

The history of BCG vaccine

Abstract

BCG vaccine continues to be controversial, live attenuated BCG is still the only vaccine in use which is able to prevent TB in humans. It is still 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. The only vaccine available is the BCG (Bacille Calmette-Guerin), that has been used for about 100 years, with remarkable results. The majority of the world followed the lead of Europe and the WHO and introduced routine BCG vaccination according to various schedules. According to the Methodological Guide for the Implementation of the National Program for the Prevention, Surveillance and Control of Tuberculosis, BCG vaccination is indicated for all newborns, at the age of 2-7 days (if there are no contraindications), before discharge from maternity and without preliminary tuberculin test.

Keywords: BCG vaccine, maternity, Tuberculosis, phthisis

Introduction

Every year, more than 2 million people die because of tuberculosis [1], despite the fact that this infectious disease is now treatable. In the 19th century, about one in four deaths was caused by tuberculosis, also known as “consumption” or “phthisis”. Treating and preventing this disease became a permanent challenge, especially because of the multi-drug resistant form and the TB-HIV epidemic. The only vaccine available is the BCG (Bacille Calmette-Guerin), that has been used for about 100 years, with remarkable results. There is no universal vaccination policy, so there are huge differences between the immunization programs in different countries.

The history of tuberculosis and the BCG vaccine

Robert Koch discovered in 1882 the intracellular pathogen responsible for TB [2]. In the last century, the *M. . bovis* BCG vaccine, isolated by and named after Calmette and Guérin (Lille, France) [3] finally gave hope that TB could be conquered. In 1900 Albert Calmette and Camille Guérin began their research for an antituberculosis vaccine at the Pasteur Institute in Lille. They cultivated tubercle bacilli on a glycerin and potato medium but found it difficult to produce a homogeneous suspension of the bacilli [1]. Trying to counteract their tendency to clump, they tried adding ox bile to the medium, which led to the observation that subculture led to a lowering of the virulence of the organism. It was this fortuitous observation that led them to undertake their long term project of producing a vaccine from this attenuated tubercle bacillus [1,4]. By 1913 the two researchers were prepared to initiate a vaccination trial in cattle which

was interrupted by the beginning of World War I. Despite the greatly increased cost of potatoes and the difficulty of obtaining suitable ox bile from the abattoir, they continued their work throughout the German occupation of Lille. They got a little help from the veterinary surgeons of the German occupying force. By 1919, after about 230 subcultures carried out during the previous 11 years, they had a tubercle bacillus which failed to produce progressive tuberculosis when injected into guinea pigs, rabbits, cattle, or horses [1,4]. So the BCG was born.

The first human administration of BCG was by Benjamin Weill-Halle (1875-1958) assisted by Raymond Turpin (1895-1988) at the Charité Hospital, Paris [1].

Calmette considered that the gastrointestinal tract was the route of infection in humans, so they first chose an oral administration. Weill-Halle then tried the subcutaneous and cutaneous routes, with some local reactions observed [1]. By 1924, they already had a series of 664 oral BCG vaccinations of infants [5]. Between 1924 and 1928, 114 000 infants were vaccinated without serious complications [6].

The BCG vaccination was also being taken up in other countries, especially in Spain (Barcelona) by Luis Saye; and in the Scandinavian countries Arvid Wallgren in Gothenburg [7] and Johannes Heimbeck in Oslo [8] pioneered the cutaneous administration of BCG [1]. In Great Britain, there was a considerable skepticism and the statistics of Calmette and Guérin were strongly criticized in 1928 by Professor M Greenwood [9]. In the United States, Petroff and his colleagues at Trudeau Sanatorium reported in 1929 that in a specimen of BCG supplied by Calmette they had isolated virulent tubercle bacilli, casting grave doubt on Calmette's assertion that BCG was a "virus fixe" [10]. Despite these disturbing reports, Calmette and Guérin remained confident that BCG was safe [1]. But then, "the Lübeck disaster" unfortunately happened.

In 1930, a tragic thing happened in Lübeck, a Northern German city. They used an oral scheme of vaccination in newborn babies, undertaken by Professor Deycke, director of the Lübeck General Hospital and Dr. Alstädt, chief medical officer of the Lübeck Health Department [1]. The BCG was supplied from the Pasteur Institute in Paris, but it was prepared for oral administration in the tuberculosis laboratory in Lübeck [1]. A lot of these children developed tuberculosis. 73 of the 250 died in the first year and the other 135 recovered [1]. After 20 months, the BCG was exonerated and it was considered that the cause of that tragic event was a negligent contamination of the vaccine by virulent tubercle bacilli in the Lübeck laboratories [11]. Two doctors went to prison in that case.

By the late 1940s, several studies had appeared providing evidence for the utility of BCG in protection against tuberculosis [1]. Tuberculosis became again a major concern in World War II, when BCG was encouraged by UNICEF, WHO and the Scandinavian Red Cross Societies [1].

The majority of the world followed the lead of Europe and the WHO and introduced routine BCG vaccination according to various schedules [1].

In the early 1990s, the World Health Organization (WHO) declared TB a global emergency [12].

The situation of BCG vaccination nowadays

Now we have many BCG vaccines in use. Some of the major producers are: Pasteur-Merieux-Connaught, Danish Statens Serum Institute, Evans Medeva, Japan BCG Laboratory in Tokyo [1]. These vaccines are produced in different manners (they have phenotypic differences between there strains).

Most of the people got a BCG vaccine procured by UNICEF on behalf of the Global Alliance for Vaccines and Immunization [1].

In Romania, there is an immunization program. According to the Methodological Guide for the Implementation of the National Program for the Prevention, Surveillance and Control of Tuberculosis, BCG vaccination is indicated for all newborns, at the age of 2-7 days (if there are no contraindications), before discharge from maternity and without preliminary tuberculin test. If for various reasons the vaccination could not be performed in the maternity ward, this can be done by the pulmonologist until the age of 3 months, also without tuberculin testing. After this age, up to 4 years, the vaccination will be performed with a previous test for tuberculin and a letter from the family doctor certifying the child's health and the last vaccine performed.

The contraindications to BCG vaccination are:

- temporary: febrile condition, eruptive skin lesions, weight less than 2500 g
- permanent: symptomatic HIV infection, congenital immunodeficiencies, leukemias, lymphomas, neoplasms, treatment with alkylates, antimetabolites

Conclusions

Even if the efficacy of BCG vaccine continues to be controversial, live attenuated BCG is still the only vaccine in use which is able to prevent TB in humans. It is still 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.

References

- [1] Luca S, Mihaescu T. History of BCG Vaccine. *Maedica (Bucur)*. 2013;8(1):53-58.

- [2] Kaufmann SH, Hussey G, Lambert P-H. New Vaccines for Tuberculosis. *Lancet*. 2010;375:2110–9
- [3] Calmette A, Guérin C, Boquet A, et al. *Paris: Masson et cie*; 1927. La vaccination préventive contre la tuberculose par le "BCG."
- [4] Calmette A. 1922. L'infection bacillaire et la tuberculose chez l'homme et chez les animaux.
- [5] Calmette A, Guérin C, Weill-Halle B. *Bull Acad Med*. Vol. 91. Paris: 1924. Essai d'immunisation contre l'infection tuberculeuse. pp. 787–96
- [6] Calmette A, Guérin C, Negre L, et al. *Ann Inst Pasteur*. Vol. 41. Lille: 1927. Sur la vaccination préventive des enfants nouveau-nés contre la tuberculose par le BCG. pp. 201–32
- [7] Wallgren A. Value of Calmette. Vaccination in Prevention of Tuberculosis in Childhood. *JAMA*. 1934;103:1341–5
- [8] Heimbeck J. Tuberculosis in Hospital Nurses. *Tuberk*. 1936:18–18
- [9] Greenwood M. Professor Calmette's Statistical Study of BCG Vaccination. *BMJ*. 1928;1:793–5
- [10] Petroff SA, Branch A, Steenken W. A Study of Bacillus Calmette-Guérin (B.C.G.). *Am Rev Tuberc*. 1929:19–19
- [11] Lange B. Weitere Untersuchungen zur Klärung der Ursachen der Unglücksfälle in Lübeck. *Tuberk*. 1931;62:335–51
- [12] World Health Organization. Tuberculosis: A Global Emergency; 1994; Geneva, Switzerland