Author’s response to reviews

Title: The impact of healthcare visit timing on reported pertussis cough duration: Selection bias and disease pattern from reported cases in Michigan, USA, 2000-2010.

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Author’s response to reviews:

>>We thank the reviewers for their valuable suggestions which we feel have improved this manuscript. Our responses (preceded by >>) to each of the reviewer comments are provided below. In addition, we can provide tracked the changes in a revised manuscript Word file. The two Reviewers' comments and our responses to each follow:

Reviewer #1:

This manuscript is a brief and narrowly focused study using an approach combining surveillance data and data simulation to demonstrate the effect health care seeking bias and case-exclusion bias has on determining the effectiveness of antibiotic treatment in reducing cough length caused by infection with Bordetella pertussis. I appreciate the study design, the simplicity, and the hypothesis.

>>We are pleased that the reviewer appreciates our efforts to keep the presentation concise and straightforward.

However, I find the methods and results confusing. While I admit the authors' expertise likely exceeds my own in conducting the present study, I should be able to follow their methods and results sufficiently to make an evaluation of the merits of the study. I fear among the journal's broad audience, only a small fraction would be able to follow this paper.

>>We agree that the work should be accessible to a broad audience. As such, we have attempted to modify language and better explain the study, including specifically responding to the reviewers' recommendations.
I recommend the following:

1) the authors provide greater detail in the methods such that others could replicate their work.

   1a) page 5, line 34: explain in more detail how the mean theoretical cough duration was calculated 5 times.

   1b) define "left truncated." I actually think they defined it on page 5, lines 37-41. However, the organization of the paragraph is confusing that I'm not sure that's what they are defining.

>>Text in Page 5, paragraph 2 has been completely replaced, and now better explains the process used to simulate a theoretical distribution, and how this distribution was truncated in weekly intervals to simulate individuals remaining in the theoretically ill population at 7, 14, 21 and 28 days following cough onset. In addition, we have more clearly defined what "left truncated" means and how it was performed.

   1c) clarify the relationship between the simulated data and the surveillance data. Perhaps add a table that shows the surveillance data and the simulated data and the difference between them.

>>Table 1 has been modified to show columns with both the simulated number of days of cough and the observed number of days by week when antibiotics were prescribed. This should help readers to compare the simulated results and actual surveillance data.

2) Reorganize Table 1 so that the results are clear and jump out at the reader (this is an extension of 1c above). For example, I expected to see a column that shows Observed data (which are hypothesized to be biased). Then a column showing the "corrected" results as a result of the simulation. Then a column showing the degree of over- or under-estimation (in days).

>>Per our previous comment, Table 1 now clearly shows both the surveillance data and the simulation results, and includes the mean differences in days of cough between each week and the preceding week.

   2a) the text of the results should be very easy to read - that even if you're not a modeler, that you can clearly understand that under assumption A, you get RESULT 1, under assumption B you get RESULT 2, etc. (Even after reading the methods and results through several times, I still can't tell you what the results of the study are.)

>>We thank the reviewer for this recommendation. First, we have revised and better organized the Methods section to more clearly explain the sources of data and comparisons. Then, text in the Results section has been changed to reflect findings based on the data sources and comparisons that are described in the Methods. These changes are extensive in both sections, and are shown in detail in the revised manuscript.
Reviewer #2:

The authors present a model, simulated population analysis of the impact of healthcare visit timing on reported cough duration in cases of pertussis. It is difficult in many parts of the manuscript to follow the logic presented to describe the rationale for this project, which deserves further clarification.

>>We have clarified the intent of the analysis in the background and added text to better explain the results and objectives, and these are described below in response to specific comments by this Reviewer.

Specific comments:

Background

Page 3, Second paragraph, last sentence, arguments regarding lack of effect of antibiotic therapy on cough duration, "even when antibiotics (like erythromycin) are prescribed prophylactically". Note that when antibiotics are given prophylactically, it is evident that this is a time when the patient is asymptomatic, and therefore there should be no measurable effect in the duration of cough, as patients should not be coughing - this definition of prophylactic treatment is not clear throughout the document.

>>We have modified the text both here and in the second paragraph in the Results to clearly reflect that prophylactic antibiotic treatment occurs in the absence of symptoms. Given that this example is drawn from surveillance data, only cases that coughed are included. The cases we identify as having been treated prophylactically are those that subsequently developed symptoms. Those who did not develop symptoms are not included in the surveillance data base. We also have added an entirely new Figure 1 that illustrates examples of cases with different temporal patterns and characteristics, including one that was treated prophylactically.

Also note that the of certain macrolides and compliance with either treatment or prophylaxis regimens might vary given the presence of side effects, particularly with erythromycin. The "effectiveness" of the antimicrobial would be altered if the treatment is no completed. This was probably the case when erythromycin was in use, as in the period covered by most of the references cited in this section, which are old, except for the Cochrane review of 2007.

>>We understand the role that compliance plays in the effective clearance of the pathogen. The first paragraph of Results indicates that only 15% of cases were treated with erythromycin, while 70% were treated with newer macrolides, shown to be slightly more effective at bacterial clearance and with less pronounced side effects. Our cases were treated with newer antibiotics that are at least as effective as the older ones. However, cough persists after bacterial clearance, which is the point that we wanted to make. Newer references have been added in a number of places throughout the article.
Finally, it is important to clearly state that the reason for starting antibiotic treatment in symptomatic patients is NOT to decrease the duration of cough, but rather, to reduce shedding and transmission of the B. pertussis pathogen. The authors might want to include some background on the pathophysiology of pertussis, or what is understood of it, including that cough is not directly associated with the presence of the organism in the upper airway, but rather toxin mediated effects which may be long lasting given the injury to respiratory epithelium and other local inflammatory effects as a result of the host response to the pathogen.

>>We thank the reviewer for this helpful observation. We have added a few words to clarify that treatment is for reduction of transmission, in the 2nd paragraph of the Background. We have added a sentence and appropriate reference concerning the toxin-mediated pathology of cough. We agree that individuals receiving prophylactic treatment will have taken antibiotics as a preventive measure while asymptomatic. Text has been modified to clarify this. Among those who subsequently became ill and are in our dataset, one would expect that if effective antibiotics would affect cough duration, these individuals would have had the shortest average cough duration because their infection had been treated with antibiotics for the greatest period of time. Our data, like others, support the idea that cough length is not shortened by use of prophylactic antibiotics.

Page 3, third paragraph, the example given to explain care seeking bias is confusing as it relates to pertussis and vaccine. Would suggest to use a different example. Page 4, top paragraph, last sentence - is not clear - in part because there seems to be cut and paste issues, and in part because it continues to talk about vaccination and pertussis while the main focus of the paper is cough symptoms in pertussis. Consider a different example to make this confusion disappear. Although one would agree that there is care seeking bias in the results of surveillance for pertussis, and that the number of cases identified do not represent all pertussis infection in a particular population, the explanation provided is confusing when trying to understand the effects of these biases in the duration of cough.

>>We agree that this passage is confusing and have rewritten the text with a simpler and more general example to clearly explain the idea of healthcare seeking bias.

Page 4, second paragraph - Explanation of case exclusion bias - please indicate WHY would cases who delay the initial visit be "under-represented" in the data? Similarly, why is it assumed that cases with a mild or short duration of symptoms (two different things), may be less likely to seek care? Again, one can agree that mild cases will likely be fewer than severe cases (case selection bias) among those who seek medical care, but the rationale presented here is not clear.

>>Text has been added to better explain these sources of bias under the fourth paragraph of the Background.

Methods

Page 5, the assumptions are clearly stated.
We are pleased that the reviewer found the assumptions easy to understand. In addition, the second paragraph now states more clearly that the theoretical analysis cannot account for nor describe any effects of prophylactic treatment, again because surveillance data only includes those who become ill.

Results:

Page 6, first paragraph - there seems to be an issue with data interpretation when the actual duration of cough is not known in the reported surveillance, given that the majority (82.2%) of patients were still coughing at the time the report was finalized.

We have addressed this issue by making changes in the third paragraph of the Discussion. While data was not available regarding the total cough duration for these cases, other studies have reported average cough length of about 30 days. Based on the reporting methodology we cannot be certain when the last update with each of case record occurred and, therefore, in this analysis we used the cough length that was provided. It is important to note, however, that this study is about the magnitude of the bias and incomplete cough length does not hamper that analysis.

The findings reported for cases presenting later in the clinical course of their disease are as expected. However, the comment regarding the use of prophylactic antibiotics is confusing - if prophylaxis was used, it would have been in asymptomatic patients, otherwise, it is not prophylaxis, rather treatment. What is unclear is when the cough started in relation to the use of prophylaxis (failure of prevention), and how severe the cough was in this group, versus those who presented in the first two weeks of cough onset, as severity of symptoms would be a more likely indicator for the healthcare visit, rather than the duration of cough.

As mentioned above, we have revised text that refers to prophylactic antibiotic treatment to make this issue clearer throughout the text. The individuals with prophylactic treatment in this dataset received antibiotics while asymptomatic, after presumed exposure and before cough onset. In these individuals, the utilization of antibiotics is done for preventive (i.e. prophylactic) purposes. Only those who subsequently became ill are included in our dataset (Week 0, N=65 in Table 1).

Discussion

Page 7 - the premise that "those who used antibiotics prophylactically should have had the shortest duration of cough" does not make sense. Prophylaxis is given after exposure, not after onset of symptoms, including cough. Persons on prophylaxis are not ill yet, although they might be infected. Again, the symptoms of pertussis, including cough, are not likely to be affected by antibiotic treatment.

The individuals with prophylactic treatment in this dataset received antibiotics while asymptomatic, following possible pertussis exposure. In these individuals, antibiotic prophylaxis
is intended to be a preventive intervention. Among those persons who subsequently became ill and are in our dataset, one would expect that if antibiotics did affect cough duration that those same individuals would have had the shortest average cough, because their infection had been treated with antibiotics for the greatest period of time. Our data, like others, supports the idea that cough length is not shortened by use of antibiotics prophylactically.

The finding that there is a 13 day difference in reported cough length between those seeking care in the first week vs. the third week after cough onset is not surprising, as this is the difference of time in cough duration. It is not clear what the author's message is about this finding.

>>The "message" that we intended was that the incremental increases of cough duration observed in surveillance data is very similar to what we observed by stratifying a theoretical population, and incrementally excluding those whose cough has resolved prior to the specified week of potential first medical visit. We have rewritten text in the Methods, Results and Discussion to better reflect our explanation in with this section.

It would be interesting to know what other factors the authors consider would influence their findings, for example, patient age, vaccination history, type of exposure, comorbidities, etc. There is no mention about this.

>>We agree with the reviewer that inclusion of these other factors in the analysis would be interesting, but our specific goal in this investigation was to narrowly focus on the topic of selection bias and its effects on mean cough duration. Quite a bit has already been published on these additional known risk factors of disease severity and cough. Because our topic was much more focused, we did not analyze other risk factors, although that may be undertaken in a different report. Additionally, the surveillance data we used did not include reliable information for many of these variables.