Reply to Kernodle and von Reyn

To the Editor—We thank Kernodle [1] and von Reyn [2] for their comments. We are glad that von Reyn finds our article [3] a useful clarification of factors explaining the wide range of efficacy of BCG in trials and that it will help inform design of new trials. We recognize the limitations of meta-regression, were careful to acknowledge and discuss these, and are pleased to contribute further.

Kernodle [1] questions our conclusion that age at vaccination, prior Mycobacterium tuberculosis infection or sensitization with environmental mycobacteria, and latitude (potentially a proxy for mycobacterial exposure) could explain the heterogeneity in BCG trial results and argues that differences in BCG strains (documented by Brosh and others) could be an important factor. We found no evidence for an effect of BCG strain in our systematic review. This does not mean that BCG strain makes no contribution anywhere, although there are several examples in our review of the same vaccine (eg, Tice and the Danish strain) performing very differently in trials in different populations. In addition, very different BCG strains (Danish/Copenhagen strain M. tuberculosis and Mycobacterium microti) used in the Medical Research Council trial performed identically well, whereas the 2 strains (Danish/Copenhagen and Pasteur) used in the Chingleput trial performed identically poorly.

Kernodle [1] refers to 3 observational studies suggesting superiority of the Japanese BCG strain. It seems to have performed better than “a Serbian formulation of BCG Pasteur or BCG Russia” in Kazakhstan. Perhaps it did, although in fact the differences in performance were less marked in culture-confirmed cases than in reports of tuberculosis, and the authors of that study themselves mention several sources of bias affecting observed levels of protection: variations in tuberculosis incidence over time, possible changes in diagnostic and notification practices, and catch-up vaccination in those unvaccinated. There is an irony in Kernodle’s reference to Comstock’s analysis of case-control studies [4], in that Comstock was himself cautious about the use of case-control studies in vaccine evaluation [5]. Of course one cannot prove a negative, but to our knowledge, BCG Japan was not used in any of the trials included in our review.

We examined the data carefully, taking into account the changes in strains over time reported by Brosh that Kernodle mentions [6]. We found no relationship between genetic changes as characterized by Brosh (our Figure 3) or trial date and protection (our Figure 4), that is, no evidence for BCG strain relevance in the trials, although we found clear evidence that age at vaccination and rigor in excluding sensitized subjects could explain the observed results. The Danish strain (in DU2 group III according to Brosh) is in current use [7]. Based on the above arguments, we believe that the Danish strain vaccines used in several of the trials and used today should be similar. We have urged that the United Nations Children’s Fund rationalize the allocation of different vaccine strains to different populations on a clear schedule (which would encourage comparisons similar to that in Kazakhstan but with a more rigorous design), but to date this has not proved feasible (P. E. M. F., unpublished communication).

When arguing that sensitization to mycobacteria does not explain variation in BCG protection in trials, Kernodle [1] cites 2 results as inconsistent with our conclusions. The first is the “low” BCG efficacy in the Muscogee County study, which used stringent testing to exclude sensitized children. However, the trial had limited power: only 7 cases were detected, and the 95% confidence interval (0.28–5.58) is consistent with no protection but also with strong protection, or even greatly increased risk. His second example is the Puerto Rico trial, in which he suggests that efficacy was similar in subgroups with different levels of sensitization. However, this is based on a post hoc subgroup analysis (determining sensitization to 100 TU of purified protein derivative after randomization to vaccine or placebo) presented in a graph of tuberculosis rates with no numbers or confidence intervals. It is well known that such analyses are also prone to bias: subgroups may be chosen based on inspecting the data, or the findings could be false-positives owing to multiple testing [8]. The evidence from these 2 trials is not robust enough to contradict our conclusions.

von Reyn [2] comments on geographic gradients and nontuberculous mycobacteria (NTM) exposure. Rather than say that latitude is a determinant of [BCG] efficacy, “we prefer to say that it is a correlation of factors explaining the effectiveness of BCG vaccines. This could be NTM exposure or—here we agree with von Reyn—M. tuberculosis, which is among the mycobacteria whose exposures are now higher at lower latitudes. Latitude (along with altitude, soil type, and urban-rural differences) correlates with many environmental and ecological factors and so is likely to correlate with patterns of mycobacterial exposure. It is important to recognize that there are many species of NTM, with different antigenic compositions (and thus with varying potential for cross-protection with M. tuberculosis) and ecological requirements, and it is inappropriate to lump them all together.

The only study that applied a single NTM assay to a very large population over a considerable area (testing of US naval recruits with purified protein derivative from a nontuberculous mycobacteria Batty strain) showed a clear geographic gradient, with far higher...
prevalence in the southeast than in the northern United States [9]. This is only a single antigen in a single country, but it illustrates a point and deserves attention. The study by von Reyn in small numbers of volunteers at different latitudes might be expanded. Geographic patterns of the incidence of NTM disease in patients with human immunodeficiency virus, also noted by von Reyn, may also be useful information, if biases in ascertainment are minimized, although it will reflect both host response and environmental exposure to NTM [10]. Several lines of evidence have demonstrated that exposure to NTM can influence risk of tuberculosis in humans [11] and the effectiveness of BCG in animals [12], findings that are consistent with the observed differential effectiveness of BCG in trials as a function of prior sensitivity to tuberculin and are also consistent with the latitude gradient in BCG effectiveness, as shown in our review of the trials. The history of BCG should caution us against simplistic interpretations. Sensitization to NTM or M. tuberculosis may not be the whole story, but it is a part.

Note
Potential conflicts of interest. All authors report no conflicts of interest.

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