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GUEST EDITORIAL

BCG – one hundred years of solitude

Christened ‘phthisis’ by Hippocrates in 400 BCE for the wasting it brought about, tuberculosis (TB) has remained humankind’s challenge for millennia, having emerged around 70,000 to 90,000 years ago and spread ‘Out of Africa’ with the waves of modern humans who went on to populate our planet, with palaeo-pathologic evidence for its existence dating back to 8000 BCE. Already prevalent widely in Europe, TB was introduced into the New World by the Spanish conquistadores Columbus, Cortes and Pizarro in the late 15th and early 16th centuries, who conquered the American Indians, the Aztecs of Mexico and the Incas of Peru. These immunologically naïve and vulnerable populations were decimated by TB and other Old World germs. However, it was not until the rapid industrialization in Britain, UK, beginning in the 17th century with its accompanying urban, overcrowded squalor that TB became rampant. In fact, every one out of four deaths in the 18th and 19th century Europe was attributed to TB. The tubercular aesthetic became so culturally entrenched that it permeated and dominated the literature, poetry, art and fashion of 19th century Europe. Once ‘germ theory’ was proposed as the cause of diseases and Robert Koch discovered in 1882 that *Mycobacterium tuberculosis* was the causative agent of TB, the disease has attracted intense scientific attention, spurring development of drugs and vaccines alike. It was in this backdrop of human despair, melancholy and horror of TB that BCG brought optimism and hope more than a 100 years ago, when it was first administered to an infant in July 1921. The League of Nations endorsed the oral BCG vaccine in 1928. Use of intradermal BCG, its most common mode of delivery, began in 1927. However, despite approximately 53–64 million lives saved between 2000 and 2018 by BCG and the existing chemotherapeutic agents, an unacceptably large number of people, about 2 million (an acknowledged underestimation) still fall prey to TB every year.

In the current era of record short time spans for vaccine development and regulatory clearance, followed by super-fast roll outs of multiple vaccines across the globe against SARS CoV-2, the laborious 230 passages over 13 years from 1908 to 1921 that was necessary to attenuate the virulence of a *Mycobacterium bovis* strain and generate the BCG vaccine would be dismissed as palaeolithic. Following Koch’s identification of the causative organism of TB, scientists across the world, including Koch himself, set out to invent a vaccine against the disease. Initial hy-

pothesis that the related *M. bovis* which causes a similar disease in cattle, would serve as a vaccine against the human form of the disease, led to disastrous human trials that revealed the dangerous potential of *M. bovis* for causing disease in humans. In 1908, Leon Calmette, a bacteriologist, and Camille Guérin, a veterinarian at the Pasteur Institute of Lille, France, inspired by the Jennerian approach began the attenuation by serial passage of a *M. bovis* strain isolated from cow milk, until it lost its virulence. BCG showed an average of 86% efficacy against miliary and meningeal TB, and dramatically reduced infant mortality due to severe forms of the disease. A meta-analysis by Colditz and co-workers in the 1990s of 70 human trials of BCG revealed an impressive 50% reduction in the global incidence of TB. However, the efficacy of BCG against pulmonary TB varied from 0% to 80%, depending on multiple factors, including geographic location and prior exposure to environmental mycobacteria. Latitude is an important factor, with the efficacy dropping in the tropical latitudes to near zero. In contrast, in tuberculin-negative recipients of BCG vaccine aged 15–29 years in the northern European countries which lie away from the equator, a relatively high 61–64% protection by BCG was noted.

This venerable vaccine, the world’s oldest in current use, of which more than 4 billion doses have been administered worldwide, has displayed an impressively remarkable and unmatched safety profile. Was this gain in safety at the expense of vaccine efficacy? Its varying and disappointing efficacy against the dominant pulmonary form of TB made BCG a much-maligned vaccine, exemplified by data showing its efficacy against adult pulmonary TB in the Chengalpattu, Tamil Nadu, India trials, to be no better than distilled water. Annually, 8–10 million people fall ill with TB, qualifying this disease as a chronic pandemic. The United Nations in September 2018 convened a high-level meeting on TB with the aim of whipping up political momentum, will and funding for its elimination. Yet, the global community of scientists have failed to deliver a second TB vaccine superior to BCG. Failure in the delivery of promised funds and the predominant occurrence of TB in poor countries have contributed not a little to this drought.

Under the United Nations Sustainable Development Goals, TB deaths need to be reduced by 90% by 2030. The scientific community has toiled to find better TB vaccines,

including those based on improving BCG. One of the more famous among these was MVA-85A, a recombinant poxvirus expressing the TB gene for antigen 85A, which was expected to boost the BCG vaccination. Unfortunately, its unremarkable efficacy of 17% in human phase 2B trials published in 2013 put paid to and short circuited several ongoing TB vaccine efforts. Why has BCG remained singularly solitary for an entire century despite wide recognition of its sub-par performance? Are TB vaccines substantially more challenging to develop than those against most other diseases? Having coexisted with its human host for at least 90,000 years, as a chronic infection going from latency to reactivation among the sparse populations of nomadic hunter-gatherers and evolving to a 'crowd disease' aided by the increase in human density in post-agricultural and industrial era settlements, the tubercle bacillus elicits a complex and unique immunological response like no other. This in turn engenders a host-pathogen interaction that has resulted in a pathogen challenging to treat or control, leave alone eradication. Another culprit was likely the mega funding in the mid-nineties from newly minted agencies such as Gates Foundation and Wellcome Trust, which advertised mouth-watering, humungous grants for downstream human clinical trials. These predictably triggered numerous sprouting claims of candidate TB vaccines poised for human trials from the scientific community at the expense of vital upstream research to understand the biology of the organism and the host immune response. It is important to note that neither the pathogen *M. tuberculosis* nor the vaccine strain *M. bovis*-BCG elicits sterilizing immunity in humans. The involved scientific enquiry required to understand these and other intricacies of this disease has generally been in short supply. Despite the availability of a bouquet of drugs against *M. tuberculosis*, the spectre of multiple and extreme drug resistance due to indiscriminate use of drugs outside the Indian Government's Revised National TB Control Programme (RNTCP) has catapulted the value of vaccines.

In reality though, BCG since the beginning of its use has turned out to be nothing short of a veritable boon for humanity. Following the serendipitous discovery of its efficacy against numerous other diseases, BCG has proven to be a multipurpose vaccine. Observed first in West Africa and validated in numerous other studies, BCG vaccination reduced infant mortality by an impressive 50% due to induced protection against unrelated infections. It was also found to confer survival advantages in healthy populations. BCG has been shown to be efficacious against numerous DNA and RNA viruses, as well as enhance immune responses to viral vaccines such as pandemic influenza. Claims of BCG vaccination preventing COVID-19 severity would still be fresh in the readers' minds. Rigorous scientific studies have proven the efficacy of BCG not only against a host of viral infections, but also (expectedly) against non-tuberculous mycobacterial infections, bladder cancer, atopic disorders and endometriosis, attributed to a broad-based activation of the immune sys-

tem. In fact, BCG has been an accepted form of treatment for invasive bladder cancer since the 1980s. It has also proven to be efficacious in treating autoimmune disorders such as multiple sclerosis and type-I diabetes. In an impressive human trial spanning 8 years of follow-up after two doses of a potent BCG strain carried out at the Massachusetts General Hospital and Harvard Medical School, USA, persistent and long-standing reduction of serum glycosylated haemoglobin and glucose levels was observed. In this study, the mechanism was shown to be a switch from the Krebs cycle to augmented aerobic glycolysis leading to accelerated glucose uptake, thus being independent of insulin, holding out hope for its use in diabetes of various aetiologies. BCG has also been used to treat and control food allergies and multiple atopic disorders. Mihai Netea and his group from Radboud University, The Netherlands, demonstrated that these nonspecific effects of BCG were mediated by long-lasting epigenetic alterations in the chromatin of immune cells, a phenomenon they termed 'trained immunity'.

Evidently, BCG is here to stay. Can we then hope to improve on the anti-TB efficacy of this well-entrenched and invaluable vaccine? The efficacy of BCG against TB as well as its bouquet of non-specific benefits have been consistently observed to be strain-specific, with the potent Moreau BCG sub-strain conferring some of the most dramatic benefits. Multiple studies have attributed the disappointing performance of BCG against TB to its over-attenuation resulting from excessive genomic deletions. Therefore, rational removal of critical virulence determinants from *M. bovis*, might hold promise for improving on BCG, and has been attempted. However, in the light of the disseminated mycobacterial disease caused by the current strains of BCG in immunocompromised individuals, this approach will require striking a fine balance between virulence and attenuation. The urgent need to understand how the human immune system responds to both TB and BCG is being addressed, aided by today's advanced cell and omics technologies. Several rationally designed knock-in and knock-out mutant strains of BCG have been developed, although most have shown little promise in human trials. A recent study at the National Institutes of Health, USA, demonstrated impressively enhanced efficacy of BCG against pulmonary TB in animal models, if administered intravenously instead of the current intradermal route. Hope continues to run high in the scientific community, this time perhaps justifiably. May we reasonably hope that our scientists and immunologists inspired by Gabriel Garcia Marquez-style magical realism will deliver the shot that will end the century-long unbearable solitude of BCG?

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