PONE-D-13-03286  
Detecting Pertussis Cases Using Voice Recognition Technology  
PLOS ONE  
  
Dear Dr Philip M Polgreen,  
  
Thank you for submitting your manuscript to PLOS ONE. After careful consideration, we feel that it has merit, but is not suitable for publication as it currently stands. Therefore, my decision is "Major Revision."   
  
We invite you to submit a revised version of the manuscript that addresses the points suggested by both reviewers  
  
  
  
We encourage you to submit your revision within forty-five days of the date of this decision.   
  
When your files are ready, please submit your revision by logging on to http://pone.edmgr.com/ and following the Submissions Needing Revision link. Do not submit a revised manuscript as a new submission. Before uploading, you should proofread your manuscript very closely for mistakes and grammatical errors. Should your manuscript be accepted for publication, you may not have another chance to make corrections as we do not offer pre-publication proofs.  
  
If you would like to make changes to your financial disclosure, please include your updated statement in your cover letter.   
  
Please also include a rebuttal letter that responds to each point brought up by the academic editor and reviewer(s). This letter should be uploaded as a Response to Reviewers file.  
  
In addition, please provide a marked-up copy of the changes made from the previous article file as a Manuscript with Tracked Changes file. This can be done using 'track changes' in programs such as MS Word and/or highlighting any changes in the new document.   
  
If you choose not to submit a revision, please notify us.   
  
Yours sincerely,   
  
Daniela Flavia Hozbor  
Academic Editor  
PLOS ONE  
  
Journal requirements:  
  
When submitting your revision, we need you to address these additional requirements.

Dear Dr. Flavia Hozbor:

Thank you for providing us an opportunity to revise and resubmit our paper. Below we address all the questions and concerns raised by the reviewers in a point-by-point fashion.

1. Please provide further details regarding the sound files used, including, for example, a table with information about the source of each file and links where appropriate.

Response: In our revised paper we now include a table with the sources of the sound files.

2. Thank you for stating in your financial disclosure: "This project was funded in part by a K01 award (AI75089) from National Institute of Allergy and Infectious Diseases/National Institutes of Health. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript." Please respond in the cover letter where the additional part of the funding of your study has come from or include the statement "No additional external funding received for this study". We can make any changes on your behalf.

Response: Other than the stated funding, we did not have additional funding for this project. Thank you for making this change.   
  
3. Thank you for stating the following in the Competing Interests (delete as necessary) section: "The authors have declared that no competing interests exist". We note that one or more of the authors are employed by a commercial company (GTD Unlimited). Please respond in the cover letter to declare the affiliation(s) to this company in the Competing Interests section of the online manuscript form, along with any other relevant declarations relating to employment, consultancy, patents, products in development or marketed products etc. If true, you should also confirm in the competing interests section that this does not alter your adherence to all the PLOS ONE policies on sharing data and materials, as detailed online in our guide for authors http://www.PLOSone.org/static/editorial.action#competing by including the following statement: "This does not alter our adherence to all the PLOS ONE policies on sharing data and materials." Please note that we cannot proceed with consideration of your article until this has been declared. We can make any changes on your behalf.  
  
Please be assured that it is the standard PLOS ONE policy to ask authors to declare any potential competing interests, for the purposes of transparency. This declaration does not affect the review process. PLOS defines a competing interest as anything that interferes with, or could reasonably be perceived as interfering with, the full and objective presentation, peer review, editorial decision making, or publication of research or non-research articles submitted to one of the journals. Competing interests can be financial or non-financial, professional, or personal. Competing interests can arise in relationship to an organization or another person. Please follow this link to our website for more details on competing interests: <http://www.PLOSone.org/static/editorial.action#competing>

Response: There is no competing interest. This is research project with no current or future plans for commercialization. We now state this in our revised cover letter.  
  
4. Please include a copy of Tables 2 and 3 which you refer to in your text on page 8.

Response: This was a typographical error. All of the necessary information is in Table 1.  
  
Reviewers' comments:  
  
Reviewer #1: While the work is very interesting, the conclusions are based on a small number of recordings.

Response: We agree with Reviewer #1, and now clearly state this in our revised manuscript. Nevertheless, even with limited data, and recordings of varying quality, we were able to reliably discriminate between pertussis and non-pertussis coughs. Traditionally, results in this domain improve with larger samples; thus, we were encouraged with our findings given this limited sample.

The source of the recordings is unclear and no diagnostic data is available to assess the accuracy of diagnosis for the patients used in the recordings.

Response: We now include a table that lists the sources of the recordings. We agree that future work should include coughs with associated microbiologic testing.

Also, the spectrum of pertussis illness is likely not captured. This is very important to account for in a highly vaccinated population.

Response: We agree with the reviewer and specifically state that we may not catch atypical cases. Many cases, especially in adults, may not present with the classic paroxysmal cough. But we also state that even in highly vaccinated populations, classic cases do occur, and they are frequently missed. There are limitations to most diagnostic approaches, and we more clearly define these limitations in our revised manuscript.  
  
I am concerned that the term "clinical decision making tool" has been used to avoid the issues of clinical accuracy (specifically, clinical specificity and sensitivity). This tool would take an audio sample of a cough from a particular patient and provide a result. The clinical accuracy of this method needs to be determined in a rigorous evaluation against a gold standard diagnosis.

Response: We agree that this method should be rigorously tested against a gold standard, and we highlight the need for this testing in future work. We agree that the term "clinical decision making tool" is too strong, and we now call this a “potential clinical decision making tool".

More information concerning the source of the audio files is needed. For example, no information is provided on the age of the patients, duration of illness, and confirmatory diagnostics.

Response: We have now included a table with the sources of the sound files. We agree that the information that the reviewer is requesting would be very helpful. However, not all of the information that the reviewer is requesting is available. We include this as a limitation in our revised manuscript.  
  
These limitations will need to be addressed in a prospective evaluation before the true usefulness of the method can be determined. Simply calling it a tool, without some measure of clinical accuracy won't be acceptable.

Response: We are not suggesting, in any way, that this is ready for clinical use. As stated in our responses to Reviewer #1’s previous points, we now clearly state this as a limitation.  
  
Your title needs to be modified. As you stated this is a tool (also described as an education approach), not a diagnostic method of detecting cases.

Response: We agree with Reviewer #1 and have changed the title of our manuscript to “Detecting paroxysmal coughing from pertussis cases using voice recognition technology”.  
  
Reviewer #2: The manuscript describes a novel approach to help and support the diagnosis of pertussis. The Authors elaborate on a principle for sound analysis that has been previously applied to cough in tuberculosis. Although the sample size is limited, the study is sound and suggests that the approach can be applied even to other respiratory diseases associated with cough.

Response: No change requested.

The Authors apply three different analytical approaches and observe a pretty good consistency across different methods. Including predictive values in the tables showing the performance of the voice recognition tool would be informative. The obtained results support the discriminant capacity of voice recognition in correctly classifying cough. The Authors may consider to discuss the need for a further study to compare the performance of voice recognition vs physician diagnosis of pertussis.

Response: We agree that this method should be tested against physician diagnosis of pertussis as well as microbiologicl tests.

Although the study does not involve patients, the Authors may consider to include as supplementary material the web sources of sounds included in the evaluation.

Response: We now include a table with the sources of the sound files.

Other Comments  
Introduction  
1. Information on clinical presentation of pertussis is correct. However, speculating on a practical application of voice recognition for differential diagnosis of cough, the Authors may underline how this approach may be useful especially in infants, when differential diagnosis between bronchiolitis and pertussis is challenging.

Response: We appreciated Reviewer #2’s suggestion, and we have incorporated it into our revised manuscript.

2. Molecular diagnosis of pertussis (by PCR) is nowadays available in most hospitals and generally results are available in 24 hours. The Authors may elaborate on the use of a cough recognition tool by physicians in the office or even by parents. If such an approach was more sensitive than clinical suspicion of pertussis, this would result in a more timely decision on antibiotic therapy start which is an advantage to secondary prevention.

Response: We appreciate Reviewer #2’s suggestion, and we have incorporated it into our revised manuscript.  
  
Methods  
3. The choice of pertussis sounds deserves a more detailed description. Was the process conducted trying to include a wide spectrum of coughs? Unfortunately pertussis may present with atypical cough. These atypical cases are even the most challenging for clinicians and may benefit most from cough recognition.

Response: Reviewer #2 raises an important issue. We included classic, paroxysmal coughs in our training set. (These were the ones available on the websites to demonstrate the “classic” case.) As the reviewer points out, these are the easiest to diagnose in practice. Based on our current sample, we can make no claims about atypical cases. We now mention this as a limitation in our revised manuscript and also highlight it as a direction for future work.

4. The Authors may explain how long the sound samples last. One can imagine that a reasonably short time sufficient to include a "cough cycle" would be enough. What about cough samples without whoop?

Response: As we describe in the methods section, the approach that we use chops each cough up into small sections. Our method allows us to incorporate coughs of different duration. We cannot comment on the accuracy of our approach in discriminating when atypical pertussis cases are included. As we now clearly identify in our revised manuscript, our results should be viewed as preliminary, and we did not specifically test our ability to discriminate atypical pertussis coughs (i.e., non-paroxysmal) from, for example, croup. It is possible that, with enough data, we could tell the difference between atypical pertussis and croup, but we cannot make this claim with our preliminary data, especially without approaches outlined by Reviewers 1 and 2.  
  
Discussion  
5. The Authors should warn more clearly about potential misclassification associated with cough recognition with the proposed tool. Unless strong results will be presented on performance of this approach compared with traditional clinical and microbiological diagnosis, recognition of cough through this tool should not be considered sufficient to guide therapeutic decisions.

Response: We have added this warning to our revised manuscript. We agree that unless this method is tested against confirmed diagnosis of pertussis, we cannot claim that this tool can be used as a definitive source for therapeutic decision-making.  
  
Reviewer #1: (No Response)  
  
Reviewer #2: Alberto E Tozzi  
  
  
  
[NOTE: If reviewer comments were submitted as an attachment file, they will be accessible only via the submission site. Please log into your account, locate the manuscript record, and check for the action link "View Attachments". If this link does not appear, there are no attachment files to be viewed.]