MILESTONE 5

BCG: to face an ancient enemy

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Of all the infectious diseases that afflict humanity, tuberculosis is certainly one of the most ancient and implacable. Over the centuries this disease has gone by many names — 'phthisis', 'consumption', 'scrofula', 'the white plague'… and has killed more people than any other infectious disease in history — by some estimations in excess of a billion people in the past 200 years. However, it was not until 1882 that Robert Koch identified the bacterium *Mycobacterium tuberculosis* (Mtb) as the infectious agent to cause the most common form of the disease — pulmonary tuberculosis. The affliction that from antiquity had caused such untold misery at last had a face, and with it offered hope of a cure.

The final years of the 19th century were an exciting time for medicine: Louis Pasteur had successfully pioneered a number of attenuated vaccines (MILESTONE 3) and Shibasaburō Kitasato and Emil von Behring had demonstrated the antimicrobial properties of convalescent serum (MILESTONE 4). It was into this milieu that stepped the physician Albert Calmette and the veterinarian Camille Guérin. In 1894, Calmette had been appointed to be the first director of the Institut Pasteur in Lille, France, and along with Guérin — who was to become a lab head at the same institute, started a close collaboration to produce an anti-tuberculosis vaccine. Their collaboration began in 1900 and would last until Calmette's death in 1933.

Calmette and Guérin's initial efforts focused on culturing a virulent bovine strain of Mtb in vitro with the hope that an attenuated version could be produced and thereby form the basis of a vaccine — much like Pasteur had managed with the cholera bacterium. However, the bacteria proved uncooperative and would readily form clumps, making them difficult to culture. A breakthrough came in 1906 when ox bile was included in the cultures to disperse the clumps and was found to weaken the bacteria. From 1908, Calmette and Guérin embarked upon a monumental subculturing effort to progressively attenuate their originally highly virulent bovine sample of Mtb. By 1919 and some 230 subcultures later, they finally had a live but highly attenuated strain of Mtb that was unable to cause disease in a wide variety of animals including guinea pigs, monkeys, calves and horses. This strain — now genetically vastly distant from its pathogenic ancestor — was christened Bacille Calmette–Guérin (BCG).

But human trials of BCG did not commence for some time, largely because of concerns that the bacteria might reacquire virulence following vaccination. BCG after all was a live organism so could they really be certain it was completely safe even if the animal data looked hopeful? Things changed in 1921 when they were approached by a physician working in Paris, Benjamin Weill-Hallé. He had as a patient a healthy infant whose mother had died of tuberculosis shortly after birth. The infant was to be raised by its grandmother who was also suffering from tuberculosis. The outcome in such cases was exceedingly grim so Weill-Hallé along with the paediatrician Raymond Turpin made the decision to orally vaccinate the infant with BCG. This was soon followed by a vaccination programme of similar at-risk newborn infants and appeared to show good protection of this vulnerable patient group. By 1927 a much larger programme involving thousands of infants demonstrated that BCG was not only very safe but might also be protective.

> "BCG was not only very safe but might also be protective"

Nearly 100 years later, BCG is the most widely administered vaccine in the world and is on the WHO list of essential medicines. However, the global uptake of BCG is patchy, with a generally lower use in the developed world. This pattern partly reflects the relatively small tuberculosis risk and availability of antibiotics but also unresolved controversy over BCG's actual efficacy — which seems to be mainly useful in childhood against disseminated tuberculosis and tuberculous meningitis but relatively poor against the most common form of the disease in adults — pulmonary tuberculosis. However, BCG appears to have unexpected beneficial effects through the generalized stimulation of the immune system (MILESTONE 13), which can protect against pathogens other than its intended target Mtb and even some forms of cancer. It seems this most venerable of vaccines is still throwing up some surprises.

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ORIGINAL ARTICLES Calmette, A. *L'infection bacillaire et la tuberculose chez l'homme et chez les animaux* (1920) | Calmette, A et al. Essai d'immunisation contre l'infection tuberculeuse. *Bull. Acad. Med. Paris* **91**, 787–796 (1924) | Calmette, A. et al. Sur la vaccination préventive des enfants nouveau-nés contre la tuberculose par le BCG. *Ann. Inst. Pasteur, Lille* **41**, 201–232 (1927) | Weil-Hallé B. & Turpin, R. Sur la vaccination antituberculeuse de l'enfant par le BCG. *Ann. Inst. Pasteur* **41**, 254–270 (1927)
FURTHER READING Calmette, A. Preventative vaccination against tuberculosis with BCG *Proc. R. Soc. Med.* **24**, 1481–1490 (1931) | Luca, S. and Mihaescu, T. History of BCG vaccine. *Medica* **8**, 53–58 (2013) | *Nature Outlook: Tuberculosis*. https://www.nature.com/collections/fdlnxgstcy (2013)