Problems With Ascribing Between-Trial Differences in BCG Effectiveness to Sensitization With Environmental Mycobacteria

To the Editor—Mangtani et al recently analyzed the results of 21 trials of BCG vaccination [1], finding that “latitude and age at vaccination/tuberculin testing stringency could explain all of the between-trial heterogeneity.” They conclude that the “absence of prior M. tuberculosis infection or sensitization with environmental mycobacteria is associated with higher efficacy of BCG against pulmonary tuberculosis and possibly against miliary and meningeal tuberculosis.”

The first test of the merit of a hypothesis is how well it explains prior observations. If the work of Mangtani et al survives scrutiny, then they will have settled a long-standing controversy regarding whether observed differences in BCG efficacy are due to sensitization with environmental mycobacteria or changes in BCG. However, there are problems with their analysis. For example, although the authors support their theory by citing a retrospective analysis involving children in the Chingleput trial with low reactivity to Mycobacterium intracellulare in whom BCG was modestly effective, they fail to mention that, in the Puerto Rico trial a large tuberculin dose (100 TU) was used to identify sensitized children and that BCG was as effective in this group as in nonsensitized children [2]. Their model also does not explain why BCG was ineffective in Muscogee County, Georgia, despite the use of a stringent skin test to exclude sensitized children. It is also unclear why 60% of adults 25–44 years old were protected.
by BCG in the Madanapalle trial (9- to 14-year follow-up), whereas adults were not protected in the Chingleput trial [3, 4]. This difference is perplexing, as these villages are only 185 km apart and a similar proportion of participants, about 47% and 58%, respectively, were excluded from analysis. In essence, in these studies BCG efficacy differed despite similar latitude, age, and proportion of excluded persons. Furthermore, Mangtani et al classify the Madanapalle and Chingleput trials as stringent and nonstringent, respectively, which requires clarification as it seems that in geographically close settings a stringent trial should exclude a higher proportion of persons than a nonstringent trial. Indeed, this example raises doubts about the legitimacy of their definition of stringency, upon which their claims rest. In summary, multiple observations from the trials analyzed by Mangtani et al do not support their hypothesis.

Mangtani et al also failed to find evidence that different BCG strains induce different levels of protection or that there was a loss of protection as BCG evolved over time. It is noteworthy that the start dates for most of the trials in which BCG demonstrated efficacy were between 1933 and 1950. During this period, BCG was still undergoing serial passage in laboratories around the world, and it was not until later in the 1950s and 1960s that most of the currently available BCG strains were preserved in their present form. Thus, as the vaccines used in most of these trials no longer exist, the authors’ findings have uncertain relevance for current BCG vaccination strategies. Yet BCG clearly changed while it was being passaged, and there is abundant evidence of gene deletions, regions of tandem duplication/triplication within the chromosome, and other, more subtle mutations [5, 6]. This raises an important question that the analysis of Mangtani et al is inadequate to answer—that is, are any of the currently available BCG vaccines still effective in preventing pulmonary tuberculosis?

In 1974, the same question confronted Comstock et al, after they found less than expected BCG efficacy in the Puerto Rico trial, which could not be explained by exposure to environmental mycobacteria [2]. These authors hypothesized that among the currently available BCG strains, some are virtually useless, some confer moderate protection, and perhaps a few are still potent. Then, in 1988, Comstock reported that he had identified an effective BCG strain by carefully analyzing case-control studies [7]. He found that the BCG Japan strain (Tokyo 172), which has undergone fewer passages than any other current BCG strain and is most like the original BCG genetically [6], exhibited 50%–60% protection in infants in 2 tropical countries (latitude 0°–20°) where the BCG Danish 1331 and BCG Pasteur 1173P2 strains lacked efficacy. Comstock then proposed that the relative effectiveness of BCG strains could be determined by switching the strain used in routine infant vaccination programs and monitoring the impact on tuberculosis cases. A cohort study based on this model was recently conducted in Kazakhstan [8], where BCG is routinely administered at birth; however, suspension of vaccination for 8 months due to adverse effects provided a control group of >160,000 unvaccinated infants that enabled relative risk values to be calculated. This study found the BCG Japan strain to be more effective in preventing clinically defined, radiologically confirmed cases of tuberculosis during the first 3 years of life (relative risk [RR], 0.31; 95% confidence interval [CI], 0.25–0.39) than a Serbian formulation of BCG Pasteur (RR, 0.57; CI, 0.47–0.69) or BCG Russia (RR, 0.78; CI, 0.65–0.93). In summary, although all 3 BCG vaccines were highly effective in preventing tuberculosis meningitis, their efficacy against pulmonary tuberculosis differed markedly, and the results verified the relatively high potency of BCG Japan identified earlier by Comstock.

In conclusion, the issue of whether the heterogeneity in BCG effectiveness is better explained by sensitization to environmental mycobacteria or by changes in BCG deserves further debate. Both factors possibly contribute; however, it is noteworthy that the hypothesis of Mangtani et al does not pass the first test of merit as it fails to explain many clinical observations—not only the between-trial differences noted above, but also the within-trial differences detected in the Kazakhstan study. In contrast, Comstock’s assessment of BCG Japan has passed a second, more rigorous test of merit; that is, it has been shown to have predictive value. Presently the most important question regarding BCG vaccination practices is whether any of the other currently available BCG strains are as effective as BCG Japan in preventing pulmonary tuberculosis.

Note

Potential conflicts of interest. Author certifies no potential conflicts of interest.

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Douglas S. Kernodle
Division of Infectious Diseases, Department of Medicine, Vanderbilt University School of Medicine, and Nashville Veterans Affairs Medical Center, Nashville, Tennessee

References


Correspondence: Douglas S. Kernodle, MD, Division of Infectious Disease, A-2200 Medical Center N, Vanderbilt University Medical Center, Nashville, TN 37232-2582 (doug.kernodle@vanderbilt.edu).

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