Author’s response to reviews

Title: The burden of laboratory-confirmed pertussis in low- and middle-income countries since the inception of the Expanded Programme on Immunisation (EPI) in 1974: a systematic review and meta-analysis

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Author’s response to reviews:

Fiona Russell (Reviewer 1): This is a systematic literature review of pertussis from 1974 and provides valuable information and provides important gaps in the literature.

The are many limitations to the individual studies including lack of vaccine coverage, many studies not having age breakdown etc. However these are discussed in the discussion.

Response to comment

Thank you for the comment. We agree with the limitations noted

MAJOR COMMENTS

Review comment 1

It should be clearly stated in Table 2 which are studies that have been performed during outbreaks and the meta-analyses and other descriptive summaries should be stratified by endemic/epidemic studies.

Response to comment 1

Only three studies included outbreak data. These have now been noted in the table (now Table 1) and subsequent results figures are highlighted to indicate these studies. In addition, the following sentence has been added to the section on characteristics of the included studies, “Three studies by Cooper et al, Strebel et al and Al-Bargish et al were conducted in outbreak settings.[26, 40, 78]”. Lines 255-256, page 10.
As the reporting format does not pool diagnostic prevalence data, the results are not affected in any way.

Review comment 2

Line 123: It is not clear what the difference between the mortality rate and the pertussis CFR-this needs to be defined in the methods. and clarity then for line 369.

Response to comment 2.

Thank you for pointing this out. Lines describing this fell out of later revisions of the manuscript. This has been corrected. The following sentence is now included in the methods section of the manuscript, “Mortality was defined as the proportion of deaths attributable to pertussis in the study sample while case fatality was defined as mortality attributable to the disease among confirmed cases of pertussis.” Lines 205-206, page 8

Review comment 3

Line 160: what study designs were eligible

Response to comment 3.

Again we are grateful to the reviewer for pointing out this omission. The following lines have been added to the methods section, “The study included randomised controlled trials, cross-sectional, cohort and surveillance studies. Case series and review articles were excluded as they failed to provide the required denominator.” Lines 169-171, page 7

Review comment 4

Analysis should be reported separately for the different lab methods, noting most studies used PCR, the most sensitive method.

Response to comment 4.

Our results have been reported stratified by diagnostic methods as we also agree that given the different sensitivities of diagnostic methods they cannot be lumped together. The following lines appear in methods to indicate this, “Bordetella pertussis prevalence data were stratified by WHO region, diagnostic method (culture, paired serology or PCR)…” Lines 177-179, page 7. The stratified reporting is also shown in the accompanying figures

Review comment 5

Line 192-193: it not clear what the dotted lines are meant to be if they have no meaning.
Response to comment 5.

Thank you for alerting us to this confusion. Although we mention in this our methods [“Instead dotted lines were used to indicate where group averages would lie without emphasizing their meaning.” Lines 201 – 202, page 8. The dotted lines are meant to serve only as an indicator of where average point estimates for subgroups and the whole sample would be in a ‘pooled’ analysis. The figure legends explain the dotted lines, however to improve clarity, we have added labels to the dotted lines in the figures.

Review comment 6

Line 208: Was a quality assessment done on the lab methods used regarding sensitivity of the method used?

Response to comment 6.

This was not possible, a limitation we noted in our discussion. We have extended this to clearly highlight this limitation. A sentence has been added that reads, “In particular this limitation is noted with our inability to assess the sensitivity and specificity of each assay.” Lines 473 – 474, page 19

Review comment 7

Line 246: ~50% of the data came from 5 countries - should each study therefore be weighted?

Response to comment 7.

We have weighted the studies in each analysis in which the data has been pooled. Where the prevalence data has not been pooled, the results was not be affected by any one study’s prevalence as each study has retained its own point estimate and 95% confidence interval. In addition each figure showing prevalence includes the country from where the data was sourced for each study.

Review comment 8

Number of doses of vaccine would be useful to know if available/reported and add to Table 2.

Response to comment 8.

We wholeheartedly agree with this. Unfortunately, this is one aspect in addition to vaccine coverage, in which data was largely missing from reports of each study. We have included this limitation to make this clear. The following sentence has been amended to read, “Our study is largely limited by paucity of data, especially longitudinal data for each included country as well
as vaccine coverage and number of vaccine doses received in the specific population studied.”
Lines 469 – 470, page 19

MINOR COMMENTS

Review comment 9
Line 93; missing words at the end of the sentence.
Response to comment 9.

Thank you for pointing this out. Part of the sentence got deleted during the last formatting. This has been correct as part on another amendment in response to another review comment in Lines 91-94, page 4.

Review comment 10
Line 100: state what settings are you referring to.
Response to comment 10.

Settings here refer to low and middle income countries. The last part of the sentence has been removed to reduce ambiguity. The sentence now reads, “The high HIV prevalence estimates in LMICs coupled with suboptimal vaccines uptake are modifiable risk factors that can fuel high pertussis burdens [7, 8].” Lines 104 -105, page 4.

Review comment 11
Table 1 can be moved to Supplementary materials.
Response to comment 11.

Thank you for the suggestion. Table1 has been moved to supplementary materials and amendments made to the order of the other Tables. See “Additional file 1”

Review comment 12
Line 140: It is not clear why the search was done over 4 different times.
Response to comment 12.

Thank you for pointing this confusion out. The initial search was done to test the search strategy for each database. Then a formal search was done. Unfortunately the study was interrupted due to unforeseen circumstance, necessitating another search on resumption. Before analysis was done a quality check search was done to make sure that no qualifying literature was missed. The
last search is the one that is reflected in this report and contains all the inputs of the previous searches. We have removed the mention of other dates from the manuscript to reduce unnecessary confusion. The sentence now reads, “The reported search was carried out in April 2019. The World Bank groupings reflect the country status at this period.” Lines 144 – 145, page 6.

Review comment 13

Line 221-223: please reword this sentence and be more specific ie ‘what does "amongst others" mean?

Response to comment 13.

The sentence has been reworded to improve communication. The sentence now reads, “Studies were excluded if they did not report clinical cases such as in laboratory studies, animal studies, economic evaluation and modelling studies. Other reasons for exclusions are shown in Figure 1.” Lines 234 – 236, page 9.

Review comment 14

Table 2: add if outbreak setting or not

Response to comment 14.

The three outbreak studies have been highlighted in Table 1 (numbering changed in response to previous comment). Part of Table1 legend reads, “NB. Cooper, Strebel and Al-Bargish conducted in outbreak settings”

Emmanuel Ekanem (Reviewer 2): The authors have attempted, using a systematic review/meta analysis where applicable, to define the burden of pertussis (a re-emerging infectious disease) in low and middle-income countries. The attempt to synthesize and produce a summary estimate of pertussis burden in the very heterogenous population of LMICs is a daunting task. There are a few comments that require the attention of the authors:

Review comment 1

Please include the search terms for the other electronic databases as a supplementary file and the total hits returned from each database on the PRISMA flow chart.

Response to comment 1.

No other terms other than those indicated in Table 1 (Now ‘Additional file 1) were used. What differed slightly was the way in which the search was conducted, which was largely informed by the interface of each search engine, other than that, the same search terms were used. Total hits for each database before duplicates were removed are now shown on the PRISMA flow chart.
Review comment 2

Page 9, lines 223-225: Please cite the studies being referred to here.

Response to comment 2.

These lines refer to most of the studies included in this systematic review. We added this section only to indicate that these were clinical cases not asymptomatic individuals. Citations of all the studies are reflected in Table 1.

Review comment 3

Page 10, lines 226-227: Please cite the studies being referred to here.

Response to comment 3.

Thank you for pointing this omission out. Studies have now been cited. The sentence now reads, “Two studies were multinational (two and seven countries in each) so that in the end the final 82 studies included, represented 88 unique populations [32, 80].” Line 241, page 10

Review comment 4

PRISMA chart: please give examples of the "other" excluded studies

Response to comment 4.

Thank you for the comment. The following has been added to the PRISMA chart “# Modelling studies, economic evaluations, grey literature and studies with unclear designs”

Review comment 5

RESULTS: A) What methodologic variations would have led to the very high prevalence of lab-confirmed pertussis in Cooper et al, Astudillo et al and Al-Bargish et al. Would a sensitivity analysis without these studies present a summary estimate with less heterogeneity and therefore a more trustworthy prevalence value?

Response to comment 5.

Cooper and Al-Bargish were both conducted during ‘outbreaks’ while Astudillo included data of contacts of index cases, i.e. secondary attack rates. We have now added a sentence to reflect on this in our discussion which reads, “Higher culture prevalence estimates than in other studies in a similar WHO group were noted when the studies were conducted before a vaccination program was fully established (Voorhoeve, 1978), during an outbreak (Cooper, 1983; Strebel, 1991 and
Al-Barghish, 1999) as well as when the study included secondary attack data of close contacts (Astudillo, 2011) [24, 26, 40, 83].” Lines 437 – 441, page 18. Analysis with and without these studies has no impact on heterogeneity.

Review comment 6

B) The component of HIV’s effect on pertussis prevalence appears to be a slight distraction to the manuscript. Would it not be more appropriate to take this as a separate paper and thereby have the opportunity to deal with more variables associated with HIV in that paper? this may help give more focus to this manuscript. Moreover, the HIV component of the work had studies mainly from South Africa with only one from Uganda and Zambia.

7. It may also be more informative to compare Pertussis prevalence by decades. This may help show more clearly a change in prevalence over decades.

Response to comment 6

Thank you for mentioning this. We did seriously consider taking out HIV data, but in the end decided that it gave a holistic picture of the epidemiology of pertussis. We believe that reporting these data as per our published protocol strengthens this Systematic Review. We have however, expanded the sentence acknowledging the limited data to reflect this concern. The sentence now reads, “Although data are limited by number of countries reporting HIV status, there is strong evidence from the metanalysis showing that the risk of pertussis is increased in HIV+ and HEU individuals.” Lines 459 – 461, page 19.

Review comment 7

It may also be more informative to compare Pertussis prevalence by decades. This may help show more clearly a change in prevalence over decades.

Response to comment 7

We have indeed done this and reported that “Pertussis prevalence declined in the 1990’s from the levels seen in the 70’s and 80’s. A slight increase was noted since the period after 2000. Figure 4a.” [Lines 308 – 309, page 12.] We also noted in the discussion that “Despite the predominant use of wP in the reviewed studies, we noted a steady increase in confirmed pertussis in studies reporting after 2000. Figure 4a”. Lines 451 – 452, page 19.

Duncan Steele (Reviewer 3): This is an extremely well conducted analysis and well written manuscript with a comprehensive systematic review of the literature over the past 45 years. The study is timely with respect to our understanding of the vaccine strategies available and the increasing observation of pertussis cases occurring world wide. It is apparent that the authors have expertise in the field of Bordetella pertussis, and they articulate their concern about the increased vulnerability of children with HIV-exposure or HIV-infection in countries.
Response to comment

Thank you for this comment. We highly appreciate it.

The manuscript would be enhanced by considering these aspects:

Review comment 1

There seems scant recognition of the EPI vaccine coverage in LMIC and LIC countries. We know from global figures of routine EPI vaccine coverage, that this seems to have stagnated at about 80% globally and many of the countries included in this analysis will be on the lower ranges globally.

Secondly, we know that the timing of the full schedule of routine immunization doses is sub-optimal and that the timeliness of EPI-2 and EPI-3 can be quite late in many developing countries.

Besides the natural epidemiology of pertussis, these factors would drive the most serious disease and highest mortality into the youngest age groups (&lt;6 month olds as reported in this study).

Response to comment 1

Thank you for pointing this out. We have added a line to indicate the importance of vaccine coverage in LMIC as well as noting that the GPI raised this as an important issue. The following lines have been added to address these important issues, “Immunisation remains suboptimal with vaccine coverage with the three infant doses (DPT3) remaining low in LMIC in general and in low income countries, in particular.[115] Even where vaccine coverage with DPT3 is acceptable, the doses are not often received in a timely manner, undermining the protective effect of the vaccine on young infants.[116, 117] “ Lines 480 – 483, page 20. In addition the following section has been amended to read “In their recommendation, the GPI in addition to prioritizing surveillance and increasing overall vaccine coverage...” Lines 493 – 494, page 20. In addition the following citations have been added:

115. Diphtheria tetanus toxoid and pertussis (DTP3) Immunization coverage estimates by World Bank Income Group [https://apps.who.int/gho/data/view.main.81200WB?lang=en]
Review comment 2

The conclusion that maternal immunization could play a significant role should be expanded on as this is an immediate and short-term solution that should be recommended.

Response to comment 2

Thank you for this recommendation. We have amended this section to now read, “In addition, the study highlights the need to urgently consider measures to reduce the high infant mortality rate, with specific consideration for maternal vaccination. There is now strong evidence to showing that immunisation of pregnant women, even when given as early as the second trimester, is safe for both the mother and the foetus; and induces sufficient transplacental antibodies to protect the young infant still too young to complete primary immunisation schedule for pertussis[119, 120]. In their recommendation, the GPI in addition to prioritizing surveillance and increasing overall vaccine coverage, made this an urgent area of action for LMICs [6]” Lines 488 – 495, page 20. Two references have been added to support this reflection:


Review comment 3

The authors do not specifically call out and describe limitations to this analysis, but surely one is that almost 50% of the studies are conducted in only 5 UMI countries.

Response to comment 3

We have amended the limitation to highlight this with the following sentence, “The available data was disproportionately provided by only a few upper middle-income countries.” Lines 471 – 472, page 19.

Review comment 4

6. The authors could make stronger recommendations, based on this study and their previous work in this field, for increasing efforts for higher coverage and more timely vaccination, for studies on maternal immunization and for other gaps in our knowledge that should be explored.

Response to comment 4

Thank you for this comment. We hope that we have addressed this comment in our response to the other comments above.
Minor factors that the authors may want to consider include:

Review comment 5

The global estimates of disease burden and mortality are relatively old now (2003 and 2008), and could be updated with more recent figures, possibly from IHME Global Burden of Disease estimates.

Response to comment 5

Thank you. This is a fair comment. The section has been updated to reflect more recent data. The section now reads, “Using a model developed in 2003, the World Health Organisation (WHO) estimated that in 2008 there were 20 to 40 million annual cases of pertussis. They further estimated that 90% of the cases and their 300,000 associated occurred in Low and Middle-Income Countries (LMICs) [1, 2]. An updated model by WHO estimated that 24.1 million cases of pertussis occurred in 2014 with 160 700 associated deaths in children under five years of age; a majority of these (58%) were estimated to have occurred in the African region and largely involved infants (53%) [3].” Lines 91-97, page 4. We used an updated estimate by a WHO group:


Review comment 6

2. Vaccine hesitancy has played a role in the increase of pertussis seen in HICs, and could be referenced without detracting from the key messages of the manuscript.

Response to comment 6

Thank you for this suggestion. We have reflected on this phenomenon in the following lines, “Unlike in HIC countries in which re-emergence of pertussis may be related to low and delayed vaccine coverage secondary to vaccine hesitancy, in LMIC this usually reflects lack of administrative capacity.[118]” Lines 483–486, page 20.