

Lessons From Bacille Calmette-Guérin for SARS-CoV-2 Vaccine Candidates

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Developers of severe acute respiratory syndrome coronavirus 2 vaccines should consider some of the lessons from a “new” vaccine introduced in 1921, namely bacille Calmette-Guérin.

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One hundred years ago, tuberculosis was among the top 3 causes of death in many countries, including the United States, Great Britain, and France. At that time, a candidate vaccine, called le bacille de Calmette et Guérin (BCG), was completing what is now called preclinical testing. In a series of reports published between 1909 and 1920, Albert Calmette and Camille Guérin showed that their strain of *Mycobacterium bovis* was safe in guinea pigs, monkeys, and calves; they even wrote that it was “inoffensif” after an unidentified human survived an intravenous challenge of 44 000 bacilli [1]. The vaccine was first used on the child of a tuberculous mother in 1921 to great acclaim, and early studies assessing 579 vaccinated children living 4 years in tuberculous families reported 100% survival [2]. After such a promising beginning, what happened next? While an unknown number of lives might have been saved by BCG vaccines, the global tuberculosis epidemic rages on with an estimated 10 million cases and 1.5

million deaths attributable to tuberculosis in 2019 [3].

What are some of the lessons from the BCG experience, spanning conceptual to technical issues, that we should consider when evaluating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine candidates in 2020?

Controlled Trials

BCG was introduced in 1921. The first randomized controlled trials were started a decade later [4] and the largest randomized trial was done 4 decades later, when its negative result was too late to change policy [5]. The trials followed the rollout. Despite pressure to act promptly on the coronavirus disease 2019 (COVID-19) pandemic, dissemination of new SARS-CoV-2 vaccine candidates should not precede the controlled demonstration of safety and efficacy, something argued already in statistical debates surrounding the early uncontrolled BCG data over 90 years ago. Incredibly, the same mistakes are now being repeated in Russia and in China, and there is talk of the Food and Drug Administration approving vaccines in the United States before trials are completed.

Target Population

Given that tuberculosis in young children is generally considered to be less transmissible [6], a tuberculosis vaccine would be most effective if it prevented contagious pulmonary tuberculosis in adolescents

and adults. But BCG is given at birth to protect infants against extrapulmonary disease. We need to define the target population to optimally thwart the COVID-19 pandemic. Is the goal of a COVID-19 vaccine to prevent morbidity and mortality in the elderly, or to prevent SARS-CoV-2 transmission, perhaps in school-age children and young adults? The answer to this question should both define the target product profiles for SARS-CoV-2 vaccine candidates and inform the clinical trial development pathway. Without considering the target population, one risks doing early human studies on healthy adults who do not represent the breadth and diversity of the individuals who will eventually be the target population for vaccination.

Manufacturing Matters

In the late 1920s, a batch of BCG was contaminated with virulent *Mycobacterium tuberculosis* resulting in the Lübeck disaster, where 251 infants were challenged with BCG vaccine contaminated with live *M. tuberculosis* [7]. In the 1940s, it was noted that BCG strains from different laboratories around the world were phenotypically different, due to evolution of the vaccine in the laboratory, as was confirmed later by genomic study [8]. In the 1970s, it was reported that the Swedish strain of BCG resulted in more adverse effects when it was produced in the Danish BCG vaccine laboratory [9]. There is no reason in 2020 for a SARS-CoV-2

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vaccine to be anything other than a defined, sequence-confirmed, phenotypically specified biologic agent. There is also no reason to repeat the Lübeck disaster, but this remains a theoretical risk with vaccines containing inactivated virus that is not completely killed. Details of manufacturing and vaccine preparation need to be resolved before trials in humans to avoid some of the pitfalls encountered with BCG, where trials on laboratory-adapted variants of BCG have been associated with different outcomes.

Outliers Are Interesting

When looking at responses to BCG, it is tempting to be satisfied if 90% of individuals have a measurable response, such as tuberculin skin test (TST) conversion or a scar at the site of vaccination. However, only 5%–10% of individuals infected with *M. tuberculosis* develop tuberculosis disease, suggesting that the statistically “normal” response overlooks the minority that propagate the epidemic. The study of outliers, including the rare individuals who develop disseminated BCG, has illuminated the biology of susceptibility, not only to BCG but also to tuberculosis [10]. As we prepare for clinical evaluation of SARS-CoV-2 vaccines, we should be careful not to disregard the outliers. A minority of those infected with SARS-CoV-2 develop severe disease requiring hospitalization, and emerging data from different countries indicate that there are individuals who are not only susceptible to reinfection but also disease [11]. The study of these outliers may be particularly informative regarding the biology of host resistance, and the best strategy for vaccine-induced protection.

Nonspecific Effects

Although BCG is a century-old vaccine, it is astonishing that our understanding of its “on-target” effects (against tuberculosis) versus its “off-target” effects (against other diseases) is quite limited. BCG protection against pulmonary tuberculosis has varied from 0% to 80% in clinical trials [12]. In contrast, the

ability of BCG to prevent recurrence and progression of nonmuscle invasive bladder cancer has been consistent across studies [13]. And we know that BCG vaccination decreases the viral titer of yellow fever vaccine [14]. BCG vaccination has also been associated with a reduction in neonatal sepsis and all-cause mortality [15]. BCG has even been proposed as a vaccine against SARS-CoV-2 and a recent BCG clinical trial in the elderly (>65 years old) indicates that the vaccination is safe and provides protection against viral respiratory tract infections [16]. As new SARS-CoV-2 vaccines are evaluated, we need to be on the look-out for unexpected, nonspecific effects, beneficial or harmful. To do so, we need to store biologic samples from the first vaccine trials. An impediment to biological exploration of BCG trials is the unavailability of the retention lots of vaccines used in the trials, as well as biosamples from the study subjects. Consequently, retrospective investigation of protection against pulmonary tuberculosis, or extrapulmonary tuberculosis, or even all-cause neonatal mortality, is challenging. SARS-CoV-2 vaccine trials provide an opportunity to collect and bank biologic and epidemiologic data on study subjects, so that after these trials assess predefined end points, there will be opportunities for a better understanding of the off-target effects of vaccination.

Mechanism of Action

For many vaccines in current usage, efficacy was demonstrated without or prior to a known mechanism of action. Likewise, there was no proposed mechanism of action for BCG in 1921. Subsequently, it was shown that BCG leads to a conversion of the TST and that BCG-associated protection was on the same order as someone already TST positive [17]. This led to the untested assumption that BCG works through the induction of cell-mediated immunity. However, an analysis of BCG clinical trials noted that protective efficacy did not correlate with TST

conversion [18]. Without knowing how BCG works, when it does, tuberculosis vaccine studies are proceeding without a surrogate of protection, and can only measure cases rather than immunologic end points. Do the mycobacterial antigens induce protection? Or is the mycobacterial cell wall a nonspecific immune adjuvant? A mechanism of action for a SARS-CoV-2 vaccine, although not a prerequisite for phase 3 studies, would be valuable information for future iterations of coronavirus vaccines. Without a mechanism of action, vaccinologists risk developing products designed to elicit a false surrogate of protection, akin to the use of TST conversion in BCG trials.

CONCLUSIONS

BCG has been given to over 4 billion infants [19]; however, its efficacy remains uncertain and its mechanism of action unknown. Because it is now standard of care, and considered to be safe, we cannot do placebo-controlled trials in infants, propagating the uncertainty about its effects against tuberculosis and other diseases. The developers of SARS-CoV-2 vaccines can learn from the lessons of BCG, where a vaccine introduced to great fanfare has had no measurable effect on the global epidemic, despite evidence of protection at the individual level. Let us hope that the tuberculosis research community may one day learn from the lessons of SARS-CoV-2 vaccine development, to finally develop a vaccine that stops tuberculosis.

Notes

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References

1. Calmette A, Guerin C. Nouvelles recherches experimentales sur la vaccination de bovidés contre la tuberculose. *Ann Inst Pasteur (Paris)* **1920**; 34:553–60.
2. Calmette A. Preventive vaccination against tuberculosis with BCG. *Proc R Soc Med* **1931**; 24:1481–90.
3. World Health Organization. Global tuberculosis report 2020. https://www.who.int/tb/publications/global_report/en/. Accessed 30 November 2020.
4. Aronson JD. BCG vaccination among American Indians. *Am Rev Tuberc* **1948**; 57:96–9.
5. Trial of BCG vaccines in south India for tuberculosis prevention: first report—Tuberculosis Prevention Trial. *Bull Int Union Tuberc* **1979**; 57:819–27.
6. Cruz AT, Starke JR. A current review of infection control for childhood tuberculosis. *Tuberculosis (Edinb)* **2011**; 91(Suppl 1):S11–5.
7. Fox GJ, Orlova M, Schurr E. Tuberculosis in newborns: the lessons of the Lübeck disaster (1929–1933). *PLoS Pathog* **2016**; 12:e1005271.
8. Behr MA, Wilson MA, Gill WP, et al. Comparative genomics of BCG vaccines by whole-genome DNA microarray. *Science* **1999**; 284:1520–3.
9. Bottiger M, Romanus V, de Verdier C, Boman G. Osteitis and other complications caused by generalized BCG-itis: experiences in Sweden. *Acta Paediatr* **1982**; 71:471–8.
10. Boisson-Dupuis S, Bustamante J, El-Baghdadi J, et al. Inherited and acquired immunodeficiencies underlying tuberculosis in childhood. *Immunol Rev* **2015**; 264:103–20.
11. Ledford H. Coronavirus reinfections: three questions scientists are asking. *Nature* **2020**; 585:168–9.
12. Mangtani P, Abubakar I, Ariti C, et al. Protection by BCG vaccine against tuberculosis: a systematic review of randomized controlled trials. *Clin Infect Dis* **2014**; 58:470–80.
13. Chou R, Selph S, Buckley DI, et al. Intravesical therapy for the treatment of nonmuscle invasive bladder cancer: a systematic review and meta-analysis. *J Urol* **2017**; 197:1189–99.
14. Arts RJW, Moorlag SJCFM, Novakovic B, et al. BCG vaccination protects against experimental viral infection in humans through the induction of cytokines associated with trained immunity. *Cell Host Microbe* **2018**; 23:89–100.e5.
15. Schaltz-Buchholzer F, Biering-Sørensen S, Lund N, et al. Early BCG vaccination, hospitalizations, and hospital deaths: analysis of a secondary outcome in 3 randomized trials from Guinea-Bissau. *J Infect Dis* **2019**; 219:624–32.
16. Giamarellos-Bourboulis EJ, Tsilika M, Moorlag S, et al. Activate: randomized clinical trial of BCG vaccination against infection in the elderly. *Cell* **2020**; 183:315–23.e9.
17. Heimbeck J. BCG vaccination of nurses. *Tubercle* **1948**; 29:84–8.
18. Comstock GW. Field trials of tuberculosis vaccines: how could we have done them better? *Control Clin Trials* **1994**; 15:247–76.
19. Ottenhoff THM, Kaufmann SHE. Vaccines against tuberculosis: where are we and where do we need to go? *PLoS Pathog* **2012**; 8:e1002607.