

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

Schaltz-Buchholzer, Frederik

Published in:
American Journal of Respiratory and Critical Care Medicine

DOI:
10.1164/rccm.202112-2863ED

Publication date:
2022

Document version:
Final published version

Document license:
CC BY-NC-ND

Citation for pulished version (APA):
Schaltz-Buchholzer, F. (2022). Are Bacille Calmette-Guérin Skin Reactions the Most Important Correlates of Bacille Calmette-Guérin's Specific and Nonspecific Effects? *American Journal of Respiratory and Critical Care Medicine*, 205(7), 748-750. <https://doi.org/10.1164/rccm.202112-2863ED>

Go to publication entry in University of Southern Denmark's Research Portal

Terms of use

This work is brought to you by the University of Southern Denmark.
Unless otherwise specified it has been shared according to the terms for self-archiving.
If no other license is stated, these terms apply:

- You may download this work for personal use only.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying this open access version

If you believe that this document breaches copyright please contact us providing details and we will investigate your claim.
Please direct all enquiries to puresupport@bib.sdu.dk

References

1. Gravlee CC. How race becomes biology: embodiment of social inequality. *Am J Phys Anthropol* 2009;139:47–57.
2. Manly JJ. Deconstructing race and ethnicity: implications for measurement of health outcomes. *Med Care* 2006;44:S10–S16.
3. Harik-Khan RI, Fleg JL, Muller DC, Wise RA. The effect of anthropometric and socioeconomic factors on the racial difference in lung function. *Am J Respir Crit Care Med* 2001;164:1647–1654.
4. Harik-Khan RI, Muller DC, Wise RA. Racial difference in lung function in African-American and White children: effect of anthropometric, socioeconomic, nutritional, and environmental factors. *Am J Epidemiol* 2004;160:893–900.
5. Lum S, Bountziouka V, Sonnappa S, Wade A, Cole TJ, Harding S, et al. Lung function in children in relation to ethnicity, physique and socioeconomic factors. *Eur Respir J* 2015;46:1662–1671.
6. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179–187.
7. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al.; ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012;40:1324–1343.
8. Burney PG, Hooper RL. The use of ethnically specific norms for ventilatory function in African-American and White populations. *Int J Epidemiol* 2012;41:782–790.
9. Gaffney AW, McCormick D, Woolhandler S, Christiani DC, Himmelstein DU. Prognostic implications of differences in forced vital capacity in black and white US adults: findings from NHANES III with long-term mortality follow-up. *EClinicalMedicine* 2021;39:101073.
10. McCormack MC, Balasubramanian A, Matsui EC, Peng R, Wise RA, Keet CA. Race, lung function and long-term mortality in the national health and examination survey III. *Am J Respir Crit Care Med* [online ahead of print] 01 Oct 2021; DOI: 10.1164/rccm.202104-0822LE.
11. Baugh AD, Shiboski S, Hansel NN, Ortega V, Barjakteravic I, Barr RG, et al. Reconsidering the utility of race-specific lung function prediction equations. *Am J Respir Crit Care Med* 2022;205:819–829.
12. Couper D, LaVange LM, Han M, Barr RG, Bleecker E, Hoffman EA, et al.; SPIROMICS Research Group. Design of the Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS). *Thorax* 2014; 69:491–494.
13. Maroko AR, Doan TM, Arno PS, Hubel M, Yi S, Viola D. Integrating social determinants of health with treatment and prevention: a new tool to assess local area deprivation. *Prev Chronic Dis* 2016;13:E128.
14. Braun L, Wolfgang M, Dickersin K. Defining race/ethnicity and explaining difference in research studies on lung function. *Eur Respir J* 2013;41: 1362–1370.
15. Kumar R, Seibold MA, Aldrich MC, Williams LK, Reiner AP, Colangelo L, et al. Genetic ancestry in lung-function predictions. *N Engl J Med* 2010; 363:321–330.
16. Bhakta NR, Kaminsky DA, Bime C, Thakur N, Hall GL, McCormack MC, et al. Addressing race in pulmonary function testing by aligning intent and evidence with practice and perception. *Chest* 2022;161: 288–297.
17. Borrell LN, Elhawary JR, Fuentes-Afflick E, Witonsky J, Bhakta N, Wu AHB, et al. Race and genetic ancestry in medicine: a time for reckoning with racism. *N Engl J Med* 2021;384:474–480.
18. Elmaleh-Sachs A, Balte P, Oelsner EC, Allen NB, Baugh AD, Bertoni AG, et al. Race/ethnicity, spirometry reference equations and prediction of incident clinical events: the Multi-Ethnic Study of Atherosclerosis (MESA) lung study. *Am J Respir Crit Care Med* 2022; 205:700–710.
19. Agrawal A, Aggarwal M, Sonnappa S, Bush A. Ethnicity and spirometric indices: hostage to tunnel vision? *Lancet Respir Med* 2019;7:743–744.

Copyright © 2022 by the American Thoracic Society



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).

Ⓒ This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0. For commercial usage and reprints, please e-mail Diane Gern (dgern@thoracic.org).

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

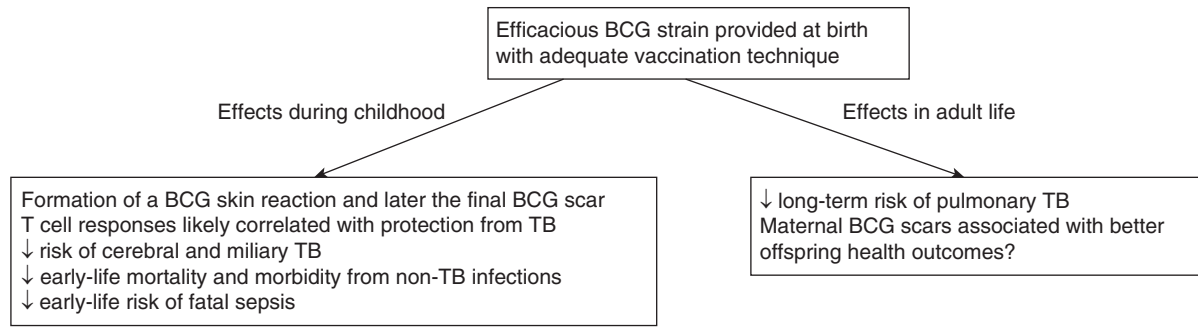


Figure 1. Specific and nonspecific effects associated with adequate vaccination with bacille Calmette-Guérin (BCG) resulting in the formation of BCG skin reactions. TB = tuberculosis.

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.

Frederik Scholtz-Buchholzer, M.D., Ph.D.

Bandim Health Project

INDEPTH Network

Bissau, Guinea-Bissau

and

Institute of Clinical Research

University of Southern Denmark and Odense University Hospital

Odense, Denmark

ORCID ID: 0000-0001-7643-8322 (F.S.-B.).

References

- Danchuk SN, Behr MA. Bacille Calmette-Guérin: one hundred years, one hundred questions. *Clin Infect Dis* 2020;71:1894–1895.
- Sterne JA, Fine PE, Pönnighaus JM, Sibanda F, Munthali M, Glynn JR. Does bacille Calmette-Guérin scar size have implications for protection against tuberculosis or leprosy? *Tuber Lung Dis* 1996;77:117–123.
- Lowry PW, Ludwig TS, Adams JA, Fitzpatrick ML, Grant SM, Andrie GA, et al. Cellular immune responses to four doses of percutaneous bacille Calmette-Guérin in healthy adults. *J Infect Dis* 1998;178:138–146.
- Valenzuela MT, Ferrer X, Leal I, Pacheco M, Castillo N, Cumsille F. Comparative study of the efficacy of two types of BCG vaccines administered in different doses [in Spanish]. *Rev Med Chil* 1998;126:1126–1131.
- Roth A, Sodemann M, Jensen H, Poulsen A, Gustafson P, Gomes J, et al. Vaccination technique, PPD reaction and BCG scarring in a cohort of children born in Guinea-Bissau 2000-2002. *Vaccine* 2005;23:3991–3998.
- Scholtz-Buchholzer F, Bjerregaard-Andersen M, Øland CB, Golding C, Stjernholm EB, Monteiro I, et al. Early vaccination with bacille Calmette-Guérin-Denmark or BCG-Japan versus BCG-Russia to healthy newborns in Guinea-Bissau: a randomized controlled trial. *Clin Infect Dis* 2020;71:1883–1893.
- Scholtz-Buchholzer F, Berendsen M, Roth A, Jensen KJ, Bjerregaard-Andersen M, Kjær Sørensen M, et al. BCG skin reactions by 2 months of age are associated with better survival in infancy: a prospective observational study from Guinea-Bissau. *BMJ Glob Health* 2020;5:e002993.
- Angelidou A, Conti M-G, Diray-Arce J, Benn CS, Shann F, Netea MG, et al. Licensed bacille Calmette-Guérin (BCG) formulations differ markedly in bacterial viability, RNA content and innate immune activation. *Vaccine* 2020;38:2229–2240.
- Favorov M, Ali M, Tursunbayeva A, Aitmagambetova I, Kilgore P, Ismailov S, et al. Comparative tuberculosis (TB) prevention effectiveness in children of *Bacillus Calmette-Guérin* (BCG) vaccines from different sources, Kazakhstan. *PLoS One* 2012;7:e32567.
- Pittet LF, Fritschi N, Tebruegge M, Dutta B, Donath S, Messina NL, et al.; BCG Immune Response Study (BIRS) group. Bacille Calmette-Guérin skin reaction predicts enhanced mycobacteria-specific T-cell responses in infants: a *post hoc* analysis of a randomized controlled trial. *Am J Respir Crit Care Med* 2022;205:830–841.
- Benn CS, Fisker AB, Rieckmann A, Sørup S, Aaby P. Vaccinology: time to change the paradigm? *Lancet Infect Dis* 2020;20:e274–e283.
- Scholtz-Buchholzer F, Aaby P, Monteiro I, Camala L, Faurholt Simonsen S, Nørtoft Frankel H, et al. Immediate bacille Calmette-Guérin vaccination to neonates requiring perinatal treatment at the maternity ward in Guinea-Bissau: a randomized controlled trial. *J Infect Dis* 2021; 224:1935–1944.
- Benn CS, Roth A, Garly M-L, Fisker AB, Scholtz-Buchholzer F, Timmermann A, et al. BCG scarring and improved child survival: a combined analysis of studies of BCG scarring. *J Intern Med* 2020;288:614–624.
- Berendsen M, Scholtz-Buchholzer F, Bles P, Biering-Sørensen S, Jensen KJ, Monteiro I, et al. Parental *Bacillus Calmette-Guérin* vaccine scars decrease infant mortality in the first six weeks of life: a retrospective cohort study. *EClinicalMedicine* 2021;39:101049.
- Scholtz-Buchholzer F, Bjerregård Øland C, Berendsen M, Bjerregaard-Andersen M, Stjernholm EB, Golding CN, et al. Does maternal BCG prime for enhanced beneficial effects of neonatal BCG in the offspring? *J Infect* [online ahead of print] 24 Dec 2021; DOI: 10.1016/j.jinf.2021.12.028.

Copyright © 2022 by the American Thoracic Society