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Authors’ reply

We thank Marcel Behr and colleagues for their comments. We share their view on the importance of endpoint specificity in tuberculosis vaccine efficacy trials but disagree with their interpretation of our data.1 Since the incidence rate ratios (IRR) for endpoints 0–4 presented in Behr and colleagues’ table do not differ statistically, no differences in vaccine efficacy might be inferred from the IRR point estimates presented. Pulmonary tuberculosis in young children is known to be pauci-bacillary, and only a minority is positive for Mycobacterium tuberculosis. However, endpoint 1 contained more microbiologically positive cases than negative cases, suggesting that our composite clinical case definition was rigorous.1 We agree that this clinical phenotype plus microbiological confirmation would represent an ideal diagnostic gold standard, however a definition of childhood tuberculosis that requires microbiological confirmation in all cases might increase sample size, duration, and cost to a degree that renders paediatric vaccine trials unaffordable.

Measurement of the effect of tuberculosis vaccines on latent infection is an important outcome for vaccine efficacy trials. The tuberculin skin test would not be an appropriate method, because of a lack of specificity. Hence our use of an interferon γ release assay (IGRA), although the variability and dynamics of IGRA are accepted.1,2 We agree that simple IGRA conversion might overestimate the true incidence of tuberculosis infection in young children, and should not be used in isolation for diagnosis of disease. Further data analysis using exploratory cutoffs might clarify the nature of true IGRA conversion.2 The biological importance of a positive IGRA is underlined by the eight-fold higher tuberculosis disease incidence among adolescents with simple IGRA conversion in our community.3 We agree with Pramod Upadhyay that socioeconomic factors, including nutrition, play a key role in the tuberculosis epidemic, and should be explored. Further analysis of the MVA85A trial dataset will look at characteristics of infants meeting efficacy endpoints, including nutritional status.

In this trial all infants received multivitamins and iron supplements for 2 months before and 1 month after enrolment. We excluded acutely ill or clinically malnourished infants from enrolment. During follow-up, triggers for admission and tuberculosis investigations included a failure to thrive or significant weight loss. In addition, these infants were referred to the health services for nutritional support. We failed to find any helmith infections in the majority of samples from admitted infants and their mothers (data not shown).

BCG does have established consistent efficacy against disseminated tuberculosis,4 and has shown efficacy in some trials against pulmonary tuberculosis,5 so basing new tuberculosis vaccine approaches on BCG is not unreasonable. Other approaches, however, are being explored.

We declare that we have no conflicts of interest other than those disclosed in the original paper.

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Department of Error

Guerin B, Pais AJ, el Mansour J, et al, and the MERS-CoV study group. Clinical features and viral diagnosis of two cases of infection with Middle East Respiratory Syndrome coronavirus: a report of nosocomial transmission. Lancet 2013; 381: 2265–72—In this Article, in the Patients and genetic analysis section and in the Appendix, two strains of Middle East Respiratory Syndrome coronavirus were incorrectly named; the names should have been England/ Qatar/2013 and Munich/Abu_Dhabi/2013. In the Results section, the partial pressure of oxygen to fraction of inspired oxygen ratio for patient 1 should have been 100, and for patient 2 should have been 90. In Table 3, for patient 1, the first row for May 9 should not have been included, and the second row for May 9 should have been listed as a plasma specimen. These corrections have been made to the online version and appendix as of June 28, 2013, and to the printed Article.