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Editorial

Addressing research priorities in community-acquired pneumonia in children: A case of a missed opportunity

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Africa is a continent with a relatively youthful population with a median age of 19 years. Under-5 mortality rates have remained stubbornly high, with community-acquired pneumonia (CAP) accounting for 800,000 deaths in Africa and SE Asia in 2018.[1] The majority of the continent are low-income countries with significant challenges in health-care delivery due to weak health systems, lack of infrastructure and human resources, and also critically lack of funding by governments to channel to research to improve the quality of life of citizens and inform public policy. Unlike high-income countries, most African countries spend <1% of GDP to fund research.[2] For research to be conducted in this setting, the majority of researchers who want to conduct high-impact and expensive research are dependent on funding from external funding bodies and collaborations with Global North researchers.

In the majority of resource-limited hospitals in Africa, there is a significant gap between demand for oxygen on pediatric wards and the supply available, thus many children do not receive oxygen when indicated by current guidelines. Furthermore, access to specialist respiratory support, facilities including mechanical ventilation or assisted respiratory support through continuous positive airway pressure or high-flow nasal therapy (HFNT) are extremely limited.

The COAST trial was multicenter controlled study designed to determine whether oxygen does save lives in children admitted with CAP with saturations 80–92% and whether high-flow humidified (HFNT) respiratory support using AirVo2 device (delivering positive end-expiratory pressure) could avert death from respiratory exhaustion compared to the standard mode of delivery through mask or nasal cannula (low flow).[3] The COAST trial was conducted by an African research collaborative group that has a strong track record in delivering high-quality policy informing clinical trials in critically sick children. The trial was approved by the ethics committees in Kenya and Uganda and the Imperial College London, with an Independent Data Safety Monitoring Committee in place. Furthermore, the trial lists had letters from the Kenya and Uganda Paediatric Associations endorsing the trial. This was not just a passive letter of support: They presented the details of the trial to the societies allowing everyone who attended one of two dedicated meetings to ask questions and they were reassured by the responses. The African pediatricians were pleased that this question was being asked as it was generally felt to be a big supply/medical issue. The trial complied with the highest standards of CIH GCP with an appropriate governance committee including an independent data and safety monitoring board which reviewed the interim date on three occasions reporting that there were no safety concerns, which is why the ethics/regulatory bodies allowed the trial to continue. Equipoise, an epistemological term, relates to the degree of uncertainty about the relative benefits (or

risks) of a clinical intervention, and mandates that a clear distinction is made between hard evidence and opinion;[4,5] the former is always to be preferred, no matter how eminent the holders of opinions, and how loud their voices may be. Although it is now common practice to give oxygen when saturations are below 94% in children with pneumonia, it is still unclear whether children can tolerate a lower saturation cutoff, while not endangering them and increasing mortality and long-term morbidity and harm. Hence, in a context where resources are limited and oxygen delivery is hampered not only due to access but other logistical reasons such as interrupted[6] power supplies, a study of this nature would be beneficial to inform clinical practice and mitigate harm from giving a scarce resource (oxygen) to a child who did not need it at the expense of one in whom it might be lifesaving, and would thus not be unethical.[7] In severe CAP, there was no good pre-existing evidence demonstrating clear benefits of giving oxygen,[8] so COAST was both ethically and scientifically sound.[9] In a situation of substantial uncertainty, it is unethical not to maximize attempts to gather high-quality evidence of benefit or otherwise.

The COAST trial ultimately terminated[10] due community concerns of apparent harm to children who did not receive oxygen and on the recommendations of the Trial Steering Committee for feasibility (recruitment having been severely hampered), albeit allowing at least some findings to be published.[11] Although the expected 48 h mortality (primary endpoint) rate was 9% in the less severely hypoxemic stratum (SpO_2 80–92%), overall mortality was 1.6%, irrespective of the oxygen strategy allocated (including the permissive hypoxemic control arm), that is, there was no evidence of harm, rather all children in the trial did better than anticipated. In addition, 48 h mortality was lower in HFNT versus low flow (adjusted odds ratio 0.60 [0.33–1.06; $P = 0.08$]) but inconclusive as the trial was stopped early. These outcomes have important implications for research in general, and research in Africa in particular.

A decade ago, the mantra was that oxygen was good for hypoxemia, and more oxygen was better, other than in the context of chronic obstructive pulmonary disease, wherein removing the hypoxic drive to breathe results in hypercapnic respiratory failure, thus to do a trial which permits hypoxemia sounds bizarre. However, medicine is the graveyard of what seemed a good idea at the time, and it has subsequently become clear that titration of oxygen actually leads to better outcomes in many different contexts.[6] Furthermore, especially in resource-poor settings or during rampant infection surges like during the recent COVID-19 pandemic, the provision of oxygen is not a trivial exercise, as has been seen tragically recently in India. We, therefore, argue that even when this study was conducted in a low-resource setting, translation of the findings could be relevant in all contexts, should the currently held belief of oxygen targets be accepted. Similarly, the FEAST trial has challenged fluid resuscitation paradigms in high-income settings. Furthermore important context, other apparently unethical trials challenging established dogma, such as fluids are always good for the shocked child[12] and blood is always good for the anemic child,[13,14] in fact clearly showed that these interventions could be harmful, and established dogma was hurting children. This is true not merely in pediatrics. The Panther trial compared a combination of prednisolone, azathioprine, and N-acetyl cysteine (NAC) with double placebo and NAC in idiopathic pulmonary fibrosis in adults, and showed that patients in the active limb were hospitalized more and died quicker than those given double placebos.[15] Yet when the identical trial was proposed two decades earlier, it was roundly denounced as unethical and did not proceed.[16] One remembers Hilaire Belloc's lines: "Oh! Let no-one ever, ever doubt, What nobody is sure about!" which could probably be repeated with advantage to every physician at least daily.

It would also be naïve to imagine that common conditions like childhood pneumonia are managed the same across the globe. Hence, research on African childhood CAP must be carried out in Africa. However, the premature termination of COAST meant that nearly 2000 children were enrolled in a project which could not achieve its aim. This result is mitigated by the fact that those in the trial did much better than expected, and the COAST team has set a high benchmark for future treatment of CAP. The COAST conclusion "should prompt further trials" is a poor outcome for a ~£3 million investment, for the reputations of all involved and more important for the families involved in the trial.

There is also a danger that major funders will be reluctant to invest in future studies unless there is a strategy to ensure this does not happen again. Of course, the conduct of clinical trials must be exemplary in all respects, and subjected to open scrutiny at all times, and all ethical and research governance requirements followed, but this was the case with COAST. So what went wrong? The answer here may not only lie in the clinical trial itself but also the fundamental role of global health researchers and the management of the collaborations as well as engagement of local communities and stakeholders that participate in the trials. Strategies to engage a broader range of stakeholders including Northern and Southern collaborators, clinicians, and community members in the research design are critical.[17-19] The engagement of the wider community and population to understand science and the complexities of trial design and scientific research has been starkly brought to the fore with COVID-19 and vaccines. The infodemic around COVID-19 and the tension of societal engagement with science and social media poses have been

highlighted.[20] This really worrying trend is also exhibited across the world by increasing numbers of politicians who are apparently truth blind, believing that what they want to be true in the face of the evidence. The pressing question to us all, everywhere in the world is, do we want our clinical practice and research to be informed by science or social media.

In the case of COAST, no Data Safety Monitoring Board would have halted the study given the interim results. Independent investigations by a range of medical bodies found that the trial was being conducted to the highest standards and that independent interim analyses had indicated no evidence of harm (see published COAST supplemental file for details).[11] Ethics and regulatory committees supported this view. In addition, National Paediatric Associations in Kenya and Uganda sent letters of endorsement. Members of the Trial Steering Committee also endorsed the trial. However a lay-led campaign to stop the trial on the grounds that children were being harmed was successful. Science versus social media requires a solution, and the best solutions will vary across the world. What is the African solution? This is for Africa to find, but one part of the solution could be the Pan-African Thoracic Society (PATS). The European Research Society will scrutinize and endorse pragmatic clinical trials; is there a role for PATS to scrutinize and endorse appropriate research in the respiratory field in Africa? Such an endorsement, with the authority of the society behind it, could greatly strengthen the hands of all those doing research in Africa, both from the continent and abroad, and provide reassurance that senior African researchers and clinicians are right behind the work. Such an approach could certainly reassure external funders.

High-quality, policy changing trials have been conducted in Africa in critically sick children, supported by approvals from the relevant ethics and regulatory boards, and resulted in guideline changes that have led to the saving of thousands of lives of African children.[12,21] If COAST had been able to deliver its objectives within the timeframe and funding window available, the tantalizing preliminary findings may have provided evidence for refinement of current guidelines. Nevertheless, another trial is now required to provide confirmation or otherwise of these findings. Finally, African children need evidence-based treatment, the search for which includes being able to challenge dogma in studies which are both ethical and conclusive.

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