Author’s response to reviews

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

Authors:

Lauren Quinn (lquinn583@qub.ac.uk)
Michael Shields (m.shields@qub.ac.uk)
Helen Groves (hgroves01@qub.ac.uk)

Version: 2 Date: 01 Dec 2019

Author’s response to reviews:

To the Editorial Team,

Thank you for your comments and advice regarding our protocol. We have taken all on board and have changed our protocol accordingly. Please see below for a detailed explanation and response to each suggestion.

1. The sequence of the background is not quite clear, ie pg5 is about risk of childhood asthma, and its causes being well established but also a need for further preventative studies – is it well established, or are further preventative studies needed? Re-ordered the paragraph to make it more clear that it is the association between bronchiolitis and asthma that is well established (not causality), and that further studies were needed to explore if this association was causal. – 102 - 111

2. The paragraph starting line 112 is about an intervention to reduce the risk of RSV, but there is no link between this paragraph and the previous paragraph, nor is the information presented clear - ie how and why is the therapy delivered to who, and to what effect? Moved sentences from previous paragraph about the most common causes of bronchiolitis to provide a link between these 2 paragraphs. Explanation of efficacy of monoclonal antibodies and why they are used inserted prior to description of how they work. – line 113 - 121

3. Line 88 – it was not infants who were surveyed (I hope), please revise this sentence Sentence reworded more clearly – changed from ‘infants surveyed’ to ‘infants in the study population’ – line 92

4. Line 94-95 reference this statement please, and expand its relevance to the topic. Line referenced and entire paragraph re-ordered to expand on this sentence and make it more relevant – line 94 - 98
5. Line 138 – this is a systematic review not a systematic literature review – please amend use of this term throughout.
Amended – line 169

6. Methods,
   Why Medline and PubMed? Please review and revise this choice
   Thank you for pointing this out, we are aware that pubmed is an interface used to search Medline. We will use Medline for the focused literature search but will use Pubmed to be sure we don’t miss any papers published ‘ahead of print’ that are not yet formally indexed for Medline. We have not changed the text however if you think this is not appropriate we would be happy to change to just Medline. – line 182

7. Will you search trial registries? If not, please put a justification
   We will search clinical trial registries such as ClinicalTrials.gov and BMC Trials. – line 213 - 214

8. Infants of any gestational age will be included, but premature babies may have different risk profiles, as may babies who receive exclusive breast feeding versus bottle feeding, will you consider sub groups based upon risk?
   Sub group analysis based on gestational age will be carried out – see paragraph in intro and methods justifying this. It is unlikely that there will be enough studies to perform sub group analysis based on demographics such as breast feeding vs bottle feeding etc. line 146 – 156, 268 - 272

9. What is the rationale for excluding infants who have congenital disorders that are unrelated to respiratory outcomes? Ie what about deaf infants, those with club foot, or craniosynostosis?
   We realise the way we worded our exclusion criteria is unclear. We feel it is important to exclude children with congenital heart disease (one of the major indications for giving Palivizumab) as these children often have respiratory symptoms that can be similar to asthma symptoms but are due to the heart defect and not due to true asthma, therefore potentially confounding the results. We definitely did not plan to exclude deaf infants or those with club foot etc. Thank you for pointing this out. – line 203 - 208

10. Do infants need to be diagnosed with wheeze/asthma or no formal diagnosis required for this review?
    No formal diagnosis required – amended in methods – line 254 - 256

11. The search – I do not know what database the search strategy is from, but its worth noting that in PubMed the term Respiratory Syncytial Virus Infections/ results in over 11,100 hits, not 1279 hits as shown in table 2. Further to this, there is a MeSH term for the virus which is specific to humans versus other mammals (again – in pubmed)
    This search strategy example is taken from Embase and this has been amended. It was carried out on 7/3/2019 so when the same search strategy is run now the numbers are slightly different (eg. ‘Respiratory Syncytial Virus Infections’ now yields 1835 results instead of 1279). However, I have kept the original search strategy example as this was when the protocol was written. – line 217
12. The background section of the protocol does not refer to ‘respiratory hypersensitivity’ but it’s a major item in the search strategy, can the background explain how its related to asthma/wheeze please
Line about asthma causing hypersensitivity and inflammation of the airways added in to background to justify the use of this term in search strategy – line 88

13. Is the reason the age range is from 0-18 because of database limitations on selecting newborns to young infants?
When setting data limitations on the database the options were to limit to ‘all child (0-18 years)’ or else it was divided up to 1 – 23 months, 2 – 5 years, 6 – 12 years and 13 – 18 years. The follow up period for this review was 1-10 years so setting the limit to ‘all child’ is most appropriate for the search strategy.

14. What is the timeframe for follow-up? This is an important metric so please provide!
This is stated in the inclusion / exclusion criteria table, but I have added it in to the main text as well for clarity. Line 196

15. What risks/harms will you seek to extract, measure and report – again this is a key metric, publishing a review of effects without considering the risks and harms possibly associated with the intervention is highly problematic. BMC Systematic Reviews will be highly cautious about publishing a protocol that does not consider the potential risks/harms to the patients receiving an intervention.
Information about safety / potential adverse effects of Palivizumab added in to introduction and section on evaluation of safety added to methods – line 280 - 283

16. Data extraction
Lines 200- the Cochrane SoF (Summary of Findings) table is not a device for data extraction, it is a device for data presentation. Please review and revise this section so its clear what data extraction instruments, how piloted, and how it will be implemented.
Data extraction tool described and example provided in appendix 2. Line 233 - 235

17. Discussion
Line 242 – asthma has been described as multi-factorial, will you use multivariate analysis to address confounders?

In this systematic review we are focusing on the intervention to prevent RSV infection and looking to see if this one specific intervention reduces the subsequent risk of asthma / wheeze, which would then indicate that RSV is a significant potentially causal risk factor. We are not looking at the myriad of currently known other risk factors for asthma. We are aware that the risk factors already known only account for a small number or cases, i.e. the cause of asthma still remains largely unknown. We are therefore not planning to do a multivariate meta-analysis as we are solely focusing on one risk factor.
18. Line 244 – rather than ‘huge implications’ – which are not specified here, please be more precise about what implications there actually are for policy, practice and future research agendas. Clinical implications elaborated and expanded upon – line 293 - 303

Reviewer #1:

19. In the title, RSV should be in its long form; Respiratory syncytial virus
Amended

20. Types of studies and participants
   * Line 177: no need of stating cohort studies as cohort and retrospective cohort. Cohort studies are either prospective or retrospective. So, saying cohort will include retrospective cohort studies too.
   Amended

21. Table 1:
   * Rather than using symbols, use words. For example. Instead of using plus (+), use the word 'and'; instead of using slash (/), use the word 'or' if appropriate.
   Amended

22. Table 2:
   * Which database is searched and gave these interactions? And have already searched the data bases and get the numbers of studies to be included?
   Database was Embase. A preliminary search was carried out on 7/3/2019 so an example search strategy could be provided for the protocol as per PRISMA-P Checklist.

Reviewer #2: Manuscript Number: SYSR-D-19-00143R1
Full Title: RSV prophylaxis for prevention of recurrent childhood wheeze and asthma: a protocol for a systematic review
I believe authors have address all concerns and the manuscript is now suitable for publication.