Defining hypoxemia from pulse oximeter measurements of oxygen saturation in well children at low altitude in Bangladesh: an observational study

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NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
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Abstract

Background: The World Health Organization defines hypoxemia, a low peripheral oxyhemoglobin saturation (SpO$_2$), as <90%. Although hypoxemia is an important risk factor for mortality of children with respiratory infections, the optimal SpO$_2$ threshold for defining hypoxemia is uncertain in low-income and middle-income countries (LMICs). We derived a SpO$_2$ threshold for hypoxemia from well children in Bangladesh residing at low altitude.

Methods: We prospectively enrolled well, 3-35 month old children participating in a pneumococcal vaccine evaluation in Sylhet district, Bangladesh between June and August 2017. Trained health workers conducting community surveillance measured the SpO$_2$ of children using a Masimo Rad-5® pulse oximeter with a wrap sensor. We used standard summary statistics to evaluate the SpO$_2$ distribution, including whether the distribution differed by age or sex. We considered the 2.5$^{th}$, 5$^{th}$, and 10$^{th}$ percentiles of SpO$_2$ as possible lower thresholds for hypoxemia.

Results: Our primary analytical sample included 1,470 children (mean age 18.6 +/- 9.5 months). Median SpO$_2$ was 98% (interquartile range, 96–99%), and the 2.5$^{th}$, 5$^{th}$, and 10$^{th}$ percentile SpO$_2$ was 91%, 92%, and 94%. No child had a SpO$_2$ <90%. Children 3–11 months old had a lower median SpO$_2$ (97%) than 12–23 month olds (98%) and 24–35 month olds (98%) (p=0.039). The SpO$_2$ distribution did not differ by sex (p=0.959).
Conclusion: A SpO₂ threshold for hypoxemia derived from the 2.5th, 5th, or 10th percentile of well children is higher than <90%. If a higher threshold than <90% is adopted into LMIC care algorithms then decision-making using SpO₂ must also consider the child’s clinical status to minimize misclassification of well children as hypoxemic.

Younger children in lower altitude LMICs may require a different threshold for hypoxemia than older children. Evaluating the mortality risk of sick children using higher SpO₂ thresholds for hypoxemia is a key next step.

Key Messages

- What is the key question? The ideal peripheral oxyhemoglobin saturation (SpO₂) threshold for defining hypoxemia among children in low-income and middle-income countries is unknown.

- What is the bottom line? A SpO₂ threshold for hypoxemia set at any of the 2.5th, 5th, or 10th percentiles of SpO₂ measurements from well children in a lower altitude setting is higher than the <90% threshold currently recommended by the World Health Organization.

- Why read on? This study is a possible model for other research seeking to establish SpO₂ thresholds for hypoxemia in children and provides evidence for health policy makers to consider before implementing higher SpO₂ thresholds than currently in practice in lower altitude settings of low-income and middle-income countries.
Introduction

Lower respiratory infections (LRIs) kill more young children than any other infectious disease in the world. The most recent 2017 global estimates report more than 800,000 LRI deaths annually among children below five years of age, equating to 1-2 deaths every minute. The vast majority of pediatric LRI deaths occur in low-income and middle-income countries (LMICs). Approximately 30% of all global LRI deaths take place in South Asia each year, and Bangladesh has the 3rd highest annual pediatric LRI incidence and mortality burden among all South Asian countries.

LRIs may be complicated by pulmonary inflammation and areas of ventilation-perfusion mismatch that cause acute hypoxemia, or a low peripheral arterial oxyhemoglobin saturation (SpO₂) as measured non-invasively by a pulse oximeter. Acute hypoxemia is an important risk factor for mortality among children with LRIs in LMICs. For LMICs at lower altitude (i.e., <2,500 meters) the SpO₂ hypoxemia threshold endorsed by the World Health Organization (WHO) is <90%, a threshold associated with elevated mortality risk among children with LRIs like pneumonia. Per WHO guidelines children with caregiver reported cough and/or difficult breathing accompanied by a SpO₂ <90% are recommended for hospitalization, parenteral antibiotics, and oxygen administration. Recent observational studies from Malawi reveal that SpO₂ thresholds higher than 90% may also be associated with elevated mortality risk among children under five years with clinically diagnosed pneumonia. This evidence suggests the current WHO SpO₂ hypoxemia threshold of <90% may be suboptimal for identifying higher risk pediatric pneumonia cases for hospitalization in some LMICs.
Despite both the importance and uncertainty around the optimal SpO₂ threshold for defining hypoxemia few studies from lower altitude settings in LMICs address this issue. One approach commonly used for deriving thresholds for diagnostic tests is to produce a reference range from a healthy population representative of the test’s intended target population.⁹,¹⁰ This approach has been applied to SpO₂ measurements in children, with most research to date focused on children residing at higher altitudes.¹¹⁻¹⁵ In this study we define hypoxemia from the SpO₂ distribution of well children residing at lower altitude in rural Bangladesh who are participating in a pneumococcal conjugate vaccine (PCV) effectiveness study. We also consider the potential health system implications of implementing a SpO₂ threshold for hypoxemia derived from a population of well children.

Methods

Study design

This is a prospective observational study within a PCV effectiveness evaluation.¹⁶

Study setting

Between June and August 2017, the Projahnmo research group, a collaboration between Johns Hopkins University, the Government of Bangladesh’s Ministry of Health and Family Welfare, and Bangladeshi non-governmental and academic institutions, conducted this sub-study in three subdistricts (upazilas) of Syhlet district, northeast
Bangladesh. The parent study took place between January 2014 and June 2018. The Projahnmo research group has a well-established community surveillance system. The three upazilas under routine surveillance, Zakiganj, Kanaighat, and Beanibazar, are at an altitude between 17 and 23 meters and have a total population of about 770,000 (Figure 1). During routine surveillance local female residents called community health workers (CHWs) visit households within an area of about 10,000 population every two months. At each surveillance visit these trained CHWs provide health counseling to families regarding illness recognition and care seeking, screen women for pregnancy, and evaluate children for respiratory illnesses.

Data collection

Twenty-two CHWs were trained in September 2015 to use a Masimo Rad-5® pulse oximeter with a LNCS® Y-I wrap sensor as a part of enhanced respiratory surveillance activities for children during the parent PCV study. The initial training was one day and included theoretical sessions on pulse oximetry supplemented by practice using pulse oximeters to measure the SpO₂ of volunteer adults and children. During the study period CHWs participated in refresher sessions at least every six months and were routinely supervised by study physicians during household participant screening with the device. Remediation was provided when needed. CHWs were trained to apply the wrap sensor to the big toe of children and gently hold the foot to mitigate movement artifact. SpO₂ values were considered adequate quality measurements when the CHW achieved the following three metrics; (1) the SpO₂ value remained stable and non-drifting for no less
than three seconds, (2) the quality index signal was of consistent amplitude and
displayed at least three green bars, and, (3) the perfusion index signal was at least
three green bars in amplitude.

Between June and August 2017 CHWs enrolled well children aged 3-35 months
participating in surveillance. CHW screening included an examination for acute signs of
an illness and asking caregivers whether the child had any symptoms during the prior
week. CHWs observed children for cough, counted the child’s respiratory rate for one
minute, measured an axillary temperature with a thermometer, and observed children
for any sign of respiratory distress (i.e., head nodding, nasal flaring, audible wheezing,
grunting, stridor, tracheal tugging, or lower chest wall indrawing). Children were
excluded and referred to the study clinic if aged 3-11 months and had a respiratory rate
of ≥50 breaths/minute, or 12-35 months old with a respiratory rate of ≥40
breaths/minute, an axillary temperature >101º F, any vomiting or diarrhea, any WHO-
declared general danger sign (lethargy, convulsions, not eating or drinking, severe acute
malnutrition), or any sign of respiratory distress as specified above. Children with
isolated nasal congestion and/or rhinorrhea were not considered acutely ill and were
enrolled.

In order to further filter potentially unwell children from our sample, post-hoc we created
three analytic samples from children with a recorded SpO₂ measurement using different
reference heart rate ranges, since an abnormal heart rate may suggest unrecognized
illness. Analytic sample 1 is our primary analytic sample, and applies the most
conservative estimate of ‘healthy’ with relatively narrow normal heart rate reference ranges of: 120-160 beats/minute for 3-5 month olds, 110-150 beats/minute for 6-11 month olds, 100-140 beats/minute for 12-23 month olds, and 90-130 beats/minute for 24-35 month olds. Analytic sample 2 is less conservative as it has less restrictive heart rate reference ranges of 100-190 beats/minute for 3-23 month olds and 60-140 beats/minute for 24-35 month olds as normal reference ranges. Analytic sample 3 ignores heart rate reference ranges altogether and assumes all children are healthy.

Statistical analysis

Normally distributed continuous variables were described using means and standard deviations, non-normally distributed continuous variables were characterized by medians and interquartile ranges, and bivariate or categorical variables were described using proportions. We considered the 2.5th, 5th, and 10th percentile of SpO2 as possible thresholds for defining hypoxemia. We used the Wilcoxon-Mann-Whitney test for comparisons including a dependent variable without a normal distribution. The Kruskal Wallis test was used for comparisons between a multi-level independent variable and a dependent variable lacking a normal distribution. We fit a linear regression model, adjusted for sex, to explore the association between SpO2 and age. Using a power of 80%, significance level of 0.05, and that 25% of children will either be ill, unavailable, or fail measurement, we needed to screen 700 households for each of the three child age strata of 3–11 months, 12–23 months, and 24–35 months (total 2,100) to estimate a mean SpO2 of 96% +/- 0.2%. Stata version 16.0 (College Station, TX) was used for all analyses.
The study’s protocol was approved by the Johns Hopkins Bloomberg School of Public Health, Johns Hopkins School of Medicine, Bangladesh Institute of Child Health, and the Ethical Review Committee of the International Centre for Diarrhoeal Diseases Research, Bangladesh, Institutional Review Boards. Written informed consent was obtained from all participant caregivers.

Patient and public involvement

The development, design, recruitment, conduct, and results of the parent PCV evaluation and this nested study were communicated to the public through local community sensitization meetings held by the Projahnmo study group consortium in Sylhet, Bangladesh.

Results

Participant characteristics

From June through August 2017 the CHWs visited 2,098 households and attempted SpO₂ measurements on 2,042 children (Figure 2). Overall, 20 children with low quality SpO₂ measurements were excluded at the analysis stage. For primary analytic sample 1 a total of 552 children were additionally omitted due to abnormal heart rates. For analytic sample 2, 157 children were excluded based on reference heart ranges. Among the 1,470 children analyzed for analytic sample 1, the mean age was 18.6 months (SD,
Average age and the proportion of participants who were female were similar across the three analytic samples.

**SpO₂ distribution**

The median SpO₂ of children included in primary analytic sample 1 was 98% (IQR, 96%, 99%) and the 10th, 5th, and 2.5th percentile SpO₂ was 94%, 92%, and 91% (Table 1 and Figure 3). Analytic samples 2 and 3 revealed similar findings (Table 1 and Supplemental Figures 1 and 2). No child included in any of the three analytic samples had a SpO₂ <90%.

**Effects of age and sex on SpO₂**

After stratifying measurements into three age strata, 3–11 months, 12–23 months, and 24–35 months, we found children 3–11 months old in primary analytic sample 1 to have a median SpO₂ of 97%, compared to 98% for each of the two older age strata (p=0.038; Table 1 and Figure 3). We observed similar findings in analytic samples 2 and 3 (Table 1 and Supplemental Figures 1 and 2). When regressing SpO₂ on age in months, adjusted for sex, we found that for every one month increase in age the SpO₂ increased by 0.01% (95% CI, 0.001%, 0.02%, p=0.030) in analytic sample 1 (Supplemental Figure 3). We did not observe any difference in the SpO₂ distribution after stratifying by child sex (p=0.959).

**Health system implications of varying SpO₂ thresholds**
To examine possible consequences on the health system of a SpO\textsubscript{2} threshold for defining hypoxemia derived from well children we report the probability of a false positive measurement in Table 2 from each analytic sample at differing thresholds. If applying a \textless 92\% threshold, for example, 76/1,470 (5.1\%) well children included in analytic sample 1 would be incorrectly recommended for referral or hospitalization. SpO\textsubscript{2} thresholds at \textless 90\%, \textless 91\%, and \textless 93\% would incorrectly identify 13 (0.8\%), 40 (2.7\%), and 117 (7.9\%) of the 1,470 children in analytic sample 1 for hospitalization, respectively.

Discussion

We derived possible SpO\textsubscript{2} thresholds for hypoxemia from the 2.5\textsuperscript{th}, 5\textsuperscript{th}, and 10\textsuperscript{th} percentile cutoffs of well children in rural Bangladesh and estimated the probability of false positive measurements assuming a revised threshold was adopted into care. The SpO\textsubscript{2} threshold is critical as it triggers a cascade of potentially life or death healthcare decisions and understanding the probability of a false positive SpO\textsubscript{2} measurement for hypoxemia permits health policy makers to decide how best to balance mortality risk with anticipated hospitalization volumes.

There are two key findings from this research. First, cutoffs for hypoxemia from the 2.5\textsuperscript{th}, 5\textsuperscript{th}, and 10\textsuperscript{th} percentile are all higher than the current WHO-defined \textless 90\% threshold and we did not find any well children below the SpO\textsubscript{2} <90\% threshold. Thus, if any of these cutoffs for hypoxemia are adopted then measuring the SpO\textsubscript{2} earlier in clinical care pathways when healthier children may be over-represented could increase
false positive measurements. This has important implications in health systems with limited resources and potential challenges coping with a higher volume of patient referrals. These results, coupled with findings from Malawi that children with LRI and a SpO\textsubscript{2} between 90% and 92% are at elevated mortality risk, suggest that the current referral threshold of SpO\textsubscript{2} <90% minimizes false positives at the expense of false negatives.\textsuperscript{6-8} In order to ensure minimal misclassification of well children as hypoxemic, we recommend care algorithms incorporating a hypoxemia threshold at SpO\textsubscript{2} levels higher than <90% also consider the child’s clinical status when deciding whether to refer and hospitalize. Second, we found that the SpO\textsubscript{2} distribution differs by age. Age may therefore need to be considered when establishing a SpO\textsubscript{2} threshold for hypoxemia. Future analyses that include unwell children should investigate whether this statistical relationship has clinical significance.

To date there have been few attempts to establish a reference range for SpO\textsubscript{2} measurements of children in LMICs living at lower altitudes. Since most children reside at lower altitudes, understanding the SpO\textsubscript{2} distribution among this population has broad relevance for identifying the optimal SpO\textsubscript{2} threshold for hypoxemia. In one study from Chennai, India (altitude 7 meters) the authors measured the SpO\textsubscript{2} of 626 healthy children aged one month to five years.\textsuperscript{19} In contrast to our findings, the authors found no difference in the SpO\textsubscript{2} distribution by age. The inclusive 5\textsuperscript{th} percentile of participants in Chennai was a SpO\textsubscript{2} \leq 96\%, which was 4\% higher than in our study. Other studies that also included healthy children from lower altitudes reported the mean and standard deviation of the SpO\textsubscript{2} distribution.\textsuperscript{13, 14, 20} Given the SpO\textsubscript{2} distribution of healthy children
is negatively skewed we described these data using median and percentiles and are therefore unable to make meaningful comparisons.

A more recent multi-country study from the Household Air Pollution Intervention Network (HAPIN) investigators evaluated the SpO₂ distribution among 1,134 healthy children <24 months old from three lower altitude settings including the same region of India as the prior study (Nagapattinam (altitude 9 meters) and Villupuram (altitude 44 meters), and also in Guatemala (Jalapa District, altitude 1,417 meters) and Rwanda (Kayonza District, altitude 1,354 meters), and one high altitude setting in Puno, Peru (altitude 3,827 meters). The 5th percentile threshold reported by HAPIN investigators in India was notably consistent with the Chennai study at 96%. Unlike the Chennai study, however, HAPIN investigators found lower 5th percentile thresholds for age in Rwanda (92%) and Guatemala (93%), and observed a correlation between younger age and lower SpO₂. None of these studies reported the 2.5th percentile cutoff. Overall, it is somewhat surprising that our data from Bangladesh aligns closer with Rwanda and Guatemala than India, another South Asian setting closer in altitude.

Methodology may largely be responsible for the variation in results across these studies. Variation may be due to a combination of device accuracy, including differences in accuracy between devices, variation inherent to measurements on children, measurement variation between healthcare workers and healthcare worker cadres with different training backgrounds, and possible varying degrees of misclassification bias of sick children in each of the three studies. Specifically, the
Chennai study used a different pulse oximeter (L&T Medical, Stellar P®) than in the HAPIN study and our study, which both used Masimo devices (Rad-97® and Rad-5®).\textsuperscript{19, 21} Pulse oximeter SpO\textsubscript{2} estimation algorithms are known to differ by manufacturer and in the United States the Food and Drug Administration requires the testing and certification of pulse oximeters to be accurate within a root mean square error of 3\% for arterial blood saturation values between 70\% and 100\%.\textsuperscript{22} Although data comparing pulse oximeter device performance in children in LMICs is notably limited, it is also well known that device performance can change under conditions common to children like motion and low perfusion.\textsuperscript{23, 24}

A key methodological difference in this study, compared to the Chennai and HAPIN studies, was formal healthcare workers at healthcare facilities conducting recruitment. In our study trained but informal CHWs recruited and screened children within the community. Although we employed intensive efforts to train and supervise CHWs our use of informal healthcare workers may have influenced both pulse oximeter measurement quality and the number of unwell children remaining in our sample. Our post-hoc data cleaning attempted to further address these possible weaknesses and our findings are reassuringly consistent across the three analytic samples. By contrast, the Chennai and HAPIN studies did not further restrict their analyses by heart rate reference ranges and therefore could remain vulnerable to these issues.

Lastly, although not explicitly stated in either of the Chennai or HAPIN studies, we intentionally did not exclude children with isolated nasal congestion and/or rhinorrhea as
anecdotally they are common to otherwise healthy rural Bangladeshi children. In Bangladesh both indoor and ambient air pollution is marked and includes environmental irritants that can cause ongoing upper respiratory mucosal inflammation, nasal congestion, and/or rhinorrhea typical of nonallergic, noninfectious rhinitis. While it is unlikely that any misclassification bias or device performance inconsistencies were substantially different in our study than in the Chennai and HAPIN studies, it is nevertheless important to interpret our results within this context.

Another issue that may impact the utility of pulse oximeters in all LMICs is the possible greater inaccuracy of SpO₂ measurements in individuals with darker skin pigmentation. Although pulse oximetry inaccuracy in individuals with darker skin pigmentation is well established, a recent publication of hospitalized adults in the United States suggests the magnitude and direction of SpO₂ measurement bias in people with darker skin tones may be clinically unacceptable. The authors reported a higher odds of hypoxemia – as measured by an arterial blood gas – among darkly pigmented adults with a normal SpO₂, compared to adults without dark skin pigmentation and a normal SpO₂. Further study is needed to better understand the relative contribution and direction of pulse oximeter inaccuracy among children in LMICs where higher percentages of the population often have darker skin pigmentation.

In sum, our findings provide possible reference SpO₂ thresholds for hypoxemia derived from a population of well children in Bangladesh residing at lower altitude. In fragile, overburdened health systems higher false positive measurements may limit the
implementation feasibility of SpO₂ thresholds above the current <90% mark without additional strengthening of clinical assessments by healthcare providers. This research suggests that age needs to be considered in further work on establishing thresholds for hypoxemia. Key next steps include determining the mortality risk of ill children with SpO₂ measurements at or below these thresholds in varying LMICs, including Bangladesh, as well as evaluating the performance of SpO₂ at or below these thresholds for diagnosing LRI. Such research will also shed light on the potential mortality implications of false negative measurements when applying a lower <90% SpO₂ threshold for hypoxemia.

Acknowledgements.

We offer our thanks to the caregivers and children participating in this research, as well as to the Projahnmo Study Group field and data management staff, the Ministry of Health and Family Welfare, Government of Bangladesh, GlaxoSmithKline, Bill and Melinda Gates Foundation, and the National Institute of Health their support of this study.

Contributors

Funding acquisition: AHB and EDM. Conceptualization and design: EDM. Data curation: EDM, AHB, NHC and SJRR. Data collection: EDM, SA, AAMH, ADR, and AI. Data analysis: EDM, NHC, and SJRR. Data interpretation: EDM, CK, SA, AAMH, ADR, AI, TC, HBS, ASG, SH, NHC, SJRR, NB, AHB, and WC. Writing—original draft: EDM. Writing—review & editing: EDM, CK, SA, AAMH, ADR, AI, TC, HBS, ASG, SH, NHC, SJRR, NB, AHB, and WC.
This study is funded by the Bill & Melinda Gates Foundation [OPP1084286, OPP1117483] and GlaxoSmithKline [90063241]. EDM was also supported by the Fogarty International Center of the National Institutes of Health under Award Number K01TW009988 for the research reported in this publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Bill & Melinda Gates Foundation, GlaxoSmithKline or the National Institutes of Health.

Figure 1. Projahnmo Research Foundation surveillance area

Figure 2. Study profile

Figure 3. Peripheral oxyhemoglobin saturation (SpO$_2$) distribution in Analytic Sample 1

Supplemental Figure 1. Peripheral oxyhemoglobin saturation (SpO$_2$) distribution in Analytic Sample 2

Supplemental Figure 2. Peripheral oxyhemoglobin saturation (SpO$_2$) distribution in Analytic Sample 3

Supplemental Figure 3. Scatterplot of the relationship between peripheral oxyhemoglobin saturation (SpO$_2$) and age in Analytic Sample 1

References

1. GBD 2017 Lower Respiratory Infections Collaborators. Quantifying risks and interventions that have affected the burden of lower respiratory infections among
children younger than 5 years: an analysis for the Global Burden of Disease Study

2017. *Lancet Infect Dis* 2020;20:60-79.

2. McCollum ED, Ginsburg AS. Outpatient Management of Children With World Health Organization Chest Indrawing Pneumonia: Implementation Risks and Proposed Solutions. *Clin Infect Dis* 2017;65:1560-1564.

3. Lazzerini M, Sonego M, Pellegrin MC. Hypoxaemia as a Mortality Risk Factor in Acute Lower Respiratory Infections in Children in Low and Middle-Income Countries: Systematic Review and Meta-Analysis. *PLoS One* 2015:e0136166.

4. World Health Organization, 2014. Integrated Management of Childhood Illness: Chart Booklet. Geneva, Switzerland: World Health Organization. Accessed: June 2021.

Available: https://apps.who.int/iris/bitstream/handle/10665/104772/9789241506823_Chartbook_eng.pdf

5. World Health Organization, 2013. Pocketbook of Hospital Care for Children. Guidelines for the Management of Common Childhood Illnesses. Second Edition. Geneva, Switzerland: World Health Organization. Accessed: June 2021. Available: https://apps.who.int/iris/bitstream/handle/10665/81170/9789241548373_eng.pdf?sequence=1

6. Hooli S, Colbourn T, Lufesi N, et al. Predicting Hospitalised Paediatric Pneumonia Mortality Risk: An External Validation of RISC and mRISC, and Local Tool Development (RISC-Malawi) from Malawi. *PLoS One* 2016;11:e0168126.
7. Colbourn T, King C, Beard J, et al. Predictive value of pulse oximetry for mortality in infants and children presenting to primary care with clinical pneumonia in rural Malawi: A data linkage study. *PLoS Med* 2020;17:e1003300.

8. Hooli S, King C, Zadutsa B, et al. The Epidemiology of Hypoxemic Pneumonia among Young Infants in Malawi. *Am J Trop Med Hyg* 2020;102:676-683.

9. Gray D, Willemse L, Visagie A, et al. Lung function and exhaled nitric oxide in healthy unsedated African infants. *Respirology* 2015;20:1108-14.

10. Sachdev HS, Porwal A, Acharya R, et al. Haemoglobin thresholds to define anaemia in a national sample of healthy children and adolescents aged 1-19 years in India: a population-based study. *Lancet Glob Health* 2021;9:e822-e831.

11. Subhi R, Smith K, Duke T. When should oxygen be given to children at high altitude? A systematic review to define altitude-specific hypoxaemia. *Arch Dis Child* 2009;94:6-10.

12. Lozano JM, Steinhoff M, Ruiz JG, Mesa ML, Martinez N, Dussan B. Clinical predictors of acute radiological pneumonia and hypoxaemia at high altitude. *Arch Dis Child* 1994;71:323-7.

13. Reuland DS, Steinhoff MC, Gilman RH, et al. Prevalence and prediction of hypoxemia in children with respiratory infections in the Peruvian Andes. *J Pediatr* 1991;119:900-6.

14. Onyango FE, Steinhoff MC, Wafula EM, Wariua S, Musia J, Kitonyi J. Hypoxaemia in young Kenyan children with acute lower respiratory infection. *BMJ* 1993;306:612-5.
15. Andrade V, Andrade F, Riofrío P, Nedel FB, Martin M, Romero-Sandoval N. Pulse oximetry curves in healthy children living at moderate altitude: a cross-sectional study from the Ecuadorian Andes. *BMC Pediatr* 2020;20:440.

16. McCollum ED, Ahmed S, Roy AD, et al. Effectiveness of the 10-valent pneumococcal conjugate vaccine against radiographic pneumonia among children in rural Bangladesh: A case-control study. *Vaccine* 2020;38:6508-6516.

17. Baqui AH, McCollum ED, Saha SK, et al. Pneumococcal Conjugate Vaccine impact assessment in Bangladesh. *Gates Open Res* 2018;2:21.

18. Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. *Lancet* 2011;377:1011-8.

19. Balasubramanian S, Suresh N, Ravichandran C, Dinesh Chand GH. Reference values for oxygen saturation by pulse oximetry in healthy children at sea level in Chennai. *Ann Trop Paediatr* 2006;26:95-9.

20. Madico G, Gilman RH, Jabra A, et al. The role of pulse oximetry. Its use as an indicator of severe respiratory disease in Peruvian children living at sea level. Respiratory Group in Peru. *Arch Pediatr Adolesc Med* 1995;149:1259-63.

21. Crocker ME, Hossen S, Goodman D, et al. Effects of high altitude on respiratory rate and oxygen saturation reference values in healthy infants and children younger than 2 years in four countries: a cross-sectional study. *Lancet Glob Health* 2020;8:e362-e373.
22. ISO 80601-2-61:2017. Medical electrical equipment — Part 2-61: Particular requirements for basic safety and essential performance of pulse oximeter equipment. Accessed: June 2021. Available: https://www.iso.org/standard/67963.html

23. Lipnick MS, Feiner JR, Au P, Bernstein M, Bickler PE. The Accuracy of Inexpensive Pulse Oximeters Not Cleared by the Food and Drug Administration: The Possible Global Public Health Implications. *Anesth Analg* 2016;123:338-45.

24. Louie A, Feiner JR, Bickler PE, Rhodes L, Bernstein M, Lucero J. Four Types of Pulse Oximeters Accurately Detect Hypoxia during Low Perfusion and Motion. *Anesthesiology* 2018;128:520-530.

25. Bousquet J, Anto JM, Annesi-Maesano I, et al. POLLAR: Impact of air POLLution on Asthma and Rhinitis; a European Institute of Innovation and Technology Health (EIT Health) project. *Clin Transl Allergy* 2018;8:36.

26. Sjoding MW, Dickson RP, Iwashyna TJ, Gay SE, Valley TS. Racial Bias in Pulse Oximetry Measurement. *N Engl J Med* 2020;383:2477-2478.
| Characteristic            | Analytic sample 1 (primary)* | Analytic sample 2** | Analytic sample 3*** |
|--------------------------|-----------------------------|---------------------|----------------------|
|                          | All N=1,470                 | 3 to 11 months N=445| 12 to 23 months N=567|
| Age in months, mean (SD) | 18.6 (9.5)                  | 7.3 (2.4)           | 18.0 (3.3)           |
| Females, n (%)           | 697 (47.4%)                 | 203 (45.6%)         | 274 (48.3%)          |
| SpO2, 95th percentile    | 100%                        | 100%                | 100%                 |
| SpO2, 75th percentile    | 99%                         | 99%                 | 99%                  |
| SpO2, 50th percentile    | 98%                         | 97%                 | 98%                  |
| SpO2, 25th percentile    | 96%                         | 96%                 | 96%                  |
| SpO2, 10th percentile    | 94%                         | 94%                 | 95%                  |
| SpO2, 5th percentile     | 92%                         | 93%                 | 92%                  |
| SpO2, 2.5th percentile   | 91%                         | 92%                 | 91%                  |
| SpO2, range              | 90% to 100%                 | 90% to 100%         | 90% to 100%          |

SpO2 indicates peripheral arterial oxyhemoglobin saturation; SD, standard deviation.

*Kruskal Wallis test comparing SpO2 by age category; p value = 0.0387

**Kruskal Wallis test comparing SpO2 by age category; p value = 0.0095

***Kruskal Wallis test comparing SpO2 by age category; p value = 0.0401
Table 2. False positive measurements for hypoxemia by analytical sample and percentile threshold

| Analytic sample | Age in months | 2.5<sup>th</sup> Percentile SpO<sub>2</sub> threshold | 5<sup>th</sup> Percentile SpO<sub>2</sub> threshold | 10<sup>th</sup> Percentile SpO<sub>2</sub> threshold |
|----------------|---------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
|                | SpO<sub>2</sub> | False positive, n/N (%)                         | False positive, n/N (%)                         | False positive, n/N (%)                         |
| 1              |               |                                               |                                               |                                               |
|                | All           | 91%                                           | 92%                                           | 94%                                           |
|                | 40/1,470      | 40/1,470 (2.7%)                               | 76/1,470 (5.1%)                               | 179/1,470 (12.1%)                             |
|                | 3-11          | 92%                                           | 93%                                           | 94%                                           |
|                | 20/445        | 20/445 (4.4%)                                 | 34/445 (7.6%)                                 | 52/445 (11.6%)                                |
|                | 12-23         | 91%                                           | 92%                                           | 94%                                           |
|                | 17/567        | 17/567 (2.9%)                                 | 35/567 (6.1%)                                 | 83/567 (14.6%)                                |
|                | 24-35         | 91%                                           | 93%                                           | 95%                                           |
|                | 13/458        | 13/458 (2.8%)                                 | 29/458 (6.3%)                                 | 72/458 (15.7%)                                |
| 2              |               |                                               |                                               |                                               |
|                | All           | 91%                                           | 92%                                           | 94%                                           |
|                | 51/1,865      | 51/1,865 (2.7%)                               | 107/1,865 (5.7%)                              | 248/1,865 (13.2%)                             |
|                | 3-11          | 91%                                           | 92%                                           | 94%                                           |
|                | 16/615        | 16/615 (2.6%)                                 | 33/615 (5.3%)                                 | 85/615 (13.8%)                                |
|                | 12-23         | 91%                                           | 92%                                           | 94%                                           |
|                | 21/673        | 21/673 (3.1%)                                 | 44/673 (6.5%)                                 | 68/673 (10.1%)                                |
|                | 24-35         | 91%                                           | 92%                                           | 94%                                           |
|                | 14/577        | 14/577 (2.4%)                                 | 30/577 (5.1%)                                 | 60/577 (10.3%)                                |
| 3              |               |                                               |                                               |                                               |
|                | All           | 91%                                           | 92%                                           | 94%                                           |
|                | 55/2,022      | 55/2,022 (2.7%)                               | 119/2,022 (5.8%)                              | 273/2,022 (13.5%)                             |
|                | 3-11          | 91%                                           | 92%                                           | 94%                                           |
|                | 18/634        | 18/634 (2.8%)                                 | 35/634 (5.5%)                                 | 88/634 (13.8%)                                |
|                | 12-23         | 91%                                           | 92%                                           | 93%                                           |
|                | 21/698        | 21/698 (3.0%)                                 | 48/698 (6.8%)                                 | 72/698 (10.3%)                                |
|                | 24-35         | 92%                                           | 92%                                           | 94%                                           |
|                | 36/690        | 36/690 (5.2%)                                 | 36/690 (5.2%)                                 | 76/690 (11.0%)                                |

SpO<sub>2</sub> indicates peripheral arterial oxyhemoglobin saturation.
2,098 households visited

55 excluded
- Ill or uncooperative
  - 2 respiratory symptoms
  - 53 uncooperative

2,097 3-35 months old

2,042 SpO₂ measurements

1 excluded
- Age <3 months

552 excluded
- Abnormal heart rate
  - 169 bradycardic
  - 383 tachycardic

Analytic Sample 3
N= 2,022
- 3-11 months old (N= 634)
- 12-23 months old (N= 698)
- 24-35 months old (N= 690)

20 excluded
- Low quality SpO₂ measurement
  - 7 SpO₂ >100%
  - 13 abnormal QI or PI signals

157 excluded
- 157 abnormal heart rate
  - 46 bradycardic
  - 111 tachycardic

455 excluded

Analytic Sample 1
N= 1,470
- 3-11 months old (N= 445)
- 12-23 months old (N= 567)
- 24-35 months old (N= 458)

Analytic Sample 2
N= 1,865
- 3-11 months old (N= 615)
- 12-23 months old (N= 673)
- 24-35 months old (N= 577)
SpO₂ (%) distribution across different age groups: All, 3 to 11 months, 12 to 23 months, and 24 to 35 months.