Author’s response to reviews

Title: Utility and feasibility of integrating pulse oximetry into the routine assessment of young infants at primary care clinics in Karachi, Pakistan: a cross-sectional study

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Author’s response to reviews: see over
Dear Dr Shally Awasthi

**Re: Utility and feasibility of integrating pulse oximetry into the routine assessment of young infants at primary care clinics in Karachi, Pakistan: a cross-sectional study**

We have provided an itemized response to reviewers’ comments, which we believe strengthen the enclosed manuscript. We thank the reviewers for their insightful comments and hope that we have responded to them adequately.

Thank you for your consideration of the manuscript, and we look forward to hearing from you.

Yours sincerely,

Connor Emdin                 Daniel Roth

Response to revisions
Reviewer: Walter Karlen  
Reviewer's report:

Discretionary Revisions

1) P6 methods: A CHW and a research assistant consisted of a study team. From the given descriptions, it was not clear to me what the roles of each were. From the procedures in P7, it seems like the CHW did everything, including interviews? Could you summarize their functions at the beginning of the paragraph?

RESPONSE: A study worker performed the IMCI evaluation, pulse oximetry and interviewed the participating infants’ caregivers. The LHW (a member of the clinical staff) was only involved in initially evaluating the infants’ clinical status and reason for visit (in case they needed to be rapidly referred to the hospital). The following sentences have been added to clarify this and provide a description of the workers’ training (line 115):

“Study procedures were performed by a pair of study personnel – a study worker and a research assistant. Each clinic site was served by a core team of two study workers and one research assistant. Less than 2% of the visits involved other trained personnel substituting for a core team member. ‘Study workers’ refer to the four personnel (two at each clinic) who directly assessed infants according to the IMCI algorithm, performed pulse oximetry and conducted the initial infant caregiver interview. These individuals had secondary school education and prior experience in health research projects involving infants and children, but they did not have professional research or health care credentials. We considered their level of training/experience to be similar to that of a CHW. ‘Research assistants’ (one at each clinic) coordinated study activities, observed study workers to record data related to timing of pulse oximetry, and conducted an exit interview with caregivers. Research assistants had post-secondary education and had long-standing professional involvement in research as employees of Aga Khan University. All personnel were trained in formal sessions as well as a pilot implementation phase. None of the team members had used a pulse oximeter prior to this training/pilot period.”

2) P10L212: WHO is abbreviated earlier and then not used

RESPONSE: World Health Organization has now been replaced with WHO after the first usage.

3) Figure1: Please add more ticks to axes for easier reading.

RESPONSE: More ticks to both axes have been added.

4) Figure 1: The application time of oximeter is shown as flat line after 0 s and 60 s. Is there an explanation that application takes much longer at the second attempt?

RESPONSE: This figure suggests that the likelihood of acquiring a successful reading declines with increasing time, that is, if a reading cannot be acquired during the first attempt, it’s not likely to be acquired on the second attempt. The most likely explanation is that the subset of infants for whom a successful reading could not be rapidly acquired (e.g., motion artifacts) were less likely to have rapid successful readings on their second attempts compared to the rest of the study population.

Minor Essential Revisions

5) P4L69: “PO is an accurate, yet non-invasive method ...”. In fact, PO is not particularly accurate in estimating SaO2 and many devices have RMS errors of +- 2 %.
However, this is considered as clinically acceptable, considering it is non-invasive.

RESPONSE: The word “accurate” was removed from the sentence (line 68) in question: “Pulse oximetry (PO) is an non-invasive method of measuring peripheral oxygen saturation (SpO2) based on the differential absorption of red versus infrared light by oxygenated hemoglobin in a narrow tissue segment (e.g. infant’s hand or foot).”

6) P4L70: “measuring oxygen saturation (SpO2) based ...”. A PO measures peripheral oxygen saturation (SpO2) and not arterial oxygen saturation (SaO2), which is measured invasively. SpO2 is an estimation of SaO2 and often used interchangeably (by mistake) in clinical practice. Since both terms are used later it would be better to be accurate when introducing the term.

RESPONSE: “Arterial” has been replaced with “peripheral” (see response above)

7) P17L369: The authors report significant differences between clinic sites. It would be helpful if authors could report in results the number and demographics of CHW that performed the measurements. What training did they receive? Experience with oximetry? How would this be different from LHW?

RESPONSE: To clarify, the LHW was not involved directly in the study, but only screened the infant upon arrival to the clinic as per normal study procedures. We have added a paragraph to detail the study workers’ training to the methods section (line 115, see response to query #1).

8) Figure 2: This figure is very interesting. The distribution of SpO2 is unexpected. When breathing room air and in healthy conditions, the expected SaO2 is around 98%. Higher values are only achievable through administration of O2. The shown distribution would suggest that there is a bias and/or error of at least 2% in the used measurement device.

RESPONSE: We have added the following sentence to the discussion (line 438): “Indeed, the most common SpO2 observed in this study was 100%, greater than the median 97% commonly observed at sea level in well neonates.”

Also, very few subjects actually had low SpO2. Recognizing this sensor bias, would more patients be included in the hypoxemia group?

RESPONSE: The study was not designed to test the accuracy of the Sp02 measurements, and thus our response to this question could only be based on speculation. However, we utilized a definition of an SpO2 of 92%, rather than the traditional 90%, which would, in part, account for the sensor bias described above.

Major Compulsory Revisions

9) P6 Study setting. As normal SpO2 and hypoxic thresholds are dependent on elevation, please provide altitude of sites in Karachi (sealevel I beleive). It would also be worthwhile to mention this limitation/particularity in the discussion eg. in P16

RESPONSE: The following sentence has been added to the methods (line 112): “Both sites are approximately located at sea level.”

The following sentence has been modified in the discussion (line 354): “Studies in low-income settings have documented SpO2<90% in about one-fifth of hospitalized newborns (irrespective of specific diagnosis), suggesting a higher burden of hypoxemia
in this group than among older children with pneumonia, although thresholds for hypoxemia vary by altitude.\(^1\)

10) P8L148: An “acceptable” or successful measurement was defined as 10 sec of stable SpO2, presence of HR, and green signal strength. Why was 10 sec as window chosen? Why did SpO2 needed to be stable? The error range of the used device is larger than the allowed variation of \(\pm 1\%\). This condition might have been too restrictive? To obtain a reliable SpO2 reading a stable signal quality would be more important. Also, if only green signal strengths were accepted, subjects with low perfusion would have been excluded? Low perfusion can be a sign for bad sensor placement, but also disease. A little more critical discussion of the study design might help future studies selecting an appropriate design.

RESPONSE: The choice for the SpO2 to be stable was based on instructions from the pulse oximetry device manufacturers, who recommended stability as a requirement for a successful measurement and to demonstrate that the displayed SpO2 is not a motion artifact. The following sentence has been added to the discussion (line 441): “Furthermore, the criteria used in this study to define an acceptable Sp02 (including a stable reading with variation within \(\pm 1\%\) over 10 seconds) were intended to standardize the procedure in a manner that could be feasibly adopted in routine practice; however, the criteria may have been too restrictive (e.g., excluded readings that were clinically meaningful) and likely included some readings that were unreliable (i.e., met criteria despite an inconsistent underlying waveform). Validation of device-specific ‘acceptability criteria’ for field applications should be a priority of future research.”

11) P9L176: The authors have made measurements with competing PO device technology, but state that this data has been excluded from the analysis for good reason. However, in the results section, this data is reported and compared, suggesting somewhat superior performance of the main study sensor. This should be avoided. Please remove all comparisons of other devices not tested rigorously.

RESPONSE: We have removed all references to comparison devices in the results/discussion section.

Reviewer: Shamim A Qazi

Reviewer’s report:

Specific Comments – Minor essential revisions

1. In several places the authors have used the term WHO/UNICEF IMNCI. WHO-UNICEF use the term Integrated Management of Childhood Illness (IMCI) and not ‘IMNCI’, which is occasionally used in some country adaptations. It would be good to give an appropriate reference of IMCI in the manuscript. Authors refer to reference 3 and 12 when alluding to IMCI, but these are not appropriate references for IMCI.

RESPONSE: IMNCI has been replaced with IMCI through out the manuscript. Reference number 12 has been replaced with a reference to the technical basis of the WHO/UNICEF IMCI algorithm, we have left reference 3 in place as it represents the validation and development of the seven sign IMCI algorithm.

2. Authors use interchangeably various terms such as ‘primary care’, ‘primary healthcare’, ‘first-level clinics’, ‘first-level health facility’, ‘primary health clinic’, or ‘primary care clinics’. It would be better to use one term instead of using so many different
terms, because it confuses the reader. In different countries the perception of these terms may be different. I suggest that they should exactly define the facility that was used and then use that specific term throughout the manuscript.

RESPONSE: The term “primary care clinic” is now consistently used throughout the revised manuscript, including the title. We have added a description to the methods section to define the services provided at the primary care clinics (line 106):

“Both clinics provide well-child care (vaccination, growth monitoring, nutrition and hygiene education) and outpatient care for common childhood illnesses. A team of community health workers add outreach capacity through regular visits to households to detect early symptoms of illness such as newborn sepsis, and refer ill infants to these clinics for physician assessment. Seriously ill infants and children are provided transport to hospital or in case of refusal, centre-based parenteral antibiotic therapy (if indicated).”

3. Similarly, authors also use interchangeably various terms such as ‘first-level health care providers’, ‘first-level workers’, or ‘first-level personnel (i.e., community health workers)’. It would be better to use one term instead of using so many different terms, because it confuses the reader. In different countries the perception of these workers may be different. First, training of community health workers (CHW) may vary from 5 days up to two years depending upon the country/region. Second, the placement of CHW may vary from a small hamlet, a village to a static health post covering a population of around 5000 – 6000 or a clinic setting described in this study. Third, the education level may vary from illiterate to 6-10 grades of education. Finally, a CHW remuneration may vary from a volunteer with some form of incentive to a fixed salary. I suggest that they should exactly define the type of CHW (training, placement, education, salaried/volunteer etc.) and then use that specific term throughout the manuscript.

RESPONSE: All references now refer to “study worker”. We have added a paragraph to the methods section clarify the roles of the study worker (line 115, see query #1 for reviewer #1 for the paragraph).

4. Procedures: line 134: Do the authors mean LHV here instead of LHW, which may mean a lay health worker of a lady health worker?

RESPONSE: Lady Health Workers (LHWs) are a specific cadre of healthcare workers in Pakistan.² The Aga Khan University informally refer to research study personnel with some clinical training (midwifery/nursing/phlebotomy) as LHWs. The LHW was not involved directly in our study; they were only involved in the initial screening procedure of the infant upon presentation to the clinic, as with routine clinic procedures.

5. Procedures: line 139: Specify here the worker who conducted the IMCI assessment. Was it CHW or LHV?

RESPONSE: The study worker conducted the IMCI, this is referred to explicitly in (new) line 153. We have also modified this sentence, now line 160, to make this explicit:

“Following the IMCI assessment, conducted by a study worker...”

6. Procedures: line 155-157: Is this statement correct? Later authors mention referring to the physician based in this study clinic (line 164-166).

RESPONSE: This statement is correct, the study worker conducted an examination of the
infant using IMCI criteria first, the physician examined the infant after the study worker conducted an IMCI examination and pulse oximetry.

7. Outcome measures: line 210-215: There is no need to give this explanation as it was neither done, nor was it the primary outcome.

RESPONSE: Although we agree that these measures are not the primary outcome, we do think that it is important to include these sentences because they provide the readers with the analysis that we originally planned in our protocol and justify our secondary analysis that is presented in the paper.

8. Outcome measures: line 215-218: No reference is given for the statement in parenthesis. WHO recommends the use of <90% SpO2 for defining hypoxemia (reference 12). If the clinical assessment is being conducted using WHO-UNICEF IMCI tool then for consistency sake the authors should use <90% cut-off recommended in reference 12. Please also see a statement using this cut-off of <90% SpO2 (reference 18) in discussion (line 337-340). It is suggested that table 4 should be revised accordingly.

RESPONSE: We believe Table 4 is more informative by including a larger subgroup of children who may meet criteria for hypoxemia. The use of Spo2 <92% is justified because it is commonly used in clinical pediatric practice, has been associated with worse outcomes among infants and children in a number of cohort studies and has been provided as a threshold to guide provision of supplemental oxygen therapy at sea level.

9. Results: line 253-256: A difference is alluded to between first and second visits but figure 1 shows only cumulative data.

RESPONSE: The difference between first and second attempts can be seen on Figure 1 – the proportion of successful attempts during the first sixty seconds (the first attempt) increases rapidly over the minute. However, after the first attempt, the proportion of successful attempts increases slowly.

10. Discussion: line 355-360: This statement based on an anecdotal account is not suitable here and should be removed, particularly in light of the study results.

RESPONSE: Statement has been removed.

11. Discussion: line 360-364: IMCI is not generally used by CHWs, who use integrated community case management (iCCM), which currently does not contain management of sick young infants. Are the authors referring to IMCI or iCCM because they used CHWs in this study?

RESPONSE: We are referring to IMCI assessment.

12. Discussion: line 400: What program?

RESPONSE: Sentence has been modified to clarify that we refer to a hypothetical health system (line 412):

“The clinical effectiveness of routine or targeted PO in this setting would depend on the specific adverse outcomes that the health system in which PO is being undertaken is able to avert.”

13. Discussion: line 408-413: In light of the above mentioned comment 3, this
statement be revised and made more specific to the study setting, which may not be
generalizable to most CHWs settings.

RESPONSE: We highlight this limitation in line 424:

“Pulse oximeters were used by personnel who had a similar professional background
and prior experience as community health workers; yet, because study staff had
substantial opportunities for training and practice, and were highly motivated
throughout the study, they may not be representative of health care workers who would
implement routine pulse oximetry outside of a research context.”

14. Discussion: line 413-420: Is it really expected in routine practice in low resource
settings that plethysmographic waveforms be evaluated?

RESPONSE: Sentence has been modified to reflect this concern (line 434):

“Although we used a device that employs a motion-resistant algorithm that has been
validated and widely implemented in neonatology7,8, it is optimal if operators confirm
regular rhythms by monitoring plethysmographic waveforms9, which would likely not be
feasible in routine clinical practice.”

15. Discussion: line 420-424: Is this clinically relevant? The text from 413-424 is a
rather an academic argument, which is not relevant for this kind of setting.

RESPONSE: We feel that it is clinically relevant to briefly discuss the issue of the
sensitivity/specificity of PO for detecting true hypoxemia; at scale, inaccuracy could have
large implications for the feasibility and efficiency of a pulse oximetry screening program;
e.g., if a device systematically overestimates SpO2, some infants who are hypoxemic may
not be referred to secondary care.

16. Discussion: line 435-437: This issue is mentioned only as ‘suggested to be’ linked
to a reference, whereas it is a reality in most low resource settings. Within this study
what was the cost of equipment, maintenance and disposable sensors even though it
was done in a research setting? This is a more realistic limitation in this low resource
than the two limitations mentioned above in comments 13 and 14.

RESPONSE: We do not feel that the specific costs of our supplies for a short-term study
would be relevant to the true implementation cost. However, we acknowledge that cost is an
important constraint, so we have edited the sentence in question (line 459): “In addition to
the initial cost of the devices, the high cost of repair and replacement of minor
components, such as sensors and cables, is likely to be an important barrier to PO
implementation in developing countries.”

17. Authors make a point of ‘statistical difference’ between the two study sites (Table
1 and Table 2), and conducted a stratified analysis, but I could not find any discussion
about why the two sites were so different? What could be potential reasons?

RESPONSE: Our analysis investigated the between-clinic differences to account for
confounding by site and study worker team in our analyses of the association between infant
factors and PO performance. Determining the reasons for the site differences was not a
focus of the study. However, a likely reason for the observed differences in performance time
and infant characteristics between sites is that Bhains Colony is a more affluent area
(primarily cattle owners/sellers) in comparison to Bilal Colony (primarily daily wagers). It is
also possible that unmeasured characteristics of study workers, infants or site facilities (such
as organizational factors) differed by site or that study factors, such as the implementation of pulse oximetry by study personnel, differed systematically between sites.

References


