

Extending strong research to high-altitude infants



See [Articles](#) page e362

The Article by Mary E Crocker and colleagues¹ in the *Lancet Global Health* taps into important scientific trends of improving the robustness of research and choosing the appropriate cutoffs for clinical diagnoses. Crocker and many global colleagues from the Home Air Pollution Improvement Network (HAPIN) write about the current WHO guidelines for diagnosing pneumonia in infants aged 0–23 months. They argue that WHO should acknowledge respiratory adaptation to high-altitude hypoxia by raising the threshold for respiratory rate (RR) and lowering that for oxygen saturation of haemoglobin (SpO₂) according to altitude. In the study, nearly 1600 infants represented four different altitude ranges from Guatemala, India, Rwanda, and Peru.

This study¹ shows that the current WHO definitions of fast breathing for age and hypoxaemia might result in misclassification of a substantial number of children who present with respiratory symptoms at moderate to high altitudes. Consideration of this important factor could help to guide pneumonia diagnosis and management at high altitude.

Although this initial study clearly makes intuitive sense, the authors acknowledge important limitations. We emphasise and detail these limitations so that more comprehensive studies using robust methods can be carried out in the future to help address this crucial question of altitude-appropriate cutoffs for common ailments such as respiratory diseases.

This study does not account for ethnicity. Indeed, samples from the various countries could include children from many ethnicities, who might respond very differently to altitude² in terms of both RR and SpO₂ because of genetic variation in adaptation. Guatemala, India, Rwanda, and Peru are home to many ethnic groups; ethnicity influences response to high altitude at all ages. For instance, Niermeyer and colleagues³ reported healthy 4-month-old Han Chinese infants with mean SpO₂ 85% while awake and 76% while asleep, by contrast with Tibetan infants at the same altitude of birth and residence (3658m) who reported mean SpO₂ of 88% during wakefulness and 86% during sleep. Future studies will need to report findings by ethnicity and by waking or sleeping state to help with the correct diagnosis of respiratory illnesses among infants at altitude.

Anaemia, which is very common in the studied sites, was not taken into account and could easily have influenced RR findings, as an anaemic child will breathe faster regardless of altitude. Current WHO guidelines⁴ recommend the use of age, sex, and altitude-adjusted haemoglobin thresholds for diagnosing anaemia at the individual and population levels. WHO recently provided an interim report on a 4-year project to review its global guidelines.⁵ The priority topics dealt with technical and statistical issues, the effects of genetic variants on haemoglobin concentration,⁶ life cycle factors, and population differences in haemoglobin concentration at high altitude. Although sufficient data exist for adult men and women to show that sex differences in haemoglobin persist at high altitude, data for infants and children are incomplete.

South American highlanders, who provided the data for the current WHO thresholds, exemplify just one haematological response to high altitude. Accurately diagnosing anaemia in this setting requires reference values defined for the many other highland ethnic groups. WHO methods for updating diagnostic thresholds for anaemia serve as an example to those proposing new criteria for diagnosing pneumonia. Nutritional status and body size⁷ might also influence RR and SpO₂.

The Strengthening High Altitude Research (STAR) guidelines,⁷ generated by a group of the International Society for Mountain Medicine, provide guidelines on data reporting in clinical high altitude medical research. STAR guidelines include providing the study location, setting, altitude, and participant ethnicity. Robust future studies should report at least the study location by name, GPS location, and barometric pressure; the setting as rural or urban, indoors or outdoors, clinic or home, specify altitude as that of data collection, current residence, or birthplace; and ethnicity in locally appropriate terms. The present paper provides only the country and the altitude range. Also, the HAPIN authors of this study are well-positioned to collect data regarding confounding factors such as indoor air pollution, which is likely common in the study sites used here. Carbon monoxide from burning biomass fuel can artificially boost oxygen saturation readings because pulse oximeters combine carboxyhaemoglobin and oxyhaemoglobin in reporting SpO₂.⁸

Finally, a 1–2% significant difference in SpO₂ is generally unhelpful. In the study by Crocker and colleagues,¹ Guatemala (1036–2107 m) and Rwanda (1449–1644 m) had 1% and 2.1 % lower SpO₂ than India (1–919m). This minor difference could easily fall within the measurement or calibration error of the equipment. Such small differences in SpO₂, although statistically significant, are generally ignored clinically⁹ for both paediatric and adult patients. At lower altitudes, physiological adaptive measures at high altitudes, such as hypoxic ventilatory response, might not be detectable or activated.

In conclusion, the authors acknowledge that they conducted this extensive study to help inform a larger study. Indeed, their findings should be validated using a set of guidelines like STAR discussed above, accounting for human biological diversity, indoor air pollution, and the many other confounders in high-altitude settings.

We declare no competing interests.

Copyright © 2020 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

**Buddha Basnyat, Cynthia M Beall*
buddha.basnyat@ndm.ox.ac.uk

Oxford University Clinical Research Unit, Patan Hospital, Kathmandu, Nepal (BB); Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, Oxford University, Oxford, UK (BB); and Case Western Reserve University, Anthropology Department, Cleveland, OH 44106-7125, USA (CMB)

- 1 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**: e362–73.
- 2 Niermeyer S, Andrade Mollinedo P, Huicho L. Child health and living at high altitude. *Arch Dis Child* 2009; **94**: 806–11.
- 3 Niermeyer S, Yang P, Shanmina, Drolkar, Zhuang J, Moore LG. Arterial oxygen saturation in Tibetan and Han infants born in Lhasa, Tibet. *N Engl J Med* 1995; **333**: 1248–52.
- 4 Garcia-Casal MN, Pasricha SR, Sharma AJ, Pena-Rosas JP. Use and interpretation of hemoglobin concentrations for assessing anemia status in individuals and populations: results from a WHO technical meeting. *Ann N Y Acad Sci* 2019; **1450**: 5–14.
- 5 Gassmann M, Mairbaurl H, Livshits L, et al. The increase in hemoglobin concentration with altitude varies among human populations. *Ann N Y Acad Sci* 2019; **1450**: 204–20.
- 6 Wajcman H, Galacteros F. Hemoglobins with high oxygen affinity leading to erythrocytosis. New variants and new concepts. *Hemoglobin* 2005; **29**: 91–106.
- 7 Brodmann Maeder M, Brugger H, Pun M, et al. The STAR Data Reporting Guidelines for Clinical High Altitude Research. *High Alt Med Biol* 2018; **19**: 7–14.
- 8 Hampson NB. Pulse oximetry in severe carbon monoxide poisoning. *Chest* 1998; **114**: 1036–41.
- 9 Basnyat B, Gertsch JH, Holck PS, et al. Acetazolamide 125 mg BD is not significantly different from 375 mg BD in the prevention of acute mountain sickness: the prophylactic acetazolamide dosage comparison for efficacy (PACE) trial. *High Alt Med Biol* 2006; **7**: 17–27.