

sample size cannot be excluded as the reason for the lack of difference found between groups. Moreover, the exclusion of children who received antibiotics 48 h before enrollment may have introduced another bias, leading to the inclusion of milder cases of disease. This potential bias differently affected severe and not severe groups, because 19% and 8% were excluded for this reason, respectively. Natchu et al (2), who reviewed clinical trials with zinc supplementation as adjuvant therapy for pneumonia, found that exposure to antibiotics before enrollment in the study may modify the recovery time. Brooks et al (3) found a benefit in recovery time (hazard ratio: 0.6; 95% CI: 0.4, 0.9) of zinc supplementation as adjuvant therapy for treatment of severe pneumonia in 270 children aged <2 y. In that trial, recent antibiotic treatment was not a reason for exclusion.

Thus, it is our understanding that zinc supplementation as adjuvant therapy in pneumonia treatment remains a controversial issue and needs to be further studied, particularly in patients with severe pneumonia, who were not adequately represented in this study.

None of the authors declared a conflict of interest.

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Reply to V Zen et al

Dear Sir:

We thank Zen et al for their interest in our study, which investigated the effect of zinc supplementation as adjuvant therapy for childhood pneumonia. Regurgitation or vomiting after zinc supplementation is a well-known side effect of zinc (1) and has been described previously in trials of zinc supplementation in acute diarrhea (2, 3).

We agree that adverse effects can compromise blinding, particularly in studies that use simple blinding instead of labeling all packages that contain the active drug or placebo with a unique code as we did in our trial. By using unique codes, the researchers do not know who belongs to each of the treatment groups until the list that links the codes to the treatments is provided. In our case, this list was given to us only after data management and cleaning were completed.

The risk of regurgitation or vomiting after zinc or placebo supplementation was highest on day 1: 13.9% compared with 4.0%, respec-

tively. Thus, the vast majority of children did not experience any side effects on day 1. Because children were randomly allocated to either of the intervention groups in blocks of 16, we believe that the blinding of the study as such was by no means compromised.

We reanalyzed the trial after excluding the children with observed regurgitation or vomiting on day 1 or during the 14 d of zinc or placebo supplementation. Nearly 95% of the children had nonsevere pneumonia, and in this stratum the estimates in those with regurgitation or vomiting and those without were almost identical. For severe pneumonia after exclusion of children with regurgitation or vomiting on day 1 (hazard ratio: 0.97; 95% CI: 0.68, 1.4) and during the 14 d of zinc or placebo supplementation (hazard ratio: 0.82; 95% CI: 0.54, 1.2), the estimate changed toward a tendency to a beneficial effect of zinc. The corresponding estimates for children who did experience regurgitation or vomiting on day 1 (hazard ratio: 1.3; 95% CI: 0.50, 3.4) and during the 14 d of zinc or placebo supplementation (hazard ratio: 1.3; 95% CI: 0.7, 2.4) pointed toward a nonbeneficial effect of zinc. If the observers were indeed not adequately blinded to treatment allocation, one would have expected an observation bias toward an enhanced effect of zinc in those with observed regurgitation or vomiting.

In conclusion, we find no indication that our trial was fraught to observation bias caused by insufficient blinding of treatment allocation. We agree that excluding children who had received antibiotics in the previous 48 h may have resulted in a bias toward milder cases, which was discussed in our article. We stratified the randomization into severe and nonsevere pneumonia partly because the follow-up of the 2 strata was different and because we wanted to ensure equal proportions of zinc and placebo recipients in the 2 strata.

We did not power our study to identify a statistically significant reduction in time to recovery or risk of treatment failure with zinc in the severe pneumonia stratum. In that case, our study design would have been different. The published trials that have assessed the effect of zinc given to children with severe pneumonia have yielded conflicting results (4–8) and we completely agree that adequately powered studies are needed to assess whether zinc may have an effect in children with severe pneumonia or other severe bacterial infections.

None of the authors reported a conflict of interest.

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Vitamin D₂ and vitamin D₃ comparisons: fundamentally flawed study methodology

Dear Sir:

The recent article by Biancuzzo et al (1) presents data showing that vitamin D is equally bioavailable from orange juice and gel caps. This equivalence of vehicle was shown for both vitamin D₂ and vitamin D₃. The article is important because it has implications for health policy.

However, health professionals, scientists, and the public alike are interpreting this article as evidence that vitamin D₂ is equivalent to vitamin D₃, which is an issue that was not addressed by Biancuzzo et al (1). The results present no direct comparison of the area under the curve (AUC) for serum 25-hydroxyvitamin D for vitamin D₂ compared with vitamin D₃.

We are writing to emphasize that the conclusion of the article by Biancuzzo et al (1) is unfortunately ambiguous and hence subject to misinterpretation; the authors failed to make it clear that their study was not designed to compare vitamin D₂ with vitamin D₃. Without such clarification, the true interpretation of the findings of Biancuzzo et al will be lost to most who read their article.

The authors had no conflicts of interest to declare.

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Reply to S Lanham-New et al

Dear Sir:

We were pleased that Lanham-New et al appreciated that this article has important implications for health policy. It is, however, surprising and disappointing that these 3 experts did not fully understand the design, outcomes, and conclusions of our study. This study was designed to compare not only the bioavailability of vitamin D₂ and vitamin D₃ in orange juice with that in capsules, but it also was designed to confirm the previous report (1) that vitamin D₂ is equally as effective as vitamin D₃ in raising and maintaining total serum 25-hydroxyvitamin D [25(OH)D] concentrations. In our article (2), we clearly showed that serum 25-hydroxyvitamin D₂ [25(OH)D₂] and 25-hydroxyvitamin D₃ [25(OH)D₃] increased in identical fashion, and thus the results were not ambiguous—ie, vitamin D₂ was equally as effective as vitamin D₃ in both orange juice and in capsular form in raising and maintaining total serum 25(OH)D. We have performed a direct comparison of the area under the curve (AUC) for both total serum 25(OH)D concentrations and individually for serum 25(OH)D₂ and 25(OH)D₃ concentrations. We looked at total 25(OH)D AUC [25(OH)D₂+25(OH)D₃] for the postbaseline period, and compared the combined group who received doses with vitamin D₃ (OJ+gelcaps) with the combined group who received doses with vitamin D₂ (OJ+gelcaps). For the 38 subjects who received doses with vitamin D₃, the mean (±SD) AUC for total 25(OH)D was 286.28 ± 93.57. For the 33 subjects who received doses with vitamin D₂, the mean (±SD) AUC for total 25(OH)D was 259.82 ± 74.28. There was no significant difference between these 2 groups in mean total 25(OH)D AUC ($P = 0.196$, independent-samples t test).

We also evaluated the difference in mean total 25(OH)D AUC between the original 5 randomization groups. The analysis results show a significant overall group difference in mean total 25(OH)D AUC ($P = 0.0406$, ANOVA F test), but post hoc testing indicated that the only significant pairwise comparison was between the placebo (PL) and OJ(D₃)+PL groups; there were no significant differences in the mean total 25(OH)D AUC between the 4 groups treated with either vitamin D₃ or vitamin D₂ (Table 1). Therefore, on the basis of all of these analyses, it can be concluded with a high degree of certainty that vitamin D₂ is equally as effective as vitamin D₃ in raising and maintaining serum total 25(OH)D concentrations and that vitamin D₂ is equally as bioavailable as vitamin D₃.

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