Author’s response to reviews

Title: Respiratory Syncytial Virus prophylaxis for prevention of recurrent childhood wheeze and asthma: a protocol for a systematic review

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Author’s response to reviews:

Please see below for detailed responses to both the Editor and the Reviewers’ comments. Responses are in dashed bullet points underneath each individual comment. We are very grateful for, and appreciate all feedback and critique. It has all been taken on board and implemented, both in the protocol and will be for the full systematic review to follow. Thank you.

Editors Comments:

1. Please ensure all acronyms and abbreviations are spelled out clearly when first presented in the protocol. 
   - Checked and corrected

2. Please provide additional detail regarding data extraction. In particular more details required regarding process for developing and testing data extraction tool, list and define all variables for which data will be sought ie. elements of PICO, and how you will manage missing date ie. any plans to contact study authors.
   - Lines 251 – 260: Data extraction tool ‘summary of findings table’ explained and referenced, PICO defined and plans to manage missing data stated.

3. Please clearly define primary and secondary outcome of interest and provide further details regarding management of continuous or dichotomous outcomes
   - Lines 268 – 276: Primary outcome stated and clarified as dichotomous data managed in 2x2 outcome tables.

4. Please provide additional detail regarding tools and methods for assessing Risk of Bias of included studies.
   - Lines 260 – 268: Explain GRADE tool used to assess risk of bias
   - Lines 282 – 283: describes use of funnel plots to detect publication bias / selective reporting
5. Please clarify how you plan to use GRADE methodology to assess quality of evidence.
- Lines 260 – 268: GRADE methodology defined and explained

Reviewer #1: Reviewer's comments

Title: add asthma together with wheezing. Asthma is described many times in the abstract and body of the manuscript. So, the title would better be written as "Respiratory Syncytial Virus (RSV) prophylaxis for prevention of recurrent childhood wheezing and asthma: a protocol for a systematic review"
- Asthma added in to title

Abstract
Line 27: Respiratory Syncytial Virus (RSV)-related... Is it RSV related or RSV caused LRTI infection? It will be better if RSV caused otherwise it will be difficult to establish RSV prophylaxis with prevention of wheezing. In addition, is it wheezing only or including asthma? The title is about wheezing but asthma was indicated many times in the abstract.
- Line 30: reworded to clarify – ‘LRTI caused by RSV……’

Lines 34-36: Can be inserted as separately as an objective
- Done

Lines 36-39: Not clear! As this manuscript is a protocol, it is difficult generate evidence supporting the hypothesis at this time.
- Line 40 – deleted this part of the sentence

Lines 41-48: Which databases will be searched? And where unpublished data be looked manually? What is GRADE? (Better to use its long form in the abstract/at its first appearance) What type of studies will be included? Is the meta-analysis already done or why you reported as it is carried out). How could you declare the model (random effects model) you are going to use at this stage of study? How heterogeneity will be measured? Which statistical methods will be employed for the meta-analysis? Which statistical software will be used?

Line 50: What if there is no casual association? And include asthma in the title or remove from the discussion.
- Line 70: ‘If this study shows RSV prophylaxis to have no effect on the outcome of recurrent wheeze / asthma, the question of causality remains.’ Asthma included in title.

Line 92: What does NHS mean?
- Removed this point as used a different reference.
Lines 117-119: Not clear. What are the notable side effects?
- Line 149 - 150: Side effect stated and referenced

Lines 130-135: This part is better to be taken to the first part of the background as it describes the characteristics of the virus itself.
- See lines 135 – 140.

Lines 147-148: a number of databases…. Which notable databases will you be searching?
- Lines 172 – 192: Databases stated

Line 160: Why matched cohort studies? What about unmatched one?
- Line 204: removed ‘matched’

Line 161: Which period includes early preterm to term?
- Line 205: gestational age range defined

Line 163: "...No adult studies will be included in the analysis" This population is not your study subject from the very beginning; so can't be part of exclusion criteria. The title is among children too.
- Line removed and also removed from inclusion criteria table (Table 1)

Line 230: Is the discussion shall on asthma or wheezing? Better to modify/add asthma in the title
- Asthma added to title

Lines 203-211: How studies assessed? Which quality assessment tools are to be used? What is GRADE?
- Lines 261 – 267: GRADE defined and explained

Reviewer #2: AUTHORS
Manuscript_SYSR-D-19-00143
TITLE: Respiratory Syncytial Virus (RSV) prophylaxis for prevention of recurrent childhood wheezing: a protocol for a systematic review

This is an interesting study. It is well constructed and addresses a very important topic, producing valuable results. Outcomes are of interest and may help support the hypothesis of a causative association between RSV and recurrent wheeze and/or asthma and might suggest a novel path for prophylaxis on such an important disease.
I have minor concerns that should be addressed.

1. Would probably choose not to define RSV acronym on title but when first mentioned in abstract, and again in the main text.

- Corrected
2. The Background section of the abstract sounds a bit confusing. Mixes the association (causal?), with RSV-specific monoclonal antibodies and hospitalizations, with the preterm births and RSV infection. I would rewrite this section to provide a more direct and robust focus on i) RSV as causal (?) agent for asthma and ii) RSV-specific monoclonal antibodies as a way of preventing infection in preterm
- Lines 30 – 35: Rewritten and wording improved to make this clearer and more succinct

3. Line 78: "ofbreath" both words seem merged.
- Line 98: Checked and not merged, must be an issue with the font.

4. From lines 77 to 81, all sentences are backed up by reference [1]?
- Lines 97 – 101: Referencing checked and made clearer

5. Lines 90-91 authors highlight that it has been estimated that recurrent childhood wheeze represents 0.15% of the NHS expenditure, highlighting it as a key global health issue. Reference [7] dates back from 2003 (16 years ago), is there anything newer to update these values? Also, [7] determined the economic impact in the UK of wheezing disorders in preschool children hence I would geographically contextualize this and avoid stating "key global health issue"
- Lines 110 – 111: More up to date reference used to make similar point and ‘global health issue’ changed to ‘public health issue’.

6. Line 118 "profile, and and questions over" please delete "and"
- Line 150: ‘and’ deleted.