risk factors are not necessarily the only causes of clinical disease in patients with the syndrome. Because of colinearity with the other factors, predictive power does not always equate to causality. The contributions of elevated triacylglycerol-rich lipoproteins, a prothrombotic state, a proinflammatory state, and insulin resistance tend to be hidden behind blood pressure and HDL cholesterol, although considerable evidence exists that these 2 factors increase the risk of atherosclerotic CVD events.

Finally, the metabolic syndrome is progressive, ie, its risk factors tend to worsen with advancing age. For this reason, risk is compounded over time. Long-term risk rises progressively so that lifetime risk exceeds that which would be extrapolated from short-term risk projections.

On the whole, I essentially agree with Zivkovic and German that both the pathogenesis and accompanying risk of the metabolic syndrome should be viewed as a problem of systems biology. I encourage them to continue to explore this concept because it has implications beyond the metabolic syndrome, ie, to the entire field of risk prediction for disease.

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

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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## Reply to S Howie et al

Dear Sir:

Howie et al raise 2 issues that have important implications for evaluating interventions for the prevention and control of severe pneumonia. The first is the lack of consensus on the definition of severe pneumonia, which typically implies pneumonia of bacterial etiology. Determining the etiology of pneumonia based on clinical findings is difficult and often controversial, owing to the dearth of highly sensitive and specific tests. The composition of a case definition of severe pneumonia may vary considerably; for example, some case definitions include wheezing, fever, C-reactive protein concentrations, and chest X-ray findings, whereas others do not. Howie et al state that bronchiolitis cases are often misdiagnosed as pneumonia, which implies that wheezing is a finding that is not consistent with the diagnosis of pneumonia. We agree that bronchiolitis can be misdiagnosed as pneumonia, especially when a clinical diagnosis is made without the advantage of roentgenographic studies of the chest. The occurrence of wheezing as part of pneumonia has been well documented. In fact, many infants present with a mixed viral and bacterial coinfection. Coinfection with virus and bacteria has been shown in several studies of pneumonia etiology in children. Data from US (1) and Finnish (2) studies indicate that 20% to 30% of community-acquired pneumonias are of mixed (viral and bacterial) etiology. Until more accurate methods for diagnosing severe pneumonia are available, it is imperative that researchers describe their case definitions in detail sufficient enough to allow these studies to be compared and the generalizability of the findings to be assessed.

The second issue that Howie et al raise is the reliable clinical detection of findings that aid in the diagnosis of pneumonia. They specifically state that reliable detection of wheezing is difficult in developing countries, which may result in the misclassification of pneumonia cases. In our opinion, the reliable detection of wheezing, crepitations, and other symptoms is problematic in every clinical setting, not only in developing countries. The use of standardized protocols for the accurate assessment of each criterion in case definitions, coupled with rigorous training, is important for reducing interrater variability and bias in pneumonia studies.

On the basis of results of prior studies, we speculated that etiology may account for the treatment effect of zinc by season. Howie et al correctly point out that the time to recovery did not differ between wheezers and nonwheezers in the hot season, which, according to their definition, would be expected if the etiology of pneumonia explained the observed difference. We agree with this point. However, if bacterial and mixed pneumonias are more prevalent during the hot season, then it is possible that there would be no difference in recovery time between wheezers and nonwheezers. Our findings are consistent with the results from a recent therapeutic trial conducted in indigenous Australian children hospitalized with severe pneumonia (3). In that study, children with wheezing were excluded, and >90% of the participants had radiographic evidence of lobar pneumonia. This study by Chang et al showed greater morbidity in those supplemented with zinc.

We agree that the therapeutic effect of zinc in severe pneumonia may depend on the extent of zinc deficiency. Howie et al also speculated that South Indian children are less zinc deficient than are children in Bangladesh or Bengal, but they do not provide any supportive evidence. We believe that such a difference is unlikely, given the fact that, in contrast with the other study populations, South Indians are almost exclusively vegetarian. Vegetarian diets are a poor source of zinc, and they contain phytates that limit zinc absorption. Nevertheless, we agree that this issue should be taken into account in interpreting data in clinical studies of the effects of zinc supplementation.

These issues underscore the need for more data to resolve the questions regarding the efficacy of zinc supplementation in the treatment of severe pneumonia. We look forward to the results of current and future studies.

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