A hundred years of Bacillus Calmette-Guerin: reasons to celebrate

A review article by Peter Eriki, Harman-Joseph Kawuma and Francis Adatu Engwau

Humans have been infected with Mycobacterium tuberculosis, the organism which causes tuberculosis disease (TB) for millennia. TB is one of the oldest infectious diseases in recorded history. It is preventable, treatable, and curable, but still devastates lives, livelihoods, and economies globally. In the past 200 years, the disease has claimed over a billion lives.

The introduction of Bacille Calmette-Guérin (BCG) vaccine and chemotherapy in the past century marked an important advance in the history of tuberculosis, leading to optimism in fighting the disease. To date, BCG remains the most widely used vaccine worldwide and has been given to more than 4 billion individuals with astonishing safety records.[1,2] Through their research into the mechanisms of tuberculosis infection carried out from 1905 to 1918, Calmette and Guerin demonstrated that injecting small doses of weakened animal bacilli could be used as a protective vaccine against TB. They cultured the bacillus and found that successive culturing weakened it.[3] Unfortunately, the research had to stop during the 1st World War; but was resumed in 1918. By 1921 the tubercle bacillus had been subcultured 230 times, and it was so weakened that it was believed that it could confer immunity without causing disease in human.

The BCG vaccine was first used in humans in 1921 when it was given to a child in Paris by Dr Weil-Hale. The baby's mother, who had tuberculosis, had died just after the baby was born, and the baby was due to be brought up by its grandmother who also had tuberculosis. The baby was given 6 mg of BCG orally. During the next three years a further 317 infants were also vaccinated.[4]

Effectiveness and safety

Between 1927 and 1928 Calmette published and reported on 969 children that had been vaccinated with BCG, of whom 303 had mothers with TB, and the remainder had close contact with the disease. Of these children only 3.9% died of tuberculosis, and the comparable death rate for unvaccinated children was 32.6%.[4]

Despite criticism of Calmette in the medical press due to the high mortality associated with the vaccine, the Conference of the League of Nations in Paris in 1928 recognised the vaccine as safe and its use was encouraged.

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The Lubeck disaster

The BCG vaccine nearly came to an end in 1930 when the Lubeck disaster occurred which also cast doubts on the safety of BCG. Out of 252 recipient of BCG in the German city of Lubeck, 72 developed TB and died from the disease within a year. However, a subsequent investigation carried out by German TB experts revealed that the vaccine originally from the Pasteur Institute in Paris was contaminated with a distinct virulent human strain during its preparation in the laboratory at Lubeck. Two people who had worked in the local laboratory were sent to prison in 1932 for 'bodily injury due to negligence'.[5]

Although the BCG vaccine itself was eventually exonerated as the cause of the Lubeck disaster, its use declined for several years afterwards, particularly in England where a number of people felt that Calmette's views on its safety had not been universally accepted. Fears had been expressed that a virulent strain of bacilli, when injected into the human body, might regain its virulence. These fears though were to prove unfounded, and eventually, with a resurgence of TB during the 2nd World War, the BCG vaccine was again used on a massive scale and public confidence in its safety was restored.

Different strains

The BCG vaccine was disseminated throughout the world in the late 1920s. It was propagated in the same conditions as at the Pasteur Institute, and with the same aims. These aims were to prevent BCG from reverting to the virulent form, whilst preserving its potency and effectiveness.[6] Over the next few decades each of these laboratories developed its own sub strains, or 'daughter strain' of BCG. These became called by the laboratory, country or person's name with which they were associated - for example the 'Japanese', 'Moscow' and 'Gothenburg' strains.

BCG vaccines today

There are several BCG vaccines in use today. The major producers for the international market are Pasteur-Merieux-Connaught, the Danish Statens Serum Institute, Evans Medeva, and the Japan BCG Laboratory in Tokyo. Each of these BCG vaccines is produced in a different manner, and they are recognised to differ in various qualities, such as the proportion of viable cells per dose.[6]

Presently, the majority of the world's population is supplied with BCG vaccine procured by The United Nations Children's Fund (UNICEF) on behalf of the Global Alliance for Vaccines and Immunization (GAVI). There have been three studies investigating protective efficacy induced by different BCG vaccine strains. In two studies (with between 4- and 50-yr follow-up), BCG Pasteur was associated with statistically significantly better protective efficacy than BCG-Phipps or BCG-Glaxo.[7] In the third study (with 15-yr follow-up), BCG-Denmark had a greater protective efficacy than BCG-Pasteur (25% and 17%, respectively).[8]

Since these studies give only limited information about protective efficacy afforded by the BCG vaccine strains commonly in use, BCG-Phipps and BCG-Glaxo are no longer in use and BCG-Pasteur is used in very few countries.

Identifying the optimal BCG Vaccine strain has major implications First, given the large population of infants receiving BCG each year even a small increment in protective immunity resulting from the use of a particular BCG strain would translate into improved protection against TB for a large number of children. Second, a range of new TB vaccines are under development, including vaccines designed to replace BCG and vaccines designed to boost BCG.[5] The most advanced are sub-unit or live vector-based booster vaccines designed for use after administration of a priming dose of a current BCG vaccine. It therefore remains important to determine which BCG vaccine strain induces the best primary immune response against TB for subsequent boosting.

One of the recent studies by Ritz et al[9] concluded that there are significant differences in the immune response induced by different BCG vaccine strains in newborn infants. Immunisation with BCG-Denmark or BCG-Japan induced higher frequencies of mycobacterial-specific polyfunctional and cytotoxic T cells and higher concentrations of Th1 cytokines than immunisation with BCG-Russia. These findings have potentially important implications for global anti-tuberculosis immunisation policies and future tuberculosis vaccine trials.

Although the efficacy of the BCG vaccine continues to be controversial, live attenuated BCG is still the only vaccine in use for the prevention of TB in humans. It is effective against the severe forms of TB and its use prevents a large number of deaths that would otherwise be caused by TB every year. The choice of the BCG strain to be used for vaccination remains an important issue. Currently, it is difficult to determine which strain should be used and further detailed analysis of the genomics and immunogenicity of BCG sub-strains may provide an answer to this important question.

Other benefits of BCG

The role of BCG in other mycobacteria infection control (Mycobacterium Leprae and Mycobacterium ulcerans): Although BCG vaccines until now are not specifically indicated for prevention of leprosy, there is evidence that BCG vaccination given at birth has also contributed to the significant decline in leprosy incidence, conferring higher protection than against TB. Further, BCG has been found to be effective against other mycobacterial infections such as Buruli ulcer disease. BCG vaccination has also been reported to have beneficial non-specific effects (NSE), in particular reducing all-cause infant mortality in certain settings.[11]

BCG and Covid-19: A multivariable analysis conducted by Danielle Klinger et al[12] revealed significantly improved COVID-19 outcomes in countries with higher BCG vaccination coverage. This followed the outbreak of COVID-19 pandemic that started in China and had spread within three months to the entire globe. They were testing the hypothesis that vaccination against TB by BCG vaccine correlates with a better outcome for COVID-19 patients. Their analysis covers 55 countries. They found a strong negative correlation between the years of BCG administration and the number of deaths per million (DPM) along with the progress of the pandemic, corroborated by permutation tests. The analysis of countries according to an age-group partition reveals that the strongest correlation is attributed to the coverage in BCG vaccination of the young population (0-24 years). Furthermore, a strong correlation and statistical significance are associated with the degree of BCG coverage for the most recent 15 years, but no association was observed in these years for other broadly used vaccination protocols for measles and rubella. They proposed that BCG immunisation coverage, especially among the most recently vaccinated seems to offer some attenuation to the spread and severity of the COVID-19 pandemic.

Bagheri and Montazeri[13] conducted an extensive review on BCG vaccine protection against COVID-19. They reiterated that BCG vaccine has been globally used to protect infants against TB for a century and that the vaccine has been shown to provide some degree of non-specific protection from other respiratory tract infections. This advantage has encouraged researchers to investigate the potential protection of this vaccine from COVID-19 infection. In their study, they comprehensively reviewed the latest articles on potential vaccine effectiveness on COVID-19 and summarised the possible impacts of BCG against COVID-19 in details. They also summarised the current and ongoing clinical trials on BCG and concluded that several clinical trials are under way in determining whether BCG could affect COVID-19.

Conclusion and recommendations

The SAGE working Group of WHO,[11] concluded that due to paucity of evidence to assess differences in the vaccine efficacy, effectiveness and safety of vaccination at different ages, no policy change regarding the age is justified. BCG vaccination at birth together with hepatitis B vaccination is strongly recommended. The group recommends continuing universal BCG vaccination in high incidence TB settings. They also expanded this recommendation of universal BCG Vaccination to high incidence leprosy settings regardless of the TB incidence. They further recommended for selective vaccination of individuals or groups at risk in low endemic countries, switching from universal to selective vaccination of HIV-exposed children, immune competent HIV-infected individuals on antiretroviral therapy (ART) and other special risk groups including adolescents and adults. They expressed the urgent need for further research in the development of new vaccines, which should be tested for effectiveness against different pathogenic mycobacterial infections and all-cause infant mortality.

During the United Nations High-Level Meeting (UNHLM) on TB in 2018,[15] the world leaders committed to delivering new, effective, safe, equitable, and affordable TB vaccines as soon as possible. With the onset of the recent Covid-19 pandemic, the world leaders further observed that it had pushed back progress on the global fight against TB considerably. The world leaders were therefore called upon to demonstrate the same leadership shown in developing COVID-19 vaccines to raise hopes that the slow-moving TB vaccines development process can be fast-tracked with strong political commitment, adequate funding, and faster research to deliver new TB vaccines by 2025 to meet the Sustainable Development Goals target to end TB by 2030.

Reference

1. McShane H. Tuberculosis Vaccines: Beyond Bacille Calmette-Guerin. Philos Trans R Soc Lond B Biol Sci. 2011;366:2782–9. [PMC free article] [PubMed] [Google Scholar]
2. Ottenhoff THM, Kaufmann SHE. Vaccines against Tuberculosis: Where Are We and Where Do We Need to Go? Chitnis CE, editor. PLoSPathog. 2012;8:e1002607–12. [PMC free article] [PubMed] [Google Scholar]
3. Calmette A. 1922. L'ninfectionbacillaire et la tuberculose chez l'homme et chez les animaux. [Google Scholar
4. Calmette A, Guerin C, Weill-Halle B. Bull Acad Med. Vol. 91. Paris: 1924. Essaid'immunisationcontrel'infectiontuberculeuse. pp. 787–96. [Google Scholar]
5. Lange B. WeitereUntersuchungenzurKlärung der Ursachen der Unglücksfälle in Lübeck. Tuberk. 1931;62:335–51. [Google Scholar
6. Milstien JB, Gibson JJ. Quality Control of BCG Vaccine by WHO: a Review of Factors that May Influence Vaccine Effectiveness and Safety. Bull. World Health Organ. 1990;68:93–108. [PMC free article] [PubMed] [Google Scholar]
7. Aronson NE, Santosham M, Comstock GW, et al. Long-term Efficacy of BCG Vaccine in American Indians and Alaska Natives: A 60-year Follow-up Study. JAMA. 2004;291:2086–91. [PubMed] [Google Scholar]
8. Tuberculosis Research Centre (ICMR), Chennai. Fifteen Year Follow-up of Trial Of BCG Vaccines in South India for Tuberculosis Prevention. Indian J Med Res. 1999;110:56–69. [PubMed] [Google Schola
9. Ritz N, Dutta B, Donath S, et al. The Influence of Bacille Calmette-Guerin Vaccine Strain on the Immune Response against Tuberculosis: a Randomized Trial. Am J Respir Crit Care Med. 2012;185:213–22. [PubMed] [Google Schola
10. Annabel Kanabus: https://tbfacts.org/bog
11. The SAGE Working Group on BCG Vaccines and WHO, 22 September 2017s
12. Danielle Klinger et all: Vaccines (Basel) >v8(3) 378; 2020 Sep. >PMC7563451
13. Narges Bagheri, Hesam Montazeri: SN Comprehensive Clinical Medicine https://doi.org/10.1007/s42399-021-00835-1
14. CK. Weerasunya et al: New TB vaccines: advances in clinical develiopment, 31 Octobwe 2020/https://doi.org/10.1111/joim13197.
15. United Nations High-Level Meeting (UNHLM) on TB in 2018