infection (See your comment on Study Outcomes), it
was not to evaluate antibiotic efficacy for RF and thus the issue of
appropriate antibiotic use for secondary prevention – is a different
question and not one that we answered in this study.**

3. With regards to abx, a narrow spectrum abx is the right choice. But many ID
physicians in the US advocate for cephalexin as first line, not second line as in
this paper, and in the US erythromycin resistance is high and usually not the
best choice for someone with a penicillin allergy. **We used the standard as
set in guidelines for our categorization of appropriate antibiotics. Note that cephalexin was not even used in our study!

4. Finally, the report is not as clear about objectives as it could be with an overemphasis on statistical testing and testing that seems inappropriate for the question asked. However, I admit the manner in which the question is stated leaves some confusion. Association is not correlation, and neither of these refer to accuracy. If prevalence is the outcome, and frequency of RX use and who it is used in, then simple descriptive statistics without statistical testing is appropriate. See comment 12.

5. Methods, page 5. Study population. This section describes the setting but is not clear about how patients were identified and approached. It is not clear if these are emergency department patients at the tertiary care center or urgent care patients, or what specifically was the site. The section is labeled study population, but it is also not just about the study population it describes the data collection. I would suggest reorganization and better use of subheadings. **We have reorganized as per your suggestion.**

6. Methods, study population. There are 2 groups of subjects in this study. The patients, and it is not clear if you excluded patients with a history of rheumatic fever, or heart disease. **The inclusion and exclusion criteria are identified in the paper.**

7. The second group of subjects are the physicians as this is really a study about MD diagnosis, and MD prescribing behavior. It is not clear if the patients and MDs were consented, the unit of analysis is the MD not the patient. **We have added that informed consent was obtained from all study participants.** The MDs were consented since they are the ones who were referring the patients to us. However the physicians were not told earlier what is Centor score, and how this score helps in deciding which patients to expect antibiotics, because that’s what we needed to evaluate, what is the pattern without help from clinical score.

8. Methods, The time frame (month A, year 20BB to month C, year 20DD) is not reported. This might be useful in the section on study design. **Done. Under Methods, Patient Recruitment.**

9. Methods, data collection. It is not clear if the treating MD collected the clinical data and the culture or if this was done by a research assistant. Were the treating MDs aware that a culture would be performed, and were the patients contacted about results (and told to stop antibiotics if the culture was
negative)? As mentioned in methods treating MDs were the one who took the consent for the study and the throat swab, so yes they knew. Patients who wished to receive the results were contacted and were told that their culture was negative.

10. Methods, page 6, definitions. The definition of inappropriate treatment and scoring of the MD behavior is based on culture results, which seems to be an issue of who should or should not be treated for the secondary prevention. We have no information about the patients assessed with pharyngitis, but not considered for the study. In order to not create an artificial environment, it was up to the clinic physician to decide whether they should be included in the study (based on fitting the inclusion/exclusion criteria). Only those patients in whom physicians suspected bacterial pharyngitis were considered for the study. There were patients with sore throat (and perhaps no fever) in whom physicians suspected viral pharyngitis and those were not included in the study.

11. The objectives never discuss what the loss function the authors will tolerate. That is, there is a trade off between sensitivity and specificity, even with a clinical tool, so we expect some under and overtreatment. What is an acceptable amount? The issue of which abx are appropriate is discussed in general comments. We did not set apriori acceptable amount for sensitivity and specificity of the McIsaac tool. However international literature suggests that the McIsaac score has sensitivity and specificity of 70%. Hence, even if there is a 10% benefit that we derive by use of this clinical tool, it is worth it – given the amount of antibiotics being used for viral pharyngitis.

12. Methods, page 7. Study outcomes and statistics. The outcomes are not stated and the analysis should address the a priori stated objectives but it seems there is an emphasis on statistical testing and use of tests that are not appropriate. The primary outcome is the prevalence of GABHS infection in this population, then secondary outcome is frequency of rx, then appropriateness of the rx. Separately there seems to be another outcome/analysis to assess the diagnostic accuracy of the modified Centor criteria. Thank you. We have made the changes as suggested. Please see Methods, Outcomes and Statistical section.

13. I see no reason to then look for association, chi-square or regression. The diagnostic performance with Sn, Sp, NPV, and PPV, describing the under and overtreatment (FN and FP) seems most important. In addition, as noted above the unit of analysis is the provider and thus the data by provider should be
considered and reported, and confidence intervals adjusted for clustering on provider. The report would be improved by focusing on the descriptive data, rather than statistical testing. **Thank you for this. We have modified the statistics section and deleted reference to odds ratio, chi-square and regression analysis. We have added more information in Table 4 on FN, FP etc.**

14. **Results para 1 should first describe enrollment.** During X months of data collection, Y subjects with pharyngitis were evaluated, Z were thought to be bacterial pharyngitis and enrolled in the study? There were A number of treating MDs during that study time, and the median number of patients per subject was B (range C-D), the treating MDs were attendings or residents and were emergency physicians or general practitioners or internists? **Thank you. We have added text on first paragraph of results section.**

15. **Limitations.** The current study is missing a section on limitations. The authors need to realize that their critics will expound on the limitations of this study in forums where the authors may have limited ability to respond. Thus, the limitation section of this article provides a "golden opportunity" to present a realistic and rationale discussion of these issues. The authors need to discuss the potential for selection bias. The authors need to consider and discuss the differences and potential problems with applying criteria from an industrialized nation to a developing country where most would advocate a different approach secondary to higher incidence of RHD. **Thank you. We have added limitations just before the conclusion.**

16. **The abstract background lists one aim, but I think the abstract may better reflect the paper if the objectives were clear as it sets up the methods, results and interpretation.** The abstract methods are not clear about what the setting is for these patients, or a definition of appropriate. The results is not clear as the N for the subjects is not clear. The results should first report the number of patients, then the number positive GAS, then the number that received abx, then the number that received the various classes. **We have added aims in abstract. Settings for the patients and definition of appropriate has been added in methods of abstract. Results and statistics have been changed as suggested.**

17. The results correlation is not clear and should not be a p-value. Rather report the number with culture positive treated and those culture negative treated, and stratify the table of demographics (provide data for the sample overall, then columns for those GABHS positive and for those GABHS negative). That
is, revise table 1. **Done. We have deleted the statistics and left it as descriptive.**

18. In addition, in table 1 and the results stratifying by male and female is not necessary as I know of no data to suggest Centor criteria or GABHS is different by sex of the patient. **Done.**

19. Table 4. Round off the Sn and Sp to appropriate significant figures and provide 95% CIs, in addition provide the NPV and PPV. **Done. We have revised Table 4.**

Thank you once again and we look forward to your response.

Sincerely,

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