Author's response to reviews

Title: Clinical Manifestations of Tension Pneumothorax: Protocol for a Systematic Review and Meta-Analysis

Authors:

Derek J Roberts (Derek.Roberts01@gmail.com)
Simon Leigh-Smith (SimonLeighSmith@gmail.com)
Peter D Faris (Peter.Faris@albertahealthservices.ca)
Chad G Ball (Ball.Chad@gmail.com)
Helen Lee Robertson (Helen.Lee.Robertson@ucalgary.ca)
Christopher Blackmore (Christopher.Blackmore@albertahealthservices.ca)
Elijah Dixon (Elijah.Dixon@albertahealthservices.ca)
Andrew W Kirkpatrick (Andrew.Kirkpatrick@albertahealthservices.ca)
John B Kortbeek (John.Kortbeek@albertahealthservices.ca)
Henry T Stelfox (TStelfox@ucalgary.ca)

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Author's response to reviews: see over
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Drs. David Moher, Paul G. Shekelle, and Lesley A. Stewart
Editors-in-Chief, Systematic Reviews

Dear Drs. Moher, Shekelle, and Stewart and the Systematic Reviews Editorial Team:

Re:

Ms. No.: 1026753557109186
Ms. Title: Clinical Manifestations of Tension Pneumothorax: Protocol for a Systematic Review and Meta-analysis

Thank you for your thoughtful reviews of our manuscript and the opportunity to resubmit a revised version for consideration of publication in Systematic Reviews. We have revised the manuscript as suggested, and feel that the appended document is an improved report, which addresses the comments and suggestions afforded by the Reviewer, Associate Editor Dr. Susan Hempel. Please find below an itemized list of detailed responses to each of the Editorial and Reviewer comments, including a description of the changes made to the manuscript (which are highlighted in yellow within the manuscript text and/or tables). Within this itemized list, we first cited each comment verbatim in bold type before providing our response for ease of review.

Editorial Comments:

1. Please include a figure title and legend section after the reference list. The figures should not be included in the main body of the manuscript.

   Thank you. The title and legend for Figure 1 have been moved and are now listed after the reference list of the manuscript. Moreover, the figure has not been included in the main body of the manuscript.

Reviewer Comments:

1. Simultaneously conducting a systematic review of published studies and an individual patient data (IPD) meta-analysis is very ambitious. Do the authors have already access to a number of datasets or will the IPD analysis rely on cold calls to authors? The chances of obtaining original datasets are low and will need a dedicated approach and considerable resources. The protocol to ensure that a systematic search of IPD-eligible studies has been performed and which steps will be undertaken to ensure a reasonable and unbiased sample should be outlined further. The authors might consider restricting the review to published case studies rather than undertaking an IPD meta-analysis.
We agree with the Reviewer that simultaneously conducting a systematic review of published studies and an individual patient data (IPD) meta-analysis would be ambitious. We apologize for the lack of clarity regarding our plans for the synthesis of data on the clinical manifestations of tension pneumothorax in this systematic review. We have revised the manuscript to clarify that we propose to aggregate patient-level data extracted from published case reports and series identified during the conduct of our systematic review and will not be conducting an IPD meta-analysis. All reference to the conduct of an IPD meta-analysis has therefore been removed from the manuscript.

2. The review is currently searching for published tension pneumothorax studies to identify clinical manifestations of tension pneumothorax. The protocol should clarify how the review will address overlap between the diagnosis and the clinical manifestations. The applied working definition appears to include clinical manifestation characteristics. A systematic review of clinical definitions included in research studies might be a reasonable alternative.

We agree with the Reviewer that a systematic review of clinical definitions is an important additional outcome. Thus, we will extract these definitions from each of the included observational studies and case reports and series where available (see Page 18, second bulleted point), and will report a list of these definitions in our final manuscript. In order to be more clear as to how our methods will address the potential for incorporation bias in our systematic review of case reports and series data [1], we added the below discussion to the manuscript:

“As tension pneumothorax is a syndrome diagnosis without an independent reference-standard diagnostic test [10,16,40], any systematic review of its clinical manifestations may be limited by incorporation bias (whereby the estimation of the frequency of clinical manifestations that may have been incorporated into the diagnosis may bias upward the results [46]). To reduce the risk of this bias, two investigators (D.J.R., C.B.) will independently determine whether the clinical condition of the study patient(s) presented in each case report aligned with a previously published tension pneumothorax working definition [7,47]. According to this definition, a tension pneumothorax is defined not only by its presenting clinical manifestations, but also according to its response to treatment as one “that results in significant respiratory or hemodynamic compromise that reverses [or at least significantly improves] on thoracic decompression alone” [7,47].” (Page 16-17)

The above published definition was chosen as it does not incorporate any specific clinical manifestations into the definition of tension pneumothorax (as respiratory and hemodynamic complications are considered equal, and no specific clinical manifestation is required to be present for the syndrome to be diagnosed), and because it also requires that a substantial clinical improvement occur after thoracic decompression alone (an event that is likely independent of the specific presenting clinical manifestations of tension pneumothorax). Thus, after conducting analyses using the data extracted from all reported cases, we will examine whether our observed associations may have been
sensitive to incorporation bias [1]. This will be done by recalculating all outcomes using only those cases where both investigators independently agreed that the clinical condition of the study patient(s) aligned with the working definition [7,47]. Using this approach, we may not only be able to examine whether incorporation bias existed among the published case reports/series, but also to potentially determine its magnitude.

Finally, as is now outlined in the risk of bias section of the Methods, in order to determine whether incorporation bias was present among the included observational studies, we will evaluate “whether the diagnosis of tension pneumothorax was determined using credible criteria that 1) were at least partially independent of the clinical manifestations under study [by examining if the clinical diagnosis was supported by radiographic findings/response to thoracic decompression and whether overlap existed between the diagnostic criteria utilized (where reported) and the reported frequency of clinical manifestations]” (see Page 21, Paragraph 1). Where possible, we will also conduct meta-regression in order to explore whether use of a definition of tension pneumothorax in which the presence of disease was determined using credible criteria that were at least partially independent of the clinical manifestations under study influenced the meta-analysis results.

3. The inclusion criteria should be described in more detail and should differentiate which criteria have to be met by published studies without access to the original patient data.

In response to a related comment from the Reviewer, the study selection section was integrated into that describing the inclusion/exclusion criteria, and this section was given a dedicated “Review Procedure” subheading. Within the text underlying this subheading, we afforded more detail on the inclusion/exclusion criteria, and explicitly described which criteria will be applied to observational studies and case reports/series. We also defined observational studies as cohort, case-control, or cross-sectional studies. We will not be attempting to obtain original patient data, and will only use the data provided by published observational studies and case reports/series. The Review Procedure section of the manuscript now reads:

“Review Procedure:

Independently and in duplicate, two investigators (D.J.R., C.B.) will screen citation titles and abstracts and review potentially relevant articles in full. We will consider published observational (cohort, case-control, and cross-sectional) studies and case reports and series, which report original data on clinical manifestations of tension pneumothorax for inclusion in the systematic review. Clinical manifestations will be defined as patient-level findings/data, which may be gathered by clinicians during a medical interview or through physical examination, invasive monitoring or treatment equipment (e.g., intravascular catheters or mechanical ventilators), and diagnostic studies (e.g., echo- and electrocardiograms) [46]. All published observational studies and case reports and series in which tension pneumothorax was diagnosed by the study authors/involved clinicians (and data on clinical manifestations were reported) will be
eligible for inclusion. Reports of fatal cases will be included if the condition causing death was attributed by the study authors to be a tension pneumothorax and associated with expulsion of air following thoracic decompression or determined by a pathologist to be present on autopsy.

As tension pneumothorax is a syndrome diagnosis without an independent reference-standard diagnostic test [10,16,40], any systematic review of its clinical manifestations may be limited by incorporation bias (whereby the estimation of the frequency of clinical manifestations that may have been incorporated into the diagnosis may bias upward the results [46]). To reduce the risk of this bias, two investigators (D.J.R., C.B.) will independently determine whether the clinical condition of the study patient(s) presented in each case report aligned with a previously published tension pneumothorax working definition [7,47]. According to this definition, a tension pneumothorax is defined not only by the type of its presenting clinical manifestations, but also according to its response to treatment as one “that results in significant respiratory or hemodynamic compromise that reverses [or at least significantly improves] on thoracic decompression alone” [7,47].

We will exclude observational studies and case reports/series that do not describe ventilation status, as well as those involving patients with diving-related pulmonary barotrauma; a previous contralateral pneumopneumectomy, traumatic diaphragmatic hernia, or tension pneumopericardium or pneumoperitoneum as well as chronic (as defined by the authors) or loculated pneumothoraces. We will also exclude observational studies and case reports/series of patients undergoing thoracic surgery or laparoscopy at the time of onset of their tension pneumothorax clinical manifestations. All of the above excluded conditions were selected as they represent special, uncommon, or less relevant associated or principal patient conditions, which have the potential to misrepresent the more common clinical manifestations of tension pneumothorax.

Disagreements between investigators regarding the above decisions will be resolved by consensus and, if needed, arbitration by a third investigator. Inter-investigator agreement will be quantified by calculating a kappa (κ) statistic and associated 95% confidence interval (CI) [48].” (Page 15-16)

4. In addition, the analysis has to consider how the lack of reporting and the absence of symptoms will be differentiated. The protocol specifies that original study authors will be contacted for missing information but it needs to be clarified how the studies will be processed when the information cannot be secured (either authors do not answer or do not have the information anymore because it was not collected at the time).

We agree with the Reviewer that the lack of reporting and the absence of symptoms must be differentiated and considered in the analysis. In support of this, although the systematic aggregation of data contained in published case reports and series may have the potential to guide clinical practice [3-5], the quality of published reports is likely to vary, mostly as a result of differences in the completeness or transparency of reporting [2]. As such, we modified the last two sentences of the second paragraph of the risk of bias section of our manuscript such that they now state:
Moreover, the adequacy of reporting on confounding/modifying and clinical manifestations data among included case reports/series will be evaluated by recording whether information on these variables was either reported or unclear/not reported (i.e. not specifically mentioned or described as being absent) in the manuscript [52,53]. Finally, we will quantify the extent of unclear/unreported information (as determined by two independent reviewers) among the potentially confounding/modifying and principal outcome variables.” (Page 22)

As was outlined in the Statistical Analyses subsection of the manuscript, our primary meta-analysis of case reports and series data will then examine whether the reported risk of adverse hemodynamic complications differs among patients receiving positive pressure ventilation versus those that were breathing unassisted (after adjusting for a variety of reported potentially confounding/modifying variables). However, when authors do not report whether specific clinical manifestations or confounding/modifying variables were present or absent (or where this was unclear and these data cannot be obtained from study authors), we will conduct the following sensitivity analysis:

“Second, as we anticipate that case reports and series may sometimes not report (or fail to clearly report) whether potentially important confounding/modifying or clinical manifestations data such as hypotension were specifically present or absent, we will also treat unclear/unreported data as missing (where they could not be clarified by writing study authors) and use imputation methods on these data. Multiple imputation is a method that may be used to perform a series of imputations for each missing observation by conducting random draws from the conditional distribution of the outcome variable given the values of the other variables [64]. After performing these imputations, regression analyses will then be conducted on each of the imputed data sets. The estimated associations and standard errors obtained from these analyses will then be combined to obtain point estimates and standard errors that account for the missing information. Simple imputation will then be used in order to provide an estimate of the extremes of influence of the missing values on the estimated outcomes between groups. This will be performed by first assigning all the missing values in the positive pressure ventilation group a value of “0” and all the missing values for these variables in the breathing unassisted group a value of “1”. After recalculating the model with the inclusion of these imputed values, we will then reverse the assignment of the “0” and “1” values and then again recalculate the model in order to provide the opposite extreme estimate.” (Page 28-29)

These results will not be reported as our primary findings, but rather will be used to test whether our observed frequencies of clinical manifestations data were sensitive to the extent of unreported data. The reported potential confounding/modifying variables were specified a priori, and were reported in the manuscript to include “patient age, administration of antihypertensive or vasopressor medications before the onset of tension pneumothorax (or chronic use of antihypertensives); past history of hypertension, heart failure, or chronic pulmonary disease; and presence of a hemothorax or other pleural
effusion, acute pulmonary disease (e.g., pulmonary contusions), or pre-existing shock” (Page 27).

5. The Study Selection section should be integrated into the inclusion criteria section and the review procedure should have a dedicated subheading. As it currently stands, this section repeats some inclusion criteria, contradicts others (e.g., Study Design) and raises red flags for potential bias (the eligibility of the publication should not depend on the review outcome, i.e., the clinical manifestation).

Thank you. As was outlined in the response to Reviewer comment #3, the study selection subsection has now been integrated into that describing the inclusion/exclusion criteria, and this subsection has been given a dedicated “Review Procedure” subheading. Within the text underlying this subheading, we afforded more detail on the inclusion/exclusion criteria, and explicitly described which criteria applied to observational (cohort, case-control, and cross-sectional) studies and case reports/series. For additional detail, please see our response to Reviewer comment #3, above. By stratifying case reports and series as to whether or not they met a previously suggested working definition that utilizes not only categories of clinical manifestations (i.e. respiratory or hemodynamic), but also response to treatment, this may allow for us to determine if differences exist in the reported frequency of clinical manifestations between those cases in which the diagnosis was determined based on varying clinical manifestations versus more objective or independent criteria. Further, in order to determine whether incorporation bias (whereby the estimation of the frequency of clinical manifestations that may have been incorporated into the diagnosis may bias upward the results [1]) was present among the included observational studies, we will evaluate whether the diagnosis of tension pneumothorax was determined using credible criteria that 1) were at least partially independent of the clinical manifestations under study [by examining if the clinical diagnosis was supported by radiographic findings/response to thoracic decompression and whether overlap existed between the diagnostic criteria utilized (where reported) and the reported frequency of clinical manifestations]” (see Page 21, Paragraph 1). Where possible, we will then conduct observational study meta-regression in order to explore whether use of a definition of tension pneumothorax in which the presence of disease was determined using credible criteria that were at least partially independent of the clinical manifestations under study versus not influenced the meta-analysis results.

6. It is not clear why CENTRAL will be searched when clinical trials are not eligible for inclusion in the review according to the study design inclusion criterion. The expression “without restriction” should be specified (without language restriction?). The term “hand-survey” should be revised. The search strategy is designed to cover studies that will not use the term “tension pneumothorax”.
We agree that searching CENTRAL would not be of use given that randomized controlled trials will not be included in the systematic review. We have therefore removed this database from our proposed electronic bibliographic search strategies in the Methods section of the manuscript and from Table 2 (Details of Electronic Bibliographic Database Search Strategies). Further, the term “without restriction” has been revised such that this now reads “without language or publication date restrictions” and the term “hand-survey” was changed to “manually search”.

We also agree that the search strategy may be more sensitive than specific and therefore may identify a number of studies of patients with simple (i.e. non-tension) pneumothoraces. As no specific or dedicated indexing terms exist in MEDLINE or EMBASE for tension pneumothorax, and because we did not want to miss any potentially relevant citations for inclusion in the systematic review, we invited an information specialist/medical librarian to join our research team. With her assistance, we created a unique tension pneumothorax search theme by combining relevant tension key terms (e.g., “tension”, “tension physiology$”, “expanding”, “needle thoracostomy”) with the MeSH term “Pneumothorax.” This unique tension pneumothorax search theme was then combined with the key term “tension pneumothorax$” using the Boolean operator “OR” to further increase sensitivity. After a number of iterative database queries in both MEDLINE and EMBASE, this strategy appeared to provide a reasonable balance between sensitivity and specificity, giving approximately 3000-5000 citations across most electronic bibliographic databases. As this number of titles/abstracts seemed feasible for review, and because we identified a number of articles we knew a priori to be highly relevant, we decided to proceed with this search strategy.

7. The inclusion criteria should specify in more detail what studies have to report in order to be eligible for inclusion in the review. If clinical manifestations will be applied to define tension pneumothorax for this review, the review result will be biased because the features were treated as inclusion criteria as well as the result of the review. The review protocol needs to address this potential source of bias.

We thank the Reviewer for asking for further clarification regarding our inclusion/exclusion criteria. All published observational studies and case reports and series in which tension pneumothorax was diagnosed by the study authors/involved clinicians (and data on clinical manifestations were reported) will be eligible for inclusion. However, as these cases may have been diagnosed based on the presence or absence of specific clinical manifestations, two investigators (D.J.R., C.B.) will independently determine whether the clinical condition of the study patient(s) presented in each case report aligned with a previously published tension pneumothorax working definition. According to this definition, a tension pneumothorax is defined not only by the type of presenting clinical manifestations, but also according to its response to treatment as one “that results in significant respiratory or hemodynamic compromise that reverses [or at least significantly improves] on thoracic decompression alone” [6]. By stratifying case reports and series according to whether or not they met the working definition, this may allow for us to determine if differences exist in the reported
frequency of clinical manifestations between those cases in which the diagnosis was determined based on varying clinical manifestations versus more objective or independent criteria. Further, in order to determine whether incorporation bias was present among the included observational studies, we will evaluate “whether the diagnosis of tension pneumothorax was determined using credible criteria that 1) were at least partially independent of the clinical manifestations under study [by examining if the clinical diagnosis was supported by radiographic findings/response to thoracic decompression and whether overlap existed between the diagnostic criteria utilized (where reported) and the reported frequency of clinical manifestations]” (see Page 21, Paragraph 1).

8. The analysis strategy should be critically reviewed. As it currently stands, the described analysis does not seem to be suitable for secondary literature and covers only high selected study types that do not seem to match up with the review’s inclusion criteria. If existing reviews are eligible for inclusion in the current review, the inclusion criteria needs to be revised. An IPD meta-analysis should follow accepted recommendations, e.g. as outlined by Stewart et al. (2012). Any reference to IPD analysis should be either removed or revised according to conventional IPD approaches.

As was outlined in the response to Reviewer comment #1 above, we will not attempt to conduct an IPD meta-analysis, and have therefore removed all reference to the conduct of this type of meta-analysis from the manuscript. We will instead conduct a systematic review and meta-analysis of the data afforded by published observational (cohort, case-control, and cross-sectional) studies and case reports and series. Although all published observational studies and case reports and series in which tension pneumothorax was diagnosed by the study authors/involved clinicians (and data on clinical manifestations were reported) will be eligible for inclusion, case reports and series will be stratified as to whether they met a previously suggested working definition of the disorder [6].

9. Page 21 and page 23 describe an analysis for a specific type of comparative study, the inclusion criteria should be adapted to cover (and potentially limit to) these studies.

We will include any observational (cohort, case-control, or cross-sectional) study that reports data on the associated occurrence rate of its clinical manifestations in the systematic review. As it may sometimes be difficult to distinguish between cohort studies and case series, a cohort study will be defined according to the definition proposed by Dekkers and colleagues as a study in which patients are sampled based on exposure and the occurrence of outcomes is assessed (as an aggregate measure) during follow-up [7] (this has now been clarified in our revised manuscript on Page 18, bulleted point one). However, because we anticipate that only non-comparative cohort [7] or cross-sectional studies may be available, individual study estimates of the occurrence rate of clinical
manifestations will be pooled separately by patient ventilatory status when studies with a similar design involving similar patient populations are available. If studies provide overall study-level estimates of the occurrence rate of specific tension pneumothorax clinical manifestations, but do not stratify by respiratory status, then those in which <50% of patients were breathing unassisted will be included in the positive pressure ventilation category during pooled analyses. The pooled estimates obtained from the above calculations will then be compared qualitatively (as odds ratios or risk ratios are unlikely to be available, thus precluding a relative comparison meta-analysis) in order to determine if differences in the type and/or occurrence rate of clinical manifestations appear to exist according to the ventilatory status of the patients. However, where available we also estimate the pooled odds of hypotension and other related clinical manifestations using random-effects models, and will report these estimates rather than the above described non-comparative results.

10. On the other hand, page 21 describes a comparison of subgroups, the suitability and alternative of conventional meta-regressions should be described. It is not clear what the “observational studies” refer to as they seem to be compared to other observational studies.

We have provided greater clarity regarding our methods for the meta-regression of observational study data meta-analysis results. We also defined observational studies as cohort, case-control, and cross-sectional studies under the Review Procedure and the Statistical Analyses subsections. The last paragraph of our Meta-Analysis of Observational Study Data subsection of the Methods now reads:

“We will examine for evidence of between-study statistical heterogeneity by calculating $I^2$ inconsistency and Cochran’s Q statistics (as part of a hypothesis test of heterogeneity) [60,61]. As suggested by Higgins and coworkers [61], we will consider $I^2$ statistics $\geq 25\%$, $50\%$, and $75\%$ to represent low, moderate, and high degrees of inter-study heterogeneity, respectively. In the presence of greater than a low degree of between-study heterogeneity, we will conduct subgroup analyses and univariate meta-regression (p-value $<0.10$ considered significant given the low power of these tests) in order to explore the influence of sources of clinical and methodological study variation on the meta-analysis results. A priori study covariates of interest will include: 1) observational study design (i.e. cohort versus case-control or cross-sectional), 2) use of antihypertensive medications or the presence of pulmonary disease among $\geq 50\%$ of patients who are breathing unassisted, 3) percentage of patients receiving positive pressure ventilation ($\geq 50\%$ versus $<50\%$), and 4) whether the presence of disease was determined using credible criteria that were at least partially independent of the clinical manifestations under study [7,46,47].” (Page 26)

As was outlined in the above paragraph of the Statistical Analyses subsection, meta-analysis and meta-regression will only be conducted on studies of similar design and which enrolled similar patient populations.
11. The imputation of clinical manifestations data, when the clinical manifestations are the primary outcome of the review, should be critically reviewed and the approach should be adapted for secondary data.

Although potentially confounding/modifying and clinical manifestations data may not be underreported in case reports/series for reasons that are completely random (i.e. completely unrelated to characteristics of the described cases), they are likely to be unreported at random among these types of studies (meaning that the probability that a value is unreported may depend on values of variables that were actually missing) [8]. As such, in a sensitivity analysis we will treat unclear/unreported data as missing (where they could not be clarified by writing study authors) and use imputation methods on these data. These results will not form our primary analysis, and will only be used to test whether our observed frequencies of clinical manifestations data were sensitive to the extent of unreported data.

12. The approach to evaluate the body of evidence should be described, i.e. how the strength of evidence across all included studies and study types will be evaluated, given the diversity of eligible study designs.

We have significantly revised the risk of bias assessment section of the methods of the manuscript in response to the above comments from the Reviewer. This section now reads:

“Risk of Bias Assessment:

The same two investigators (D.J.R., C.B.) will determine risk of bias among the included studies. Using the recommendations proposed by Richardson and colleagues, we will evaluate: 1) whether the diagnosis of tension pneumothorax was determined using credible criteria that were at least partially independent of the clinical manifestations under study (by examining if the clinical diagnosis was supported by radiographic findings/response to thoracic decompression and whether overlap existed between the utilized diagnostic criteria (where reported) and the reported frequency of clinical manifestations); 2) whether patients were representative of the population of patients with tension pneumothorax (by evaluating the setting from which study patients were recruited, the methods used to identify/exclude patients, and whether any important subgroups may have been excluded); 3) whether clinical manifestations were sought thoroughly and consistently by the study authors (by determining the methods by which clinical manifestations were gathered, and whether this was done similarly for all patients); and 4) whether the estimates of the frequency of reported clinical manifestations were precise (by evaluating the width of the reported or calculated 95% confidence interval around these estimates) [46]. We will also describe the temporality (prospective versus retrospective) of the included cohort studies as well as whether their patient enrollment method was consecutive versus non-consecutive.
Case reports and series will be evaluated as to whether authors provided absolute numbers rather than narrative or subjective descriptions when reporting the presence or absence of hypotension among patients with a tension pneumothorax [52,53]. Moreover, the adequacy of reporting on confounding/modifying and clinical manifestations data among included case reports/series will be evaluated by recording whether information on these variables was either reported or unclear/not reported (i.e. not specifically mentioned or described as being absent) in the manuscript [52,53]. Finally, we will quantify the extent of unclear/unreported information (as determined by two independent reviewers) among the potentially confounding/modifying and principal outcome variables.

Disagreements in methodological assessments will be resolved by consensus or arbitration by a third investigator (H.T.S.).” (Page 21-22)

13. Minor revisions. The PROSPERO number should not be called “trial registration” in the abstract. The review question should be explicitly stated in the protocol.

We have removed the term “trial registration from the abstract” and now only list the PROSPERO number. We have also added an explicit description of the review question to the protocol. This now reads:

“Structured Clinical Question:
Is the reported type and/or frequency of clinical manifestations of tension pneumothorax different among adults/adolescents (≥12 years old) or children (<12 years old) who are receiving positive pressure ventilation as compared to those that are breathing unassisted (i.e. spontaneously breathing and not receiving positive pressure ventilation)?” (Page 14)

Thank you once again for the kind and thoughtful reviews of our manuscript. The comments and suggestions have significantly improved our manuscript and are greatly appreciated. We hope that you will find this version suitable for publication in Systematic Reviews, and look forward to your response.

Sincerely,

Derek J. Roberts, MD and H. Thomas Stelfox, MD, PhD
References


