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:

Reviewer #1: I appreciate the edits to the manuscript as they have largely clarified both the methods and results. However, I believe additional minor edits are still required to the results.

We are pleased that the methods and results are now clearer, and thank the reviewer for the additional minor edits that have been made.

Specifically, pg 7, lines 33-38, the authors state "cases presenting later in the clinical course of disease were MORE LIKELY to have experienced..." Similarly, on pg 7, line 57, they state "Left-truncation of the simulated data showed that care-seeking bias results in LONGER mean cough duration..." These comparative statements of "more likely" and "longer" should be accompanied with appropriate corresponding statistics (like p-values) to demonstrate the observed results were statistically significantly different (as opposed to caused by random variation). While the statistical analysis should be relatively simple and straight-forward, it is critically important to be included.

We have incorporated the 95% confidence intervals for all percentages and means into the table. This allows the reader to observe which week-to-week estimates are significantly different.

Additionally we have calculated a comparison between the week 1 values and subsequent weeks providing a difference measure along with a p-value which is incorporated into the text at the point the reviewer referenced (pg 7, lines 33-38,).

The second point of clarification (pg 7, line 57) is a direct observation from the table. The observed cough duration has an increasing trend from 24.8 days in week 1 to 58.3 days in weeks 5 and later. The statistical significance of the increase can now be determined from in the newly included confidence intervals.
Reviewer #2: The authors have addressed the majority of the comments provided by the reviewers and have produced a more clear and improved manuscript.

There are a few additional points that deserve further clarification though.

<>We are pleased that Reviewer 2 finds the manuscript to be more clear and improved, and thank her for the suggestion that a few additional changes be made.

In general, it is clear from the study and the literature review that it is unlikely that the use of antimicrobials will have an effect on the duration of cough.

The main conclusion of this article is also well accepted, that is, that the timing of presentation of the patient for medical care in relation to the onset of cough (care seeking behavior), influences the assessment of the effect of treatment on the duration of cough, and introduces a number of biases on the assessment of the illness itself.

The addition of figure 1 is greatly appreciated as it helps to visualize the different clinical scenarios that can occur in real life.

<>We thank Reviewer 2 for the suggestions that led to changes which improved understanding of our main findings, and the inclusion of the Figure.

However, the differentiation between true prophylactic treatment (started prior to the onset of symptoms) and treatment of infection (started after the onset of symptoms) remains an important piece in this discussion. The discussion in page 7 seems to imply that prophylactic treatment does not work. Similarly, the discussion in page 8, lines 40-42, referring to lack of effect of antibiotics when used before the onset of cough, talks about cases 5 and 6 which are quite different, but the implication remains that prophylaxis does not work.

<> Thank you for your comment. Our intent was not to imply that prophylaxis does not work. We agree there is a fundamental difference between hypothetical cases 5 and 6, but we were unable to discern whether the antibiotics were provided before or during the catarrhal stage. We have reworded the results section on page 7, to indicate that weeks 0 through 2, are not statistically different in mean cough duration based on the newly included confidence intervals.

<> Because prophylaxis must occur after exposure, during the incubation period, we would expect prophylaxis to be primarily effective at inhibiting bacterial growth, and mitigating clinical signs and symptoms of illness. The extent to which this would prevent symptoms in these cases is beyond the scope of our data, although it would be expected to decrease the risk of further transmission.

<> Both examples 5 & 6 could have been found from among our cases. However, this does not affect the point we make on page 8, which is that if antibiotics truly shorten cough duration, receipt of antibiotics at day -2 should still be shorten then at +2, relative to cough onset.
The cases are different because in one, case 5, antibiotics are started prior to the onset of cough, but in the presence of other symptoms (catharral stage), therefore the person is already infected. However, in case 6, the prophylaxis is given prior to the onset of ANY symptoms, which could indicate that the person was not infected at the time, and therefore, there would be no expectation that antibiotics would have any effect. Furthermore, this person could complete a 5 day course of prophylaxis, and still become infected after that, which means that the antibiotics will have no effect on the symptoms or duration of cough. would it be possible to explain this in the document?

<>Thank you for considering in such detail these two cases. On average these hypothetical “prophylactic” cases received antibiotics around 7 days prior to cough onset, about the time the catarrhal symptoms would begin. Thus, we believe that 7 days should not be enough time for the proposed scenario to occur. Furthermore, we expect that these “prophylactic” cases, intended to illustrate the range of possible situations, would be predominantly like that of type 5.

Please comment on the implication that prophylaxis is ineffective for reducing the duration of cough, in the context of its potential effect in reducing the risk of transmission. The only true effect of the antibiotic is to eliminate the bacterial burden and reduce the risk of transmission, and this needs to be clear, as duration of cough is not the main purpose for offering treatment. Misinterpretation of these findings might result in misinterpretation of the use of prophylaxis.

<>Yes, we agree with your comment. We have added a sentence clarifying the purpose of antibiotics, in the second paragraph of the background.

In Figure 1 legend, sentences in lines 20-28 are not clear, please rephrase.

<>We have reworded this section.

Lastly, the very important limitation of this study is that indeed, the duration of cough in patients with pertussis is prolonged, on average 3 months, which is longer than the duration of follow up used in this study (7 weeks), as such, the interpretation of the results needs to be placed in this context.

<>This issue is addressed in the final paragraph of the Discussion. We agree that those with cough duration of many months would affect any analysis focused on final cough length or the effects of antibiotics on cough duration.

<>Our study describes how the means estimates are affected by stratification. Modification of the text has been made at this point to indicate that the expected change would only be an increase in the mean reported duration, it would not affect the final conclusions drawn from this study.

Overall, this manuscript contributes to the knowledge of how to assess the clinical impact of pertussis and the importance of biases, particularly medical attention seeking behavior and timing of medical attention, on the assessment of treatment outcomes. The concordance of real life data with a modeling tool is also appreciated.
We are pleased that this Reviewer now finds that our study makes a useful contribution.