Authors' responses

I. We thank Raina[1] for the interest in our research article[2]. We had clearly highlighted that the current study was conducted on children enrolled as part of a larger placebo-controlled, randomized trial on micronutrient supplementation in children with intrathoracic tuberculosis. Levels of 25-hydroxy vitamin D were measured in the stored samples after completion of the trial, as mentioned. The details of recruitment of children and randomization in the randomized controlled trial (RCT) and the results have been published elsewhere[3]. We agree with the author about the utility of a placebo arm in RCTs. The main study was a RCT with a factorial design where one of the four arms received a placebo. In this study, we had compared the outcomes in children who had received vitamin D with those who did not[2].

References

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3. Lodha R, Mukherjee A, Singh V, Singh S, Friis H, Faurholt-Jepsen D, *et al* and the Delhi Pediatric TB Study Group. The effect of micronutrient supplementation on treatment outcomes in children with intrathoracic tuberculosis: a randomized controlled trial. *Am J Clin Nutr* 2014; *100* : 1287-97.

II. We thank Onal *et al*[1] for interest in our article and for the opportunity to clarify some of the issues. In our study, which was performed in children enrolled in a randomized controlled trial, we assessed if the vitamin D status influenced the type of tuberculosis disease and also the outcomes[2]. We did not address the issue of susceptibility to tuberculosis, where presence of controls would have been mandatory. As is well known, cavitary disease in children is uncommon. In the children enrolled for this study, only 14 had cavitary disease and 11 of these were microbiologically confirmed; of these 11 children, four had sputum conversion at two months. The small numbers prevented any meaningful subgroup analyses. We agree with authors that there is a need for understanding the immune mechanisms better in the

children with TB and to study the influence of vitamin D status on these. We do not have data on proportion of children developing paradoxical response as it was not a predefined outcome.

References

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2. Khandelwal D, Gupta N, Mukherjee A, Lodha R, Singh V, Grewal HM, *et al* & Delhi Pediatric TB Study Group. Vitamin D levels in Indian children with intrathoracic tuberculosis. *Indian J Med Res* 2014; *140* : 531-7.

III. We thank Bhaumik and Hazra[1] for the interest in our article[2]. We agree that early sputum conversion may be beneficial; more data are required for confirming this effect. It is likely that multiple factors influence the sputum conversion and cure in tuberculosis. With advent of short course rifampicin based therapy, the cure rates have improved substantially. There are efforts to improve this further by using micronutrients, particularly those that may have some immune-modulation effects. Vitamin D is currently being examined for its role in various infectious diseases as it influences multiple immune pathways. As discussed in our paper, the results of use of vitamin D as an adjunct have been variable; this may partly be influenced by the genetic make-up. While it will be worthwhile to study the genetic polymorphisms influencing the immunomodulation pathways, the same is not feasible in our study population at present.

References

1. Bhaumik S, Hazra N. Role of genetic variants of vitamin D immunomodulation genes in clinical response to treatment of tuberculosis. *Indian J Med Res* 2015; *141* : 840-1.
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IV. We thank Kartal and Kartal[1] for the interest shown in our study[2]. We agree that LC-MS/MS is a very sensitive method for total 25-OH vitamin D measurement; however, it has been concluded that chemiluminescent immunoassay (CLIA) technology also has the required sensitivity to identify low levels of 25-OH vitamin D[3].

The aim of our study was to assess the association of baseline 25-OH vitamin D levels with type and outcome of tubercular disease. Baseline levels were measured before any antituberculosis drugs were started; the enzyme induction by rifampicin would not have affected these levels. The children were not receiving any concurrent comedication like anti-retroviral agents or glucocorticoids.

We agree that low socio-economic status/poor nutrition may be co-prevalant with both tuberculosis and low vitamin D levels. Nutritional status (weight for age z score) was considered as a covariate in the adjusted analysis done to assess the association of baseline 25-OH vitamin D with outcome of tubercular disease. Since we did not have any healthy control group, we did not conclude that vitamin D deficiency was associated with increased incidence of tuberculosis. We did not record the duration of sun exposure in these children; this has been mentioned as a limitation of the study.

References

1. Kartal AT, Kartal Ö. Evaluation of vitamin D levels in Indian children with intrathoracic tuberculosis. *Indian J Med Res* 2015; *141* : 841-2.
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3. Wallace AM, Gibson S, de la Hunty A, Lamberg-Allardt C, Ashwell M. Measurement of 25-hydroxyvitamin D in the clinical laboratory: current procedures, performance characteristics and limitations. *Steroids* 2010; *75* : 477-88.

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