

The 100th anniversary of bacille Calmette-Guérin (BCG) and the latest vaccines against COVID-19

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Vaccines against COVID-19 have become the most important commodities in the world. The race to develop, produce and distribute these vaccines has intensified discussions about the safety and efficacy of vaccines, and raised a host of issues from vaccine hesitancy to the inequality of vaccine distribution. One hundred years ago, on 18 July 1921, similar arguments surrounded the first use in humans of bacille Calmette-Guérin (BCG) vaccine against TB. BCG has since gone on to become the oldest approved vaccine in the world still being administered, and billions of people have been vaccinated with it worldwide.

THE EFFICACY OF BCG

A series of meta-analysis by Colditz and colleagues in the 1990s, including 70 trials to determine the efficacy of BCG, revealed a reduction in the incidence of TB worldwide by 50%, with an efficacy varying between 0% and 80%.¹ Latitude has a major influence on efficacy (i.e., efficacy declines near to the equator), and environmental mycobacteria may interfere as well.¹ Although the efficacy of BCG varies, the vaccine has led to an extraordinary drop in TB cases worldwide, particularly in reducing infant mortality due to severe forms of TB.² BCG administration in children under 5 years provides strong protection against the severe forms of tuberculous meningitis, disseminated disease and pulmonary TB.^{2,3} However, the protection of adolescents and adults wanes over time.⁴ BCG is safe and cost-effective,² but can lead to disseminated BCGosis in immune-compromised individuals.⁵ A more recent study in north European countries has confirmed a higher (61–64%) protection in 15–29-year-olds, in tuberculin-negative vaccinees.⁶ This higher level of BCG protection away from equatorial regions has been confirmed by other studies. For example, a recent meta-analysis by Mangtani et al. confirmed the protective efficacy of BCG against tuberculous meningitis and miliary TB, with higher efficacy far from the equator.³ The exposure to non-tuberculous mycobacteria (NTM), before vaccination could interfere with the efficacy of BCG,³ and vaccine efficacy may also be reduced by pre-exposure to helminths.⁷ Although the cause remains a matter of debate, the differences between BCG strains do not account for the variability of efficacy of the vaccine.³

HETEROLOGOUS PROTECTION OF BCG

In a randomised placebo-controlled human challenge study, BCG vaccination protected against experimental infection with an attenuated yellow fever virus vaccine strain.⁸ This proof-of-concept study has shown that BCG has heterologous effects against viral diseases. Additionally, BCG-vaccinated infants in Guinea Bissau and Spain had lower rates of neonatal

sepsis and respiratory infections.^{9,10} Although several theories have been proposed to explain this heterologous protection, given that infants do not possess a fully matured adaptive immune system, there is increasing evidence of a mechanism designated ‘trained immunity’ or ‘innate immune memory’, involving extensive metabolic and epigenetic reprogramming,^{8,11,12} which could partially explain the heterologous protection of BCG (Table).

RECENT ADVANCES TO IMPROVE BCG

Different strategies to improve BCG have been developed, including recombinant BCG strains, attenuated forms of *Mycobacterium tuberculosis*, re-vaccination strategies and sub-unit vaccines. Alternative routes of vaccination have been explored, but our current knowledge of the most relevant mycobacterial antigens remains limited. The identification of the most relevant antigens is crucial for the development of optimal sub-unit vaccines.

Recent advances in mass spectrometry and bioinformatics have allowed the precise identification of peptide sequences presented by major histocompatibility (MHC) I and MHC-II molecules, which are able to induce CD8⁺ and CD4⁺ T-cells, respectively.²⁰ In a recent immunopeptidomics study, 112 antigens were identified in human macrophages infected with BCG. Three highly expressed antigens, recognised by the peripheral blood mononuclear cells of volunteers vaccinated with BCG, were selected. Viral vectors encoding these antigens were used to boost BCG-vaccinated mice, resulting in a significant protection against an aerosol challenge with *M. tuberculosis*.²⁰ Antigens identified by immunopeptidomics will be further explored as new antigen candidates for vaccines against TB either in conventional sub-unit vaccination strategies or using the new self-amplifying RNA vaccines recently approved against COVID-19.

CAN BCG PROTECT AGAINST COVID-19?

Ecological studies suggested a possible association between BCG vaccination and protection against severe disease and reduced mortality from SARS-CoV-2 infection,^{21,22} or the spread of COVID-19.^{22,23} Although the data could suggest a protective effect of BCG against COVID-19, the differences in the demographic structure, socio-economic status and the current developments of the pandemic of each country or region contributes to the definition of a particular scenario for each population, making it difficult to establish comparisons between countries. The median age of the population, population density, access to healthcare, non-pharmaceutical control interventions (such as quarantine, face mask enforcement, social distancing, diagnostic testing and reporting), all contribute to a dynamic development of the

pandemic, which may be confounding factors to determine the hypothetical contribution of BCG to the heterologous protection against COVID-19. Indisputable evidence is needed to demonstrate that BCG can offer protection against COVID-19. For that purpose, a total of 51 randomized control trials are currently under way in many countries.²⁴ These were designed to provide the highest possible quality evidence to address this question. The WHO, which provides regularly recommendations on the use of vaccines, currently does not recommend the use of BCG for prevention of COVID-19.²⁵ Nevertheless, as a consequence of the publicity resulting from these ecological studies, some members of the public, including healthcare workers, have requested BCG revaccination as protection against COVID-19. This threatens BCG stocks with potential serious consequences to new-borns and under 3-year old infants, who should constitute a priority population for BCG vaccination, particularly in high-burden countries.^{26,27}

Although several COVID-19 vaccines have been approved for emergency use and have a high efficacy of 85% (95% confidence intervals 71–93),²⁸ and have been quickly administered in high-income countries, most low- and middle-income countries are struggling to vaccinate their population. This in spite of the efforts of COVAX, a major global collaboration between the Coalition for Epidemic Preparedness Innovations (CEPI), the Global Vaccine Alliance (GAVI), the United Nations Children’s Fund (UNICEF), and the WHO, which promotes equitable distribution of COVID-19 vaccines. Interest in the hypothetical use of BCG against COVID-19 declined when the new vaccines were approved for emergency use. However, using BCG as an alternative vaccination strategy could still be of relevance, particularly for countries with no access to COVID-19 vaccines, or if the current vaccines lose efficacy against SARS-CoV-2 variants of concern. However, the results of the clinical trials will be critical in determining whether BCG is effective in reducing the severity and mortality of COVID-19.

THE 100TH ANNIVERSARY OF BCG

The centenary of BCG has been celebrated in different ways: the Validate vaccine network, an international network of researchers focussed on the development of vaccines against intracellular pathogens, delivered public lectures about the centenary on World TB Day;²⁹ The Virtual Global Forum on TB Vaccines (organised by a large group of stakeholders devoted to the development of vaccines against TB) held a session on the 100 years of BCG on 20–22 April 2021.³⁰ The development of the BCG vaccine and the formation of the International Union Against Tuberculosis and Lung Disease (The Union) in 1920, both serve to highlight

the benefits of international cooperation in the fight against TB. Indeed, the focus of The Union to improve health for people in low- and middle-income countries should be an example to follow, to reduce inequality of vaccine distribution.

The vaccines against COVID-19 were developed in less than one year and have high efficacy. Nevertheless, concerns about the effectiveness of vaccination remain, as SARS-CoV-2 variants of concern continue to emerge. As we celebrate the centenary of the oldest vaccine in the world – and the success of the vaccines for COVID-19 – we must remember the features they have in common, and the ongoing need for further research to improve and develop better vaccines.

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Table Some examples of heterologous effects of BCG

Disease/condition	Effect	Reference
Mycobacterial diseases		
Leprosy*	Meta-analysis to assess the protective effect of BCG against leprosy The overall efficacy was 26% (95% CI 14–37) in 7 experimental studies, and 61% (95% CI 51–70) in 19 observational studies	13
Buruli ulcer*	BCG had an efficacy of 50% (95% CI 37–69) in two randomised trials on Buruli ulcer, and four case-control studies had conflicting results	14
Bacterial and viral diseases		
Sepsis	BCG can reduce mortality caused by neonatal sepsis; however, the exact mechanism is unknown	10,15
Respiratory infections	BCG can reduce mortality caused by neonatal respiratory infections unrelated to TB	10
Yellow fever	In a randomised placebo-controlled human challenge study, trained immunity induced using BCG vaccination protected against experimental infection with an attenuated yellow fever virus vaccine strain	8
Non-transmissible diseases		
Non-muscle invasive bladder cancer [‡]	BCG therapy induces modest efficacy in patients with non-muscle- invasive bladder cancer	16
Melanoma [†]	Direct injection of BCG into metastatic melanoma lesions or combination of BCG with monoclonal antibodies has been used as therapy against melanoma, although not often employed	17

*Leprosy and Buruli ulcer are caused by *M. leprae* and *M. ulcerans* respectively, and there is a large antigenic overlap between BCG and these organisms. Hence, the mechanism of protection against these diseases is likely to be different from the heterologous protection induced by trained immunity.

[†]Therapeutic administration of BCG.

[‡]BCG has been used as the gold-standard immunotherapy for patients with high-risk non-muscle-invasive bladder cancer. Again, trained immunity has been proposed as a mechanism mediating BCG immunotherapy,¹⁸ as well as the induction of T-helper 1 immune response or the direct cytotoxic effect of mycobacteria in the tissue.¹⁹ Although this vaccine has brought enormous advantages against a plethora of diseases, we need a better vaccine to improve, boost or replace BCG.

BCG = bacille Calmette-Guérin.