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LETTER TO THE EDITOR

Severe pneumonia research and the problem of case definition: the example of zinc trials

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Dear Sir:

We read with great interest the report by Bose et al (1) of their randomized controlled trial of zinc supplementation in young children with severe pneumonia in southern India—they are to be commended for making an important contribution to a little-studied question. Mixed evidence from a small number of trials leaves unresolved the question of the role of zinc in severe pneumonia (2, 3).

One problem that attends research in childhood pneumonia, to which the authors refer, is that of case definition. The World Health Organization's clinical definition of pneumonia, a modified version of which was used in the study of Bose et al, does not attempt to distinguish between pneumonia and bronchiolitis. However, clinicians have long recognized that these are in fact 2 distinct conditions (albeit with a degree of clinical overlap) whose prognosis and clinical features are different. Bronchiolitis tends to be viral, self-limiting, and associated with wheezing, whereas pneumonia tends to be bacterial (especially in the developing world; 4), to have a significant mortality, and not to have associated wheezing. The reliable detection of wheezing is problematic in primary care settings in the developing world, and thus in a pneumonia study including children with wheezing may enhance the study's generalizability to these settings. However, the danger is that what is intended to be a study of pneumonia becomes a study of bronchiolitis. That may have been the case in the study of Bose et al: nearly two-thirds of patients had wheezing, and therefore they are likely to have had bronchiolitis (or possibly asthma), which is consistent with the very low reported case fatality (1 death in 300 participants; 0.3% case fatality rate). We suggest, therefore, that the ability to exclude bronchiolitis from the analysis is helpful to the meaningful study of pneumonia. Practical options for doing this include designing and powering studies to detect a difference in the nonwheezing subgroup, excluding wheezers altogether, or including radiologically confirmed pneumonia only.

Bose et al speculated that zinc may be harmful in bacterial pneumonia, at the same time that they acknowledged the limitations of the subgroup analysis on which the speculation was based. They showed prolongation of recovery (risk ratio in the placebo group: 0.60; $P = 0.015$) in a subgroup of 97 participants in the hot season, when nonwheezing apparently is more common. However, it is notable that no difference in recovery time was found between wheezers and nonwheezers in the study, which would be expected if the etiology of the pneumonia accounted for the difference in treatment effect by season. In contrast, Brooks et al (2) showed more rapid recovery from signs of severe disease in a nonwheezing subgroup of 164 participants (risk ratio: 0.61; 95% CI: 0.4, 0.92).

It is not clear whether the population studied by Bose et al was zinc deficient or not. Although the 3 completed trials were conducted in South Asia, soil and food zinc content could be substantially lower in deltaic Bangladesh and West Bengal than in southern India, which would make Bangladeshi children more likely than children from the other regions to benefit from zinc supplementation.

We agree with Bose et al that more studies are needed in a variety of populations before rational policy recommendations can be made on the role of zinc in the treatment of severe pneumonia. We know of 4 studies in progress, 2 in Africa [Tanzania (Clinical Trials.gov identifier NCT00133432) and Gambia (Current Controlled Trials registration no. ISRCTN335484593)] and 2 in Nepal (Clinical Trials.gov identifiers NCT00252304 and NCT00148733). In all of these trials, as in the trial of Bose et al, the possibility exists that the study group may not be zinc deficient and thus would show no benefit from zinc supplementation. The Gambian study (our study) is seeking to determine zinc status by measuring linear growth and immune status, in addition to plasma zinc concentrations, in a subgroup supplemented with zinc or placebo for 6 mo. As far as case definition goes, the Tanzanian study addresses the problem by including radiologic criteria, and the Gambian study does so by excluding wheezers, whereas the Nepali studies use definitions similar to those used by Bose et al. It is to be hoped that, with the completion of these studies, the picture will become clearer.

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