Response to Reviewers

Editors

1. Thank you for your work in revising your paper, and patience while we have sent it back out for review and discussed it among the editorial team. Editors feel it sets out an important and interesting issue, and is a valuable addition to our previously published articles on too much medicine.

2. Editors are still not convinced that the manuscript fits the typical overdiagnosis structure. Again we wonder whether it would be more appropriate to publish the paper as part of our Too Much Medicine collection but without the constraints of the overdiagnosis format. I would be happy to discuss this further with you.

Response: We are grateful to the editors for considering our work for publication. We have modified the manuscript to fit in the Too Much Medicine collection without the overdiagnosis series format. As discussed we have trimmed the word count to around 2500 and have reformatted the manuscript with a different flow and section titles. We believe this new version still very much reflects our belief that there is evidence in the literature for overdiagnosis of hypoxemia in infants with bronchiolitis that has led to a shift in practice which may not be entirely beneficial to patients. Thank you again for considering our work and we hope that this new version is satisfactory.

Reviewer 1

Overall this revision has better balance. Some of the remaining possibly better reflects my perspective on the topic and the authors may wish to present alternative perspectives to this review.

Response: We thank the reviewer for his thoughtful and thorough review and believe his input has been invaluable to make our review more balanced.

1. Summary Box

Diagnostic change – ‘accurate’; the tenet of much of this commentary is that pulse oximetry is not accurate. The ability of oxygen saturation to estimate partial pressure of oxygen in blood is limited by a range of factors in both patients and machines (algorithms in particular). It may be more precise to say that oxygen saturation monitors provide a rapid and readily understood estimate of hypoxaemia. Leap of faith: The leap of faith for many is that untreated borderline hypoxaemia will not lead to (subtle) neurocognitive deficit for that child. This concern is prescient in the decision making of many clinicians working with children with bronchiolitis – it therefore should be addressed here.

Response: We thank the reviewer for these suggestions, however the summary box has been deleted from this version of the manuscript given the new format suggested by the editors and accepted by the authors.
2. Reduction in mortality.
Commentators repeatedly note that mortality for bronchiolitis has not changed in the last 3 decades at a time when admission to hospital have increased, and conclude that admissions are in excess and not caused by increased disease severity.
It is equally arguable from current data, that the lack of change in mortality for bronchiolitis over the observed period may be associated with worse disease (and therefore increased admission), but a greater capacity of PICU to retain mortality at a steady state. There has been reduction in mortality for a range of paediatric conditions managed in intensive care over the last three decades because of improvement in paediatric intensive care.

Response: We thank the reviewer for these observations. We know of no data to suggest RSV or bronchiolitis severity in general has increased over time in fact we referenced data suggesting there has not been a difference in severity that correlates to the nearly 300% rise in admission rates. See page 4 in the introduction:

“Different strains of respiratory syncytial virus (RSV), the most common agent responsible for bronchiolitis, contribute to differences in disease severity." However, the trends in temporal variations for individual RSV strains have no direct correlation with a noted significant increase in hospitalization rates for bronchiolitis. While we agree that mortality may be unaffected due to improvement in ICU care, we would expect some indication that disease severity over time would explain such impressive increase in hospitalization rates.

Limitations
It may be more helpful to say that medium term, dominantly healthcare benefits, have been addressed in studies, though as secondary outcomes they are underpowered. Longer term effects of borderline hypoxaemia remain controversial, but have not yet been addressed in infants with bronchiolitis.

Response: We have reworded some of the discussion to addresses the reviewer’s input the new sentence now reads:

“While no investigations in bronchiolitis, to our knowledge, have been able to demonstrate a measurable benefit to increased pulse oximetry use in short or medium term outcomes, such as preventing escalation of care, re-presentation, or mortality, most studies are underpowered to detect small differences in these uncommon, but important end points.”

We do discuss long term outcomes later in the piece:

“....there may be potential long term cognitive benefits of detecting and treating episodes of mild hypoxemia, an outcome that has not been rigorously evaluated.”

3. Background, Page 4 line 14. The authors present possibly the most important consideration for the use of pulse oximetry, but do not develop this adequately within the remaining text (there is some
discussion on page 11, but it should be expanded). Context, is all important for interpreting pulse oxygen saturation information. A key tension in considerations of borderline hypoxaemia is how clinicians (particularly those less experienced) will adequately judge acute phase of illness (with potential as described for displacement of the oxygen dissociation curve and greater risk for hypoxaemia) with a convalescent phase. A recurring concern is that knowledge of oxygen saturation provides a safety net for inexperience within this judgement zone. The authors need to either consider convalescence as not important, rather judgement of disease severity and safety netting for medical review if an infant is less well more important, or that considerations for borderline hypoxaemia should restrict themselves to infants who are demonstrating themselves to be within a convalescent phase of illness.

Response: We thank the reviewer for this observation. We believe he is referring to our discussion about the ubiquity of pulse oximetry and that it has become “the fifth vital sign”. Given the new format of the paper and the more restrictive word limit we have not expanded on the discussion as suggested. We agree that pulse oximetry offers a safety net for less experienced clinicians. However, we also believe that it has also led to overdependence for even seasoned clinicians, as has been demonstrated by the literature of the influence of pulse oximetry for admission. In the Schu RCT, for example, experienced ER physicians were reassured by higher oxygen concentration, as shown by decreased rate of admission, despite all oxygen concentrations being at or above the 90% threshold.

4. Background Page 4 Line 51. Reference 13 does not report morbidity, only mortality. Please provide a reference to support the statement re: morbidity, or remove.

Response: Thank you to the reviewer for pointing this out we have removed the word “morbidity”

5. Evidence for overdiagnosis
Page 6, Line 23: It is not correct to say that BIDS increased displayed values by 4% to a maximum of 100%. BIDS oximeters had altered algorithms for oxygen saturation above 85%, such that a true oxygen saturation of 90% would display at 94% (over the whole range, the difference in SpO2 was c2% between groups).

Response: We thank the reviewer for this clarification. We have simplified the statement to be more precise, it now reads:

“The Bronchiolitis of Infancy Discharge Study (BIDS) randomized 615 infants hospitalized with bronchiolitis to monitoring with either a standard pulse oximeter or one that had been modified with altered algorithms.22 The oxygen saturation threshold for initiating or weaning oxygen was 94%, which represented a saturation of 94% in the true oximetry arm and 90% in the modified oximetry arm.”

6. How to do Better
Page 10, Line 56. Please define ‘stable’. Clinician perspectives on this are the key to differential management of infants with bronchiolitis.
Response: We agree this term is vague. We have changed the word stable to “non-critically ill” to better reflect the patients we are addressing with this statement.

7. Page 11. Line 47. I’m not sure that hypoxaemia can be redefined. It is a physiological measure defined by normality. It is not normal to be hypoxaemic. What could be redefined is the clinical tolerance level to hypoxemia during disease.

Response: In this revision we have deleted that part of the discussion to better fit the word limit. We believe the rest of the discussion precisely addresses the issue of tolerance of different oxygen concentration limits as described by the reviewer.

8. Page 11. Line 52. It would have been great had BIDS demonstrated better outcomes – but it did not. The improvements were post hoc analyses that were not powered, as such they do not demonstrate, but suggest better outcomes for infants managed at lower oxygen saturation targets.

Response: We thank the reviewer for pointing this out. In this review we considered decreased LOS as an “outcome” for which BIDS demonstrated a statistically significant decrease. However as suggested by the reviewer we changed the discussion in that area of the discussion so as to better describe all of the outcomes measured. That section now reads:

"Cunningham et al’s work has demonstrated this threshold is safe and suggests better outcomes than higher targets."

9. Page 11. Line 55. The discussion doesn’t adequately differentiate for the reader the consideration of baseline oxygen saturation values (i.e. the median value over a period of time) versus intermittent self-resolving desaturation. BIDS, McCulloch etc attempt to focus clinicians on baseline oxygen saturation and to understand, but limit responses to minor self-resolving desaturation. The effects of minor self-resolving desaturation are probably of little relevance in otherwise healthy children. A low baseline over a period of days within a borderline hypoxaemic appears safe from a short and medium term health and societal basis, but longer term aspects on cognitive function are not assessed (and the authors may suggest do not need to be assessed, but parents may think otherwise).

Response: We thank the reviewer for this viewpoint and we agree. We have pointed out in the “Limitations of the evidence” section that indeed “....there may be potential long term cognitive benefits of detecting and treating episodes of mild hypoxemia, an outcome that has not been rigorously evaluated.”

To be less assertive we have modified the sentenced pointed out by the reviewer to not make any mention of outcomes it now simply reads:

“However, given that oxygen desaturations to well below 90% are common in infants with bronchiolitis, even this lower target may result in substantial overdiagnosis of hypoxemia.”

10. Page 12, Line 3 (and Table). NICE Bronchiolitis does have thresholds for respiratory rate and temperature at which clinicians are requested to consider actions.
Response: This version of the manuscript has omitted the section mentioned by the reviewer.

Reviewer 2

Hello, I would like to congratulate the authors for a job well done on a topic which badly needs addressing. The authors have done an admirable job summarizing the relevant literature and outlining the rationale as to why we need to question certain accepted dubious dogmas about oximetry. I especially like the recommendation that perhaps there should be no specific oximetry threshold: hospitalization should be dictated clinically, irrespective of oximetry.

An excellent first step to re-examine our steps toward retrofitting our use and interpretation of oximetry.

Please re-read the manuscript: there are several words merged into one.

Response: We thank the reviewer for her thoughtful review of our work and kind words. We have thoroughly re-reviewed the manuscript and corrected any errors we came across.