Body: 29-Oct-2016

Dear Dr. Quinonez

# BMJ.2016.034392 entitled "BMJ: Too Much Medicine

Title: When Technology Creates Disease: pulse oximetry and the search for hypoxemia in bronchiolitis"

Thank you for sending us your article, which we read with interest, and for your patience while we have been considering it.

We think your paper covers an important and original topic and we would like to work with you towards publishing the article if you are able to amend it in the light of our and reviewers' comments.

The reviewers' comments are at the end of this letter.

The editors' comments are listed below:

1) Editors felt that this is a great topic but were not sure if it should form part of the overdiagnosis series. It is a contribution that relates to too much medicine but the problem is not overdiagnosis per se; the issue is over monitoring (of sats) leading to over treatment (with O2 and admission). To make a good contribution to the series, the article really ought to focus on diagnosis but we were not convinced that it is the diagnostic label of bronchiolitis which is the problem here. Might it better to focus on hospitalization rather than bronchiolitis?

2) If you agree, one option would be to liberate the article from the shackles of the series, which means that
the argument can develop without the constraints of the overdiagnosis article format. As an Analysis article the paper could make the case that we admitting and treating too many children with bronchiolitis and low o2 levels

3) We also wondered if this scenario of reliance on pulse oximetry is true of other respiratory conditions in children - viral-induced wheeze, croup for example? It might be worth a brief mention.

4) How strong is the evidence? You mention the three RCTs - we thought these could be more clearly described in the paper. Has there been any meta-analyses in this area, or are there plans MA the RCT evidence?

5) How did oximeter use become widespread - was it a case of the technology being available for people to use or did the guidelines initially suggest targeting treatment to a particular level?

6) On the subject of guidelines: What lead to the guidelines recommending those particular cut-offs? And why the variation between different guidelines and different conditions? (Also the pneumonia and asthma guidelines you refer to are from BTS/SIGN and BTS respectively)

7) Under evidence of harm: "A prospective study of children admitted for bronchiolitis found that preventable adverse events during hospitalization can occur in as many as 10 per 100 admissions" - might you elaborate on what kind of harm?

8) Are you aware of any patient/parent perspectives on this topic?

9) Depending on the level of evidence available to back a
change in practice, we could also consider an Education article on this topic. If the evidence is clear then a 'Change Page' article is one possibility http://www.bmj.com/specialties/change-page. A softer call would be an Uncertainties article (http://www.bmj.com/specialties/uncertainties-page).

When submitting your revised manuscript please provide a point by point response to our comments and those of any reviewers.

Please note that resubmitting your manuscript does not guarantee eventual acceptance, and that your resubmission may be sent again for review.

Once you have revised your manuscript, go to https://mc.manuscriptcentral.com/bmj and login to your Author Center. Click on "Manuscripts with Decisions," and then click on "Create a Resubmission" located next to the manuscript number. Then, follow the steps for resubmitting your manuscript.

You may also click the below link to start the resubmission process (or continue the process if you have already started your revision) for your manuscript. If you use the below link you will not be required to login to ScholarOne Manuscripts.

https://mc.manuscriptcentral.com/bmj?URL_MASK=adb5447e82d3478fb48e9bbec4f92df9

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

I hope you will find the comments useful. Please don't hesitate to contact me if you wish to discuss this further.

Thank you again for all your hard work on the article and please accept my apologies for the delay in the editorial
process.

Yours sincerely

Navjoyt Ladher
nladher@bmj.com

**IMPORTANT INFORMATION TO INCLUDE IN A RESUBMISSION**

Instead of returning a signed licence or competing interest form, we require all authors to insert the following statements into the text version of their manuscript:

**Licence for Publication**
The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd to permit this article (if accepted) to be published in BMJ and any other BMJPGL products and sublicences such use and exploit all subsidiary rights, as set out in our licence (http://group.bmj.com/products/journals/instructions-for-authors/licence-forms).

**Competing Interest**
Please see our policy and the unified Competing Interests form http://resources.bmj.com/bmj/authors/editorial-policies/competing-interests. Please state any competing interests if they exist, or make a no competing interests declaration.

Reviewer(s)' Comments to Author:

Reviewer: 1

Recommendation:

Comments:

Title: When Technology Creates Disease: pulse oximetry
and the search for hypoxemia in bronchiolitis
Reviewer Steve Cunningham

The authors provide a perspective on the development and integration of pulse oximetry into routine clinical practice and the impact on clinical decision making in the diagnosis and management of bronchiolitis. This is a comprehensive and thoughtful review of this field.

From my ‘perspective’ however I would hope that the subject could be better balanced in a number of areas with more detail provided.

Title:
I wouldn’t agree that pulse oximetry as a technology has created disease. Overall, pulse oximetry has been of benefit to the management of children with bronchiolitis. I would place better equipoise to the arguments for and against the use of pulse oximetry in bronchiolitis, and better identify where there is lack of evidence rather than evidence of lack of benefit. Whilst pulse saturation oximetry has not created disease, it is creating clinical uncertainty – and that needs to be tackled.

Specific points:

Summary Box
Rationale for change: Whilst the sentence could be considered correct, it would be better reworded to reflect the fact that routine clinical examination would detect hypoxemia below c85% oxygen saturation. The principle discussion is with regard to the clinical effect of saturation values between clinical cyanosis and normoxia.
Leap of faith: I would not consider this a leap of faith – there is very good evidence that detection of hypoxemia is important to prevent clinical deterioration and negative neurologic sequelae. The question is more nuanced and relates to the clinically opaque zone where someone is not cyanosed, but also not normoxic.
Conclusion: Lack of evidence is not evidence of no benefit. There should be adequate clinical trials to support restricted use of pulse oximetry in acute lower respiratory tract disease. It is quite possible that outcomes are better than they were 30 years ago
(excluding deaths - surely is an outcome of extreme), we possibly haven’t measured outcomes appropriately.

Defining Hypoxemia.
I would like to see a more balanced perspective on behalf of patient safety. Imperative within a ‘re-education’ of clinicians on the use of pulse oximetry is the need to aid understanding of oxygen saturation in health and disease. The oxygen dissociation curve is not static, and in disease where they may be a raised CO2 and lower pH then a higher threshold for oxygen saturation is required. The authors should present this dynamic relationship, as this dynamism is of vital importance when using pulse oximetry as a clinical tool; a child that is adequately perfused and looks well will tolerate lower oxygen saturation that a child who is clinically dry and in early respiratory failure. There isn’t a one size fits all – I understand that is key to the message being presented in this perspective – but it requires education that it isn’t sufficient to simply push down the limits of oxygen saturation without understanding patient risk.

Overdiagnosis
The authors could make clearer what overdiagnosis relates to – I interpreted this as bronchiolitis – whereas I understand the intention would be for overdiagnosis of hypoxemia. Bronchiolitis is a clinical diagnosis that does not require a knowledge of oxygen saturation to make the diagnosis and a normal oxygen saturation does not preclude the diagnosis. It should not be suggested in the article that bronchiolitis is being overdiagnosed by the additional use of pulse oximetry. There is good evidence that bronchiolitis is underdiagnosed in most primary care settings. ‘Overdiagnosis’ –seems a clumsy term in this setting, especially for borderline hypoxemia.

Randomized controlled trials
The studies by Schuh and Cunningham used different algorithm strategies. In Schuh the oximeter was artificially increased by absolute 3% (for triage true values above 88%). For Cunningham the oximeter was artificially increased to a maximum of 4% at all values above 85%.
Evidence of Harm
The assessment of the evidence base could be more critical. For example, in the Schuh study whilst there was a higher rate of admission in those in the routine oximetry arm compared with the modified arm, the number of patients within this study that fell within the borderline hypoxemia group was very small – possibly reflecting the single site setting and change in protocol during the study to assess at a triage of 88% rather than initial 90%. Only 17 infants in the study had an oxygen saturation <92% at triage, with only 11 infants <90% SpO2 across both groups. The Schuh study appears to demonstrate that providing ED physicians with ‘hyper’normal SpO2 boosts confidence to discharge, but is limited in its ability to inform the discussion of this manuscript, i.e. borderline hypoxemia. Clearly there could be critical assessment of BIDS too with regard to this topic!
Reference to other uses of oxygen in respiratory conditions could support the discussion on risk/benefit for oxygen targets. BOOST II was associated with increased deaths in preterm infants when the difference in their oxygen saturation over time was just 3% (89% vs 92%) (Stenson NEJM 2013). In children with lower respiratory tract infection, deaths were reduced when children were provided with oxygen supplementation for an oxygen saturation below 90% oxygen (Duke Lancet 2008). These may not be studies in bronchiolitis – but they are studies of oxygen in children and as such a component of the discussion on risks and benefits.
How to do better
There are important lessons to provide to clinicians about the sensible, safe and effective use of pulse oximetry. It is a clinical tool, not a decision tool. The authors should rephrase use of the word hypoxemia as this message could be confused by clinicians – borderline hypoxemia or something similar could be more appropriate. NCT01646606 is a pilot trial that has completed and recruited just 33 patients: it is unlikely to provide an answer to the question posed, but may inform a larger multicenter study.
Lacking within all this are the perspective of parents as to what they would consider possibly acceptable risks and benefits from challenging current oxygen saturation
target strategies. The SUPPORT trial (NEJM 2013) was criticized for moving forward with trial outcomes that were of significant potential detriment to patients, without adequate understanding of how trial participants (parents) would view these risks. I don’t think these perspectives are available from parents for bronchiolitis – but it would be really helpful that this was acknowledged within the perspective.

Conclusion
As above I would not agree that there has been technological creation of disease - the child has bronchiolitis. There may be an over reliance on pulse oximetry as a decision tool, and that should be appropriately evaluated.

Additional Questions:
Please enter your name: Steve Cunningham
Job Title: Consultant & Honorary Professor in Paediatric Respiratory Medicine
Institution: NHS Lothian & University of Edinburgh
Reimbursement for attending a symposium?: Yes
A fee for speaking?: No
A fee for organising education?: No
Funds for research?: No
Funds for a member of staff?: No
Fees for consulting?: Yes
Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No
Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No
If you have any competing interests (<A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'>please see BMJ policy</a>) please declare them here: Consultancy and attendance at Symposium by Ablynx Pharmaceuticals as Chief Investigator for ALX0171 RSV treatment. Fees paid to NHS Lothian.

Reviewer: 2

Recommendation:

Comments:
This is the most comprehensive review to date examining the impact of routine measurement of oxygen saturation in infants with bronchiolitis on hospitalization and potential complications related to hospitalization and overuse of supplemental oxygen. The authors have wisely divided the available evidence into a) evidence for over-diagnosis of hypoxemia: RCTs affecting diagnosis of hypoxemia, missed diagnosis of hypoxemia without detectable patient harm, and increasing detection of hypoxemia without clinical impact and b) real and perceived limitations of evidence to date and c) evidence of harm related to the impact of overuse of oximetry. They conclude that routine use of oximetry in bronchiolitis has led to an increase in hospitalizations without any evidence of improved outcomes.

The authors are to be commended for this excellent job. The literature review is very complete, up to date and performed in a critical manner. The paper summarizes the evidence for growing suspicion of many clinicians that oximetry can act both as a falsely reassuring factor when an infant is sick and contribute to admitting otherwise well children due to a perceived need for supplemental oxygen.

The Table with the challenging assumptions is particularly interesting. I wonder if the authors want to include more specific thoughts about how to overcome these assumptions? As long as people believe that a
saturation below 90% adversely affects infants' brains, we shall have a problem with translating this evidence! Any specific thoughts on how to proceed next?

Congratulations on this excellent work!

Additional Questions:
Please enter your name: Suzanne Schuh

Job Title: Emergency Staff Pediatrician and Senior Associate Scientist

Institution: The Hospital for Sick Children

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <a href='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'>please see BMJ policy</a> please declare them here:

Date Sent: 29-Oct-2016