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Are Bacille Calmette-Guérin Skin Reactions the Most Important Correlates of Bacille Calmette-Guérin's Specific and Nonspecific Effects?

Despite not being a perfect vaccine against tuberculosis (TB), bacille Calmette-Guérin (BCG) has been in use for a century, and the BCG vaccination program remains one of the world's major health achievements with more than 4 billion humans inoculated. Nevertheless, BCG still leaves us with many questions (1). For example, how can it be assessed after vaccination whether long-term protection against TB was induced?

Are measurable proxies of vaccination such as BCG skin reaction characteristics (reaction yes or no, reaction type and size) and the tuberculin skin test (TST) response (yes or no, size) informative to that end?

Surprisingly, for the world's oldest vaccine still in use, this is still debated.

Previous work, with important limitations, did not find an association between BCG scar size and protection against TB (2).

However, studies from when the infant dose of BCG was halved from 0.1 ml to 0.05 ml indicate that the dose of BCG is important for the formation of BCG scars and TST responses (3, 4). Furthermore, many studies, including randomized controlled trials (RCTs), have revealed that vaccination technique and the BCG strain are the main determinants for both developing a skin reaction and the skin reaction size and TST responses (5–7). BCG is difficult to administer intradermally, especially in the thin dermis of a neonate, and adequate vaccination technique increases the likelihood of developing a skin reaction. Regarding strains, BCG-Japan and BCG-Denmark have been better at inducing skin reactions than BCG-Russia. This is in concordance with laboratory studies showing that those strains contain far more mycobacteria with a higher ratio of live versus dead mycobacteria when compared with strains such as BCG-Bulgaria and BCG-Russia (8). Corroborating an association between skin reaction characteristics and TB protection, a large cohort study from Kazakhstan found that BCG-Japan was more efficacious than BCG-Russia in preventing clinical TB notifications and culture-confirmed TB (9).

Originally Published in Press as DOI: 10.1164/rccm.202112-2863ED on January 31, 2022

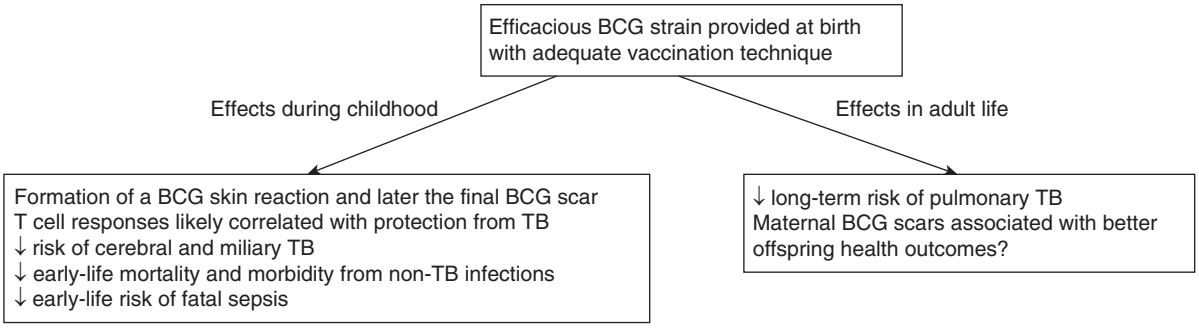

Figure 1. Specific and nonspecific effects associated with adequate vaccination with bacille Calmette-Guérin (BCG) resulting in the formation of BCG skin reactions. TB = tuberculosis.

In this issue of the *Journal*, Pittet and colleagues (pp. 830–841) scrutinize the importance of early BCG skin reactions and their association with immune responses correlated with TB-specific protection (10). Nested within an Australian RCT that tested effects of newborn vaccination with three major BCG strains, the authors conducted elaborate analyses of stimulated whole blood to assess *in vitro* mycobacteria-specific immune responses. These correlated positively with the BCG skin reaction size and characteristics, also after adjusting for BCG strain and age at vaccination.

Larger reaction size was positively associated with the magnitude of mycobacteria-specific T-cell responses, which are vital for host defense mechanisms against mycobacteria (10). In line with previous RCT data (6), Pittet and colleagues also found that inoculation with BCG-Russia was least likely to result in a skin reaction. When a reaction did arise, the median size was only 2 mm for BCG-Russia, compared with 5 mm for both BCG-Denmark and BCG-Japan (10). An important limitation is that the actual degree of long-term clinical protection against TB can only be assessed through a large cohort study with several decades of follow-up.

The novel data add to a series of studies pointing to the importance of BCG and its associated skin reaction characteristics (5, 7, 9, 11–15).

Aside from providing protection against TB, BCG has been shown to have beneficial nonspecific effects, providing marked protection against infections other than TB (11). Across four RCTs conducted in Guinea-Bissau, BCG at birth reduced the neonatal mortality from non-TB infections by 40% (11–60%) (12).

A meta-analysis that included seven child cohorts reported that among BCG-vaccinated children, having developed a BCG scar was associated with a 39% (26–49%) lower all-cause mortality risk when compared with not having a scar (13).

The final vaccine scar takes 4–6 months to develop, but the early skin reaction kinetics also appear indicative: in a large cohort of more than 6,000 infants who had received BCG within a week after birth, "BCG reactors" with a visible early BCG skin reaction by 2 months of age had a 51% (5–74%) reduction in subsequent infant all-cause mortality risk (7). Important in the light of the data presented by Pittet and colleagues, there was a marked reduction in mortality with increasing reaction size, and BCG reactors had higher specific and nonspecific cytokine responses, responses that were highest among those with large skin reactions (7).

Emerging data furthermore indicate that being born to a mother with a BCG scar is associated with improved health outcomes (14, 15). A retrospective study reported that maternal BCG scars were associated with a 60% (4–83%) reduction in all-cause offspring mortality risk by 6 weeks of age when compared with no maternal scar (14), and in a prospective study encompassing more than 10,000 BCG-vaccinated newborns, maternal BCG scars were associated with a 51% (9–74%) reduction in the risk of fatal sepsis in the offspring (15).

Given that the BCG skin reaction is vital for overall health, one might presume that the prevalence of skin reactions would be monitored during the first months after vaccination. However, despite representing an obvious target for monitoring the efficacy of BCG vaccination programs, this is not done. The universal policy in low-income countries is to provide BCG at birth, but the program performance is assessed by BCG vaccination coverage estimates at 12 months of age, which fails to address the frequent and often substantial delays in vaccination and the frequency of failed vaccinations. In the literature, large cohort studies have reported a BCG scar prevalence as high as 99% (7) but also as low as 52% in a cohort vaccinated with BCG-Russia (13). All children should develop an adequate BCG skin reaction that later forms a permanent visible BCG scar for their own sake and their future offspring; effects of revaccinating scar-negative children and adults should be further investigated.

Pittet and colleagues' work is important also in regard to the different BCG strains that are prequalified for use by UNICEF and widely used, despite not having bioequivalent properties. As demonstrated, BCG-Russia produces fewer BCG skin reactions that are considerably smaller, likely reducing the vaccine efficacy for both specific and nonspecific outcomes.

Pittet and colleagues are to be congratulated for the addition of important data indicating that the BCG skin reaction size is likely associated with enhanced specific protection against TB. This adds to a growing pool of data providing policy makers with a list of good reasons (Figure 1) to emphasize the prevalence of BCG skin reactions and their sizes as important metrics for BCG vaccination program efficacy. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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