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EDITORIALS

History of BCG Vaccine

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ABSTRACT

Tuberculosis (TB) is still responsible for 2 million deaths every year despite being a treatable airborne infectious disease. "Consumption" and "Phthisis" were terms historically used to describe TB, which was responsible for one in four deaths in the 19th century. Due to its infectious nature, chronic progression and long treatment, TB is a great burden for society. Moreover the emergence of multi-drug resistant TB and the current TB-HIV epidemic has raised even greater concern. Treating and preventing TB has become a permanent challange since the ancient times. Bacille Calmette-Guérin (BCG) is the only vaccine available today and has been used for more than 90 years with astonishing safety records. However, its efficacy remains controversial. No universal BCG vaccination policy exists, with some countries merely recommending its use and others that have implemented immunization programs. In this article we review several important milestones of BCG vaccine development from the discovery till today.

Keywords: Tuberculosis, BCG, vaccine, history, review

INTRODUCTION

Humans have been infected with M. tuberculosis (Mtb) for millennia. TB infection is characterized by a complex immunologic response, which leads to a unique host-pathogen interaction therefore make it difficult to treat and control. Moreover TB is a poverty related disease and has severe social implications. The introduction of Bacille Calmette-Guérin (BCG) and chemotherapy in the past century marks an important advance in the history of tuberculosis (TB), which accounted for optimism to fight the disease especially in endemic area. To date, BCG remains as the most widely used vaccine worldwide and has been given to more than 4 billion individuals with astonishing safety records (1,2). Next to BCG, no other vaccines are available for treating TB and of the many new candidates in the pipeline none is close to market use. In this review we discuss the major landmarks in the history of TB and BCG.

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Early history of tuberculosis

Mtb, the intracellular pathogen that causes TB, was discovered in 1882 by Robert Koch and is responsible for more human deaths than any other single pathogen today (3-5). Early last century, hopes were that TB could be conquered by vaccination with the newly developed M. bovis BCG vaccine, isolated by and named after Calmette and Guerin in Lille, France (6). These hopes were further boosted by the development of the first anti-tuberculous drugs during WWII by Selman Waksman, who discovered streptomycin bacteriostatic activity towards Mtb (7). Initially, treatment with streptomycin appeared highly efficacious, but the tide turned when drug resistance rapidly developed, an early testimony of Mtb's ability to acquire drug resistance when treated by single antibiotics. Despite this early writing on the wall, the misconception that TB could be conquered by antibiotics and BCG vaccination led to complacency for several decades. This situation dramatically changed only in the early 1990s, when the World Health Organization (WHO) declared TB a global emergency (8). From that time onwards TB scientists, who had been focusing much of their efforts on other areas of research and development due to a lack of interest in and funding for TB, were able to reorient efforts and initiate significant activities in the study of TB (9). The advent of Multidrug-resistant TB (MDR-TB), fueled by the HIV epidemic, were responsible for this shift of interest. Soon, researchers determined Mtb's genome sequence and began to dissect TB's immunology and cell biology (10).

2012 - 91 years of BCG vaccination

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. In an attempt to counteract their tendency to clump they tried the effect of adding ox bile to the medium and, to their surprise, they noted that subculture led to a lowering of the virulence of the organism. It was this fortuitous observation that led them to undertake heir long term project of producing a vaccine from this attenuated tubercle bacillus (11).

In 1908, starting with a virulent bovine strain of tubercle bacillus supplied by Nocard (originally isolated by him in 1902 from the udder of a tuberculous cow), they cultured it on their bile, glycerine and potato medium and then proceeded to subculture at roughly three weekly intervals. By 1913 they were prepared to initiate a vaccination trial in cattle which was interrupted by outbreak of World War I. Subculturing was continued throughout the German occupation of Lille, despite the greatly increased cost of potatoes and the difficulty of obtaining suitable ox bile from the abattoir. Yet, they managed to obtain this by grace of 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. At Guerin's suggestion, they named it Bacille Bilie Calmette-Guerin; later they omitted "Bilie" and so BCG was born (11).

In 1921, Calmette decided that the time was ripe for a trial of the vaccine in man. The first human administration of BCG was by Benjamin Weill-Halle (1875-1958) assisted by Raymond Turpin (1895-1988) at the Charité Hospital, Paris. A woman had died of tuberculosis a few hours after giving birth to a healthy infant. On 18 July 1921, Weill-Halle and Turpin gave a dose of BCG by the oral route to the infant. There were no undesirable sequelae. The oral route was chosen since Calmette considered the gastrointestinal tract to be the usual route of natural infection by the tubercle bacillus. Weill-Halle then tried the subcutaneous and cutaneous routes on other infants but local reactions were objected to by the parents, and so the oral method was continued, an emulsion of BCG prepared by Boquet and Negre being used. By 1924 they were able to report a series of 664 oral BCG vaccinations of infants (12). The Pasteur Institute at Lille began the mass production of BCG vaccine for use by the medical profession. From 1924 to 1928, 114 000 infants were vaccinated without serious complications (13). In 1928, Calmette called Guerin to join him in Paris, since he did not feel it necessary for Guerin to continue the BCG experiments on animals in Lille. By 1931, there was a special laboratory for the preparation of BCG and Guerin was placed in charge.

The method of BCG vaccination was therefore proved to be safe. But just as important was the question of its effectiveness. The statis-

tics of Calmette and Guerin showed a fall in tuberculosis mortality among those susceptible infants who had been vaccinated with BCG. Outside France BCG vaccination was being taken up also, especially in Barcelona by Luis Saye; and in the Scandinavian countries Arvid Wallgren in Gothenburg (14) and Johannes Heimbeck in Oslo (15) pioneered the cutaneous administration of BCG. In Great Britain, however, there continued to be considerable skepticism and the statistics of Calmette and Guerin were strongly criticized in 1928 by Professor M Greenwood (16). Moreover, 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" (17). Despite these disturbing reports, Calmette and Guerin remained confident that BCG was safe, until "the Lübeck disaster" happened.

The Lübeck disaster (1930)

In 1930 the tragic disaster in Lübeck shattered confidence in BCG. In this Northern German city, a scheme to vaccinate newborn babies was undertaken by Professor Deycke, director of the Lübeck General Hospital, and Dr. Alstädt, chief medical officer of the Lübeck Health Department. BCG was supplied from the Pasteur Institute, Paris, but prepared for administration in the tuberculosis laboratory in Lübeck and the oral route was used. After four to six weeks a large number of the infants developed tuberculosis. Of 250 vaccinated, there were 73 deaths in the first year and another 135 were infected but recovered. The German government set up an inquiry headed by Professor Bruno Lange of the Robert Koch Institute, Berlin, and Professor Ludwig Lange of the German Ministry of Health. After 20 months their report exonerated BCG as the cause of the disaster, which they attributed to negligent contamination of the vaccine by virulent tubercle bacilli in the Lübeck laboratories (18). Two of the doctors concerned were given sentences of imprisonment.

As the news of the Lübeck disaster spread around the world, Calmette and Guérin were the objects of considerable criticism and both men came under great strain. In August 1930, at the Oslo meeting of the International Union against Tuberculosis, Calmette defended himself and received a great ovation. Though, the report of the German inquiry exonerated BCG as the cause of the disaster, confidence in the vaccine had been undermined.

The first studies on BCG

By the late 1940s, several studies had appeared providing evidence for the utility of BCG in protection against tuberculosis. Tuberculosis had emerged as a major concern in the aftermath of World War II, and BCG use was encouraged, stimulated in particular by UNICEF, by the fledgling World Health Organization (WHO), and by Scandinavian Red Cross Societies. The campaigns spread to the developing countries over the next decade. Also in the 1950s, major trials were set up by the Medical Research Council in the United Kingdom and by the Public Health Service in the United States. Soon it became evident that the procedure employed in the United Kingdom (a Copenhagen strain BCG, given to tuberculin negative 13-year-olds) was highly eficacious against tuberculosis (19) whereas that in the United States (Tice strain, given to tuberculin negatives of various ages) provided little or no protection (20). On the basis of these results, the respective public health agencies recommended BCG as a routine for tuberculin-negative adolescents in the United Kingdom, whereas BCG was not recommended for routine use in the United States but restricted to certain high-risk populations. The majority of the world followed the lead of Europe and the WHO and introduced routine BCG vaccination according to various schedules (e.g., at birth, school entry, school leaving), whereas the Netherlands and the United States decided against routine BCG use and based their tuberculosis control strategy upon contact tracing and the use of tuberculin to identify individuals for preventive therapy.

Efficacy of BCG

Two hypotheses emerged early as explanations for the disparate results observed between different evaluations of BCG. One attributed the differences to variation between strains of BCG (21). In fact, BCG had never been cloned and had been passaged under different conditions, by different laboratories, ever since its original derivation in the 1920s. It was recognized that strains produced by different manufacturers differed in microbiological properties

(22) and hence it was not unreasonable to suggest that these might be reflected in differences in immunogenicity (23). An alternative hypothesis grew up around the USPHS trials, which noted that the poor results were observed in Alabama, Georgia, and Puerto Rico, in populations known to be exposed to many different "environmental" mycobacteria. It was thus proposed, originally by Palmer and colleagues, that exposure to various environmental mycobacteria could itself provide some protection against tuberculosis and affect the immune system in various ways and that BCG could not improve greatly upon that background (24).

In an effort to decide between these views, a large trial was organized in the Chingleput area of South India, starting in 1968, with assistance of the Indian Council of Medical Research, the WHO, and the U.S. Public Health Service (25). The plan was to compare two different BCG strains (Paris/Pasteur versus Danish), each in two doses, in an area known to have a very high prevalence of environmental mycobacterial exposure. A companion trial was to planned to be set up in an area in northern India with little exposure to environmental mycobacteria, but unfortunately, due in part to political unrest, this was never initiated. The results of the Chingleput trial were made public in 1979, and they revealed that neither vaccine imparted any protection against pulmonary tuberculosis (25). The detailed results of this trial are strange in several ways. The risk of disease among individuals considered tuberculin "negative" at the start was far lower than predicted at the outset, and it appeared that there were actually more cases among the vaccines than among the controls in the interval shortly after vaccination (though the statistical significance of this observation is questionable). Though two WHO-organized workshops reviewed the trial and concluded that the results could not be attributed to methodological error (26), a fully detailed presentation of the results of this massive trial has never appeared, and without detailed data it is difficult to understand exactly what happened. The surprising results of the Chingleput trial led to a series of observational studies aimed at evaluating BCG use in different populations of the world (27). Although most studies showed some degree of protection, the overall impression is one of great variation, for which there is as yet no universally agreed-upon explanation.

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 (which has taken over the old Glaxo vaccine), and the Japan BCG Laboratory in Tokyo. Each of these BCG vaccines is produced in a different manner, and they are recognized to differ in various qualities, such as the proportion of viable cells per dose (22). BCG strains derived from the original Paris strain after 1925 (e.g., the current Pasteur, Copenhagen, Glaxo-Evans strains) lack a region of the genome known as the RD-2, which is still present in strains derived earlier than that date [represented by the current Brazilian (Moreau), Japanese and Russian strains] (28,29).

Phenotypic differences between these BCG vaccine strains were first recognized in the 1920s and, more recently, molecular studies have defined their genomic differences. Although several animal and human studies suggest that the particular BCG vaccine strain used for immunization influences the mycobacterial-specific immune response, there is currently insufficient data to favor or recommend one BCG vaccine strain.

However, the majority of the world's population is supplied with BCG vaccine procured by UNICEF (The United Nations Children's Fund) on behalf of the Global Alliance for Vaccines and Immunization. UNICEF uses only four BCG vaccine suppliers who produce only three different BCG vaccine strains: BCG-Denmark produced by the Statens Serum Institute in Denmark, BCG-Russia (genetically identical to BCG-Bulgaria) produced by Bulbio (BB-NCIPD) in Bulgaria and by the Serum Institute in India, and BCG-Japan produced by the Japan BCG Laboratory.

In humans, there have been three studies investigating protective efficacy induced by different BCG vaccine strains (insert ref). 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 (30). In the third study (with 15-yr follow-up), BCG-Denmark had a greater protective efficacy than BCG-Pasteur (25 and 17%, respectively) (31).

These studies give only limited information about protective efficacy afforded by the BCG

vaccine strains currently most commonly used because 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 vaccine 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 subunit 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 of N.Ritz and co. (32) concluded that there are significant differences in the immune response induced by different BCG vaccine strains in newborn infants. Immunization with BCG-Denmark or BCG-Japan induced higher frequencies of mycobacterial-specific polyfunctional and cytotoxic T cells and higher concentrations of Th1 cytokines than immunization with BCG - Rusia. These findings have potentially important implications for global antituberculosis immunization policies and future tuberculosis vaccine trials. ❑

CONCLUSIONS

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. The World Health Organization and the International Union against Tuberculosis and Lung Disease could identify the BCG sub-strains that provide the best protection and recommend them for future vaccination.

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