Review Article

Pediatric Education and Research
Volume 3 Number 4, October - December 2015

BCG Vaccine

Ninza Rawal*, Sunil Mhaske, Pratap Patare***, Liza Bulsara***

*Post- Graduate **Professor & Head **Associate Professor., Department of Paediatrics, PDVVPF's Medical College, Ahmednagar.

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.

Keywords: Tuberculosis; BCG; Vaccine.

Introduction

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.

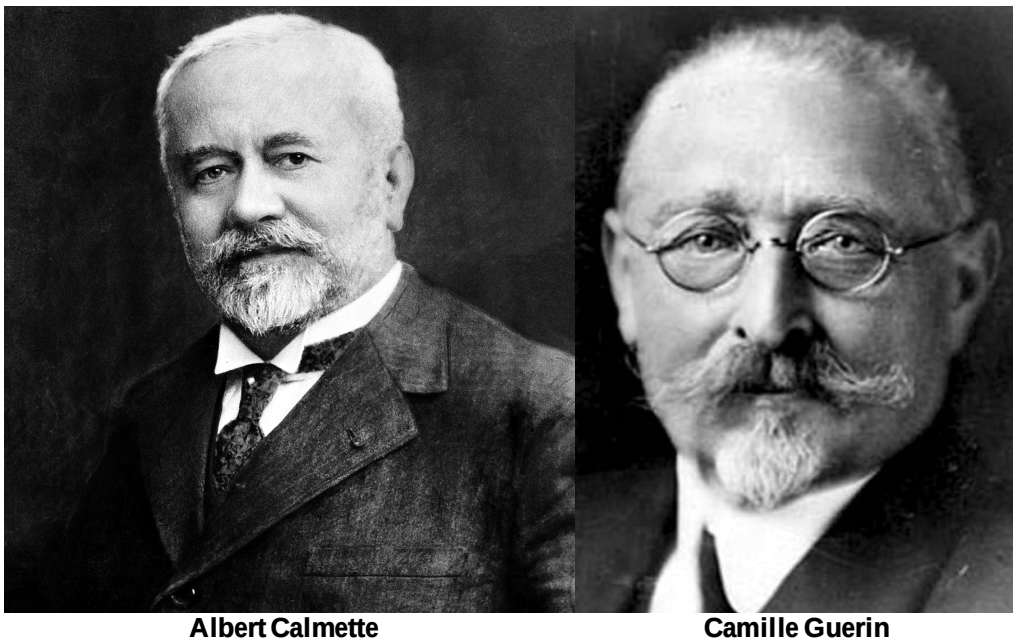
History

Mycobacterium Tuberculosis, 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.[3,4,5]

BCG vaccine is derived from the bovine tuberculosis strain and was first developed in 1921. It was the result of painstaking efforts by the French microbiologist, Albert Calmette, and the veterinary surgeon, Camille Guerin, who performed 231 repeated subcultures over 13 years. It continues to be the only effective vaccine against tuberculosis.

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

Corresponding Author: Ninza Rawal, Post- Graduate, Department of Paediatrics, Department of Paediatrics, Dr. Vithalrao Vikhe Patil Foundation's Medical College & Hospital, Vilad Ghat, Opposite Government Milk Dairy, Ahmednagar, Maharashtra 414111.
E-mail: ninza16@gmail.com



Albert Calmette (1863-1933) **Camille Guerin (1872-1961)**

Fig. 1: Albert Calmette & Camille Guerin)

were further boosted by the development of the first anti-tuberculous drugs during WWII by Selman Waksman, who discovered streptomycin bacteriostatic activity towards Mycobacterium Tuberculosis[7]. Initially, treatment with streptomycin appeared highly efficacious, but the tide turned when drug resistance rapidly developed, an early testimony of Mycobacterium Tuberculosis' 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].

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[9].

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[9].

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[10]. 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[11]. 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.

Current Status in India

Globally, about 1 million cases of pediatric tuberculosis are estimated to occur every year accounting for 10–15% of all tuberculosis (TB)[12]. The exact burden of childhood TB in India is unknown due to diagnostic difficulties but it is estimated to be 10% of the total adult incidence[13]. The proportion of pediatric TB cases registered under RNTCP has shown an increasing trend, from 5.6% in 2005 to 7% in 2011[14]. Prevention of childhood tuberculosis is thus an important priority. However, in comparison to other EPI vaccines, efficacy of BCG vaccine is limited. Several new vaccines against tuberculosis are in development phase, and many are designed to boost pre existing immunity induced by BCG[15] and some candidates aim to ultimately replace BCG as the priming vaccine[16].

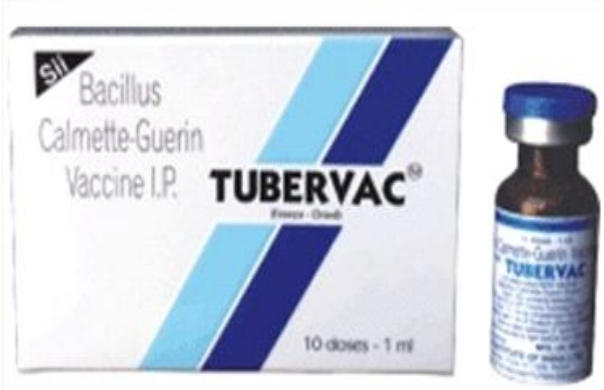


Fig. 2: BCG vaccine

Composition & Method of Administration

The two common strains in use are Copenhagen (Danish 1331) and Pasteur, of which the former was produced in India at the BCG Laboratories, Guindy, Tamil Nadu till recently. BCG induces cell-mediated immunity, but the protective efficacy is a matter of debate and is very difficult to quantify. It has an efficacy of 75–86 % for prevention of miliary and meningeal form of the disease. Protective efficacy for pulmonary tuberculosis is 50%[17].

The vaccine contains 0.1–0.4 million live viable bacilli per dose. It is supplied as a lyophilized (freeze-dried) preparation in vacuum sealed, multi-dose, dark colored ampoules or 2 ml vials with normal saline as diluent. The vaccine is light sensitive and deteriorates on exposure to ultra violet rays. In lyophilized form, it can be stored at 2 to 80 0 C for up to 12 months without losing its potency.

The long necked, BCG ampoule, should be cut carefully by gradual filing at the junction of its neck and body, as sudden gush of air in the vacuum sealed ampoule may lead to spillage of the contents. Diluent should be used for reconstitution. Sterile normal saline may be used if diluent is not available. As the vaccine contains no preservative, bacterial contamination and consequent toxic shock syndrome may occur if kept for long after reconstitution. The reconstituted vaccine should be stored at 2 to 8 0 C, protected from light and discarded within 4–6 hours of reconstitution. The recommended dose is 0.1 ml or 0.05 ml as suggested by the manufacturer of the vaccine. Dosage does not depend on the age and weight of the baby. Injection of BCG should be strictly intradermal, using a tuberculin syringe and a 26G / 27G needle. The convex aspect of the left shoulder at level of deltoid insertion is preferred for easy visualization of the BCG scar and for optimum lymphatic drainage. Other sites such as thigh should be avoided. The selected site may be swabbed clean using sterile saline and local antiseptics should be avoided.

Reaction

A wheal of 5 mm at the injection site indicates successful intradermal administration of the vaccine. Subcutaneous administration of BCG is associated with an increased incidence of BCG adenitis. The injected site usually shows no visible change for several days. Subsequently, a papule develops after 2–3 weeks, which increases to a size of 4–8 mm by the end of 5–6 weeks. This papule often heals with ulceration and results in a scar after 6–12 weeks. The ulcer at vaccination site may persist for a few weeks before formation of the final scar. No treatment is required for this condition.

Adverse Effects

Secondary infection at the vaccination site may require antimicrobials. Ipsilateral axillary / cervical lymphadenopathy may develop a few weeks / months after BCG vaccination. Antitubercular therapy is of no benefit in such situations and should not be administered. The nodes regress spontaneously after a few months. It should also be noted that if fine needle aspiration cytology of the nodes is carried out, stain for acid-fast bacilli may be positive. These are bovine vaccine bacilli and should not be misconstrued as being suggestive of tuberculous disease. In some

children, the nodes may even liquefy and result in an abscess. Surgical removal of the nodes or repeated needle aspiration is the treatment of choice; again antitubercular therapy is not recommended. Disseminated BCG infection is extremely unusual but may occur in children with cellular immunodeficiency.

BCG & HIV

BCG should be avoided in the immunocompromised, especially those with cellular immunodeficiency; it may, however, be given at birth to children born to HIV positive mothers. BCG may be given with other vaccines on the same day or at any interval with the exception of measles / measles mumps rubella (MMR) vaccine where a gap of 4 weeks between the two vaccines is recommended.

Conclusion

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.

References

1. McShane H. Tuberculosis Vaccines: Beyond Bacille Calmette-Guerin. Philos Trans R Soc Lond B Biol Sci. 2011;366:2782–9.
2. Ottenhoff THM, Kaufmann SHE. Vaccines against Tuberculosis: Where Are We and Where Do We Need to Go? Chitnis CE, editor. PLoS Pathog. 2012;8:e1002607–12.
3. Ottenhoff THM. Overcoming the Global Crisis: "yes, we can," but also for TB ... ? Eur J Immunol. 2009;39:2014–20.
4. Kaufmann SHE, Winau F. From Bacteriology to Immunology: The Dualism of Specificity. Nat. Immunol. 2005;6:1063–6.
5. Kaufmann SH, Hussey G, Lambert P-H. New Vaccines for Tuberculosis. Lancet. 2010;375:2110 9.
6. Calmette A, Guerin C, Boquet A, et al. Paris: Masson et cie; 1927. La vaccination préventive contre la tuberculose par le "BCG."
7. Waksman SA. Conquest of Tuberculosis. First Edition. University of California Press. 1965.
8. World Health Organization. Tuberculosis: A Global Emergency; 1994; Geneva, Switzerland.
9. Calmette A. 1922. L'ninfection bacillaire et la tuberculose chez l'homme et chez les animaux.
10. Calmette A, Guerin C, Weill-Halle B. Bull Acad Med. Vol. 91. Paris: 1924. Essai d'immunisation contre l'infection tuberculeuse. pp. 787–96.
11. Calmette A, Guerin 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.
12. World Health Organization. Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children, WHO, Geneva, 2006.
13. Nelson LJ, Wells CD. Global epidemiology of childhood tuberculosis. J Tubercul Lung Dis. 2004; 8: 636–647.
14. Central TB Division. Tuberculosis India 2012. Annual Report of the Revised National Tuberculosis Control Programme, Directorate of General Health Services, Ministry of Health and Family Welfare, Government of India, 2012.
15. Hoft DF, Blazevic A, Abate G, et al. A New Recombinant BCG Vaccine Safely Induces Significantly Enhanced TB-specific Immunity in Human Volunteers. J Infect Dis. 2008; 198(10): 1491–1501.
16. Hanekom WA, Hazel M, Dockrell HM, et al. Immunological Outcomes of New Tuberculosis Vaccine Trials: WHO Panel Recommendations PLoS Medicine July 2008, 5: 1033–1036.
17. Rodrigues LC, Diwan VK, Wheeler JG. Protective Effect of BCG against Tuberculous Meningitis and Miliary Tuberculosis: A Meta-Analysis. Int J Epidemiol 1993; 22 (6): 1154–1158.