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Authors' Reply to "Refining Oxygen-Carrying Capacity Metrics in Pediatric Pneumonia Mortality Risk"

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Reply

To the Editor:

We appreciate the thoughtful letter by Sati et al. The authors make several points, which we consider below. First, we wish to distinguish between delivery of oxygen (the oxygen distributed to tissues by the combined actions of the heart, lungs, and blood) vs tissue uptake of oxygen, which is affected by local capillary circulation, oxygen dissociation from hemoglobin, and intracellular transport of oxygen to mitochondria. We agree that the relationship between oxygen delivery and tissue uptake is complex and affected by a multiplicity of factors. However, if one were to hold all covariates constant (ie, cardiac output, pH, temperature, pCO2, 2,3-disphosphoglycerate, percent of fetal hemoglobin), increased oxygen carrying capacity would be expected to improve tissue delivery of oxygen. Prior work by Dzik et al in Uganda has demonstrated the dramatic effect of correction of anemia via transfusion in treating cerebral tissue hypoxia and lactic acidosis.[1,2]

We further appreciate the authors' note that lactate is present in several pathways that can contribute to death in children with pneumonia. We did not include lactate (a mediator) as a covariate in the multivariable model in order to avoid "overadjustment" bias.[3] Future studies with additional biomarker measurements and phenotyping would help distinguish between hypoxia- and non-hypoxia related lactic acidosis; mediation analysis would also be appropriate to determine direct vs indirect effects of lactate.

Finally, we agree that the heterogeneity of anemia within the cohort limits our ability to determine potential therapeutic interventions; future studies which allow subgroup analyses will be helpful in translating these observational findings into interventions. We are grateful for the opportunity to draw attention to anemia as an important factor in childhood pneumonia, and believe the authors' observations highlight important priorities for future investigation.

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[1] Dhabangi A, Ainomugisha B, Cserti-Gazdewich C, Ddungu H, Kyeyune D, Musisi E, et al. Cerebral Oximetry in Ugandan Children With Severe Anemia: Clinical Categories and Response to Transfusion. JAMA Pediatr 2016;170:995–1002. https://doi.org/10.1001/jamapediatrics.2016.1254.

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