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Controversies and Challenges in Pediatric Vaccination Today

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BCG Vaccination: Is there light at end of the Tunnel?

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REVIEW ARTICLE

BCG Vaccination: Is there light at end of the Tunnel?

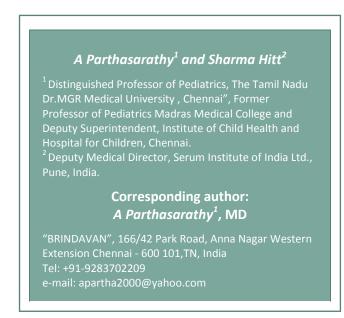*A Parthasarathy[1] and Sharma Hitt[2]*

Abstract:
The first Human BCG Vaccine was developed in 1921.Since 1960s billions of beneficiaries have received the vaccine in almost all the countries of the world .However its efficacy has been rated from 0 - 80% in several studies world over which include large randomized/controlled/case-control studies. Since 1974 BCG vaccine was included in the Expanded Program on Immunization(EPI) benefitting approx. 2 billion infants. Despite controversy BCG vaccine efficacy has been established in preventing hematogenous spread of TB infection like TBM, Miliary TB etc. and disseminated TB. Recent meta-analysis studies also have shown BCG vaccine's efficacy against prevention of 50% of Lung lesions both in children, adolescents and adults. More efficacious NEW TB Vaccines viz, Recombinant modified vaccines, attenuated strains of Mtb, subunit vaccines and DNA vaccines are expected to revolutionize global TB Disease control, elimination and possible eradication in future.

History of BCG Vaccination

The Bacille Calmette–Guérin (BCG) vaccines are the oldest of the vaccines currently used throughout the world [1]. They have been given to billions of people and have been used routinely since the 1960s in almost all countries of the world. Yet, despite their widespread use, tuberculosis remains the leading cause of death from a curable infectious disease, worldwide [2]. The World Health Organization (WHO) estimates that 9 million new cases of disease and 2 million deaths were attributed to this organism in 2004 [3]. Although, most technologically advanced countries have managed to essentially control tuberculosis, the incidence of disease and infection is increasing in many poorer areas of the world.

Albert Calmette, a French bacteriologist, and his assistant and later colleague, Camille Guérin, a veterinarian, were working at the Institut Pasteur de Lille (Lille, France) in 1908 [4].   Their work included subculturing virulent strains of the tubercle bacillus and testing different culture media. They noted that a glycerin-bile-potato mixture grew bacilli that seemed less virulent, and changed the course of

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their research to see if repeated subculturing would produce a strain that was attenuated to be considered for use as a vaccine. Throughout World War I, the research continued until 1919, when the now non-virulent bacilli were unable to cause tuberculosis disease in research animals. They transferred to the

Paris Pasteur Institute in 1919. The BCG vaccine was first used in humans in 1921 [5].

In 1948, the First International BCG Congress in Paris stated that BCG vaccine was effective and safe (despite the total lack of reported controlled trials or case-control studies). After World War II, the WHO and the United Nations International Children's Emergency Fund (UNICEF) organized campaigns to promote vaccination with BCG in several countries. Rates of BCG vaccination increased dramatically; by the end of 1974, more than 1.5 billion individuals had received the vaccine.

World wide efficacy studies
From 1974 to the present, BCG vaccination has been included in the WHO Expanded Programme on Immunization to strengthen the fight against infectious diseases among children in developing countries. Approximately, 100 million children receive a BCG vaccine each year, expanding the total number of individuals who have received BCG to more than 4 billion.

The true effectiveness of BCG vaccine has been debated for decades. Large clinical trials conducted from the 1930s through the 1970s yielded wide-ranging and conflicting results, demonstrating efficacy ranging from 0 to 80%. The first large scale trial evaluating the efficacy of BCG was conducted from 1956 to 1963 and involved almost 60,000 school children who received BCG at the age of 14 or 15; this study showed an efficacy of 84% up to 6 years after immunization [6]. However, a US Public Health Service trial of BCG in Georgia and Alabama published in 1966 showed an efficacy of only 14%, [7] and did much to convince the US that it did not want to implement mass immunization with BCG.

The most recent trial, conducted in South India (the "Chingleput trial") and published in 1979, showed no protective effect. This trial was designed with hopes of settling the question of BCG efficacy once and for all, had discouraging results and methodologic difficulties that only served to continue the argument [8,9]. Experts have offered a number of explanations for the variation in results among trials, but no one theory has been proved [10-15]. In recent years, researchers have studied BCG efficacy using case-control, cohort, household contact and meta-analysis study designs, but conclusions still diverge.

Despite the controversy, there are two areas in which BCG vaccine has shown consistent benefits: protection against disseminated tuberculosis disease [16-19] and protection against leprosy [20-25].

Various studies, including controlled trials, case-control studies and meta-analyses, have demonstrated high levels of protection against miliary tuberculosis and tuberculous meningitis, especially among vaccinated infants. It is generally accepted that BCG vaccine is most efficacious in preventing severe childhood disease. BCG vaccines also appear to have good efficacy against leprosy and likely have contributed toward lower rates worldwide [26,27].

Challenges in evaluating the controlled field trials of BCG vaccine
Comparing the major controlled trials was difficult because they differed in a number of important aspects, including eligibility criteria, methods of disease surveillance, diagnostic criteria, vaccine strain and administration and environmental factors.
The randomized controlled trial is the ideal study design to address vaccine efficacy, but several considerations have complicated the evaluation of BCG vaccine with use of this method. First, the lack of a blood test for immunity precludes laboratory determination of protection, requiring long-term clinical observation of a large population. Second, the low incidence of tuberculosis and long incubation period for disease mean that huge study groups must be observed for long periods at great cost. Third, there is no gold standard for diagnosis of tuberculosis disease other than acid-fast stain and mycobacterial culture, which can have low sensitivity, especially among children. Also, many of these trials were conducted in developing countries in which resources for diagnosis, vaccination, follow-up and tracking were inadequate. These challenges as well as the lack of understanding of the immunology involved in protection against tuberculosis make the design and execution of clinical trials extremely difficult.

Although the efficacy of BCG vaccine in the prevention of miliary and meningeal tuberculosis among children has been noted consistently, the

variable efficacy of BCG vaccines against pulmonary disease has been attributed to differences

in the vaccines and/or the study populations, blunting of the apparent efficacy of the BCG response by partial protection from infection with nontuberculous mycobacteria, higher rates of exogenous exposure to tuberculosis, and varying virulence of strains of M tuberculosis [28,29].

Efficacy of BCG vaccine against pulmonary, meningeal and disseminated disease in infants and young children

The cost, extensive length of follow-up, and large numbers of subjects needed to conduct a large, randomized clinical trial, as well as the lack of consensus reached in previous studies, have led to the use of alternative methods for evaluating the efficacy of BCG vaccine [30].

In the 1980s, the WHO initiated a global study to evaluate programs in developing countries using a standardized case-contact protocol that evaluated children who were household contacts of cases with infectious disease. These children were evaluated by use of the WHO clinical scoring system and were observed during 3 months for development of tuberculosis disease. These methods as well as case-control and cohort studies, have yielded results similar to those of the major controlled trials, with efficacy ranging from 0% to more than 80% [31-34].

In summary, there is no question that BCG vaccination has worked well in some situations but poorly in others. Because only a small fraction of the cases in the general population of contagious, smear-positive adult pulmonary tuberculosis are potentially preventable by BCG vaccination, BCG has had essentially no effect on the ultimate control of tuberculosis. The best use of BCG appears to be for the prevention of life-threatening forms of tuberculosis such as meningitis and disseminated disease in infants and young children. Vaccination with BCG remains the standard for tuberculosis prevention in most countries because it is available, is inexpensive, and requires only one encounter with the patient; in addition, it rarely causes serious complications, and systems for early diagnosis and effective treatment of tuberculosis are lacking in many areas of the world.

Variable efficacy

The most controversial aspect of BCG is the variable efficacy found in different clinical trials that appears to depend on geography. Its effects in extremely large randomized, controlled, and case-control studies have been widely disparate, in some cases demonstrating a great degree of protection and in others offering no benefit. However, trials of BCG vaccines have provided some of the best and most complete information on tuberculosis in human populations and have played an important role in the development of vaccine trial methodology [35].

BCG is very efficacious against tuberculous meningitis in the pediatric age group, but its efficacy against pulmonary tuberculosis appears to be variable. As of 2006 only a few countries do not use BCG for routine vaccination. The USA and the Netherlands have never used it routinely. In both countries BCG vaccination is not routinely given to adults because it is felt that having a reliable Mantoux test and being able to accurately detect active disease is more beneficial to society than vaccinating against a relatively rare (in those countries) condition.

Reasons for variable efficacy

The reasons for the variable efficacy of BCG in different countries are difficult to understand. A number of possible reasons have been proposed but none have been proven, and none can explain the lack of efficacy in both low TB burden countries (US) and high TB burden countries (India).

1. **Background frequency of exposure to tuberculosis** It has been hypothesized that in areas with high levels of background exposure to tuberculosis, every susceptible individual is already exposed prior to BCG, and that the natural immunizing effect of background tuberculosis duplicates any benefit of BCG.

2. **Genetic variation in BCG strains** There is genetic variation in the BCG strains used and this may explain the variable efficacy reported in different trials [36].

3. **Genetic variation in populations** Difference in genetic make-up of different populations

may explain the difference in efficacy. The Birmingham BCG trial was published in 1988. The trial was based in Birmingham, United Kingdom, and examined children born to families who originated from the Indian subcontinent (where vaccine efficacy had previously been shown to be zero). The trial showed a 64% protective effect, which is very similar to the figure derived from other UK trials, thus refuting the genetic variation hypothesis [37].

4. **Interference by non-tuberculous mycobacteria** Exposure to environmental mycobacteria (especially *M. avium*, *M. marinum* and *M. intracellulare*) results in a non-specific immune response against mycobacteria. Administering BCG to someone who already has a non-specific immune response against mycobacteria does not augment the response that is already there. BCG will therefore appear not to be efficacious, because that person already has a level of immunity and BCG is not adding to that immunity. This effect is called masking, because the effect of BCG is masked by environmental mycobacteria. There is clinical evidence for this effect from a series of studies performed in parallel in adolescent school children in the UK and Malawi [38]. In this study, the UK school children had a low baseline cellular immunity to mycobacteria which was increased by BCG; in contrast, the Malawi school children had a high baseline cellular immunity to mycobacteria and this was not significantly increased by BCG. Whether this natural immune response is protective is not known. This hypothesis was first made by Palmer and Long.[39.] An alternative explanation is suggested by mouse studies: immunity against mycobacteria stops BCG from replicating and so stops it from producing an immune response. This is called the blocking hypothesis [40]. This appears unlikely as the vaccine proved ineffective in the United States, an area of low background levels of TB.

5. **Interference by concurrent parasitic infection** Another hypothesis is that simultaneous infection with parasites changes the immune response to BCG, making it less effective. A Th1 response is required for an effective immune response to tuberculous infection; one hypothesis is that concurrent infection with various parasites produces a simultaneous Th2-response which blunts the effect of BCG [41].

BCG Vaccine
BCG vaccine is a live freeze-dried vaccine derived from attenuated strain of mycobacterium bovis (Bacillus Calmette Guerin), used for the prevention of tuberculosis. It is available since many years and still continued in the 'National Immunization Schedule' of many countries.

The current vaccine strains are all descendants of the original M. bovis isolate that Calmette and Guérin passaged through numerous cycles during the 13-year period 1909– 1921. Subsequent passages under different laboratory conditions resulted in a variety of new BCG strains showing phenotypic as well as genotypic differences. In order to prevent further deviation from the original BCG, lyophilized seed lots of the vaccine strains have been kept by WHO since 1956. New batches of vaccine are prepared from seed-lot material by growing the bacilli in an artificial medium. After 6–9 days, the culture is harvested, filtered, concentrated and then homogenized and diluted before lyophilization of the final product.

The reconstituted vaccine contains both living and dead bacilli. The number of cultivable bacilli per dose and the biochemical composition of the vaccine vary considerably depending upon the strain and production method of the vaccine. Though a number of BCG vaccine strains are available, no BCG strain is demonstrably better than another in terms of efficacy and there is no global consensus as to which strain of BCG is optimal for general use.

Administration of the vaccine
WHO recommends intradermal application of the vaccine, preferably on the deltoid region of the arm using syringe and needle, although other application methods such as the multiple puncture technique are practised in some countries. The number of bacilli per dose is vaccine-strain dependent, varying with bacillary virulence and the number of live bacilli.

Newborn vaccinees normally receive half the dose given to older children. BCG vaccine can be given simultaneously with other childhood vaccines.

Adverse events

Complications following BCG vaccination are rare: the incidence of fatal dissemination of BCG is estimated to be 0.19–1.56 per million vaccinees and has almost exclusively occurred in inadvertently immunized persons with severely compromised cellular immunity. Significant local reactions, such as extensive local ulceration and regional lymphadenitis occur in <1:1000 and in most cases (>99%) in immunodeficient persons. Since neonates have a higher risk of vaccine-induced suppurative lymphadenitis than older children, infants aged <30 days should receive a reduced dose of the vaccine. Osteitis has been reported in connection with certain vaccine batches but now occurs very rarely.

Duration of immunity

The duration of immunity after BCG vaccination is not known. Estimates are based on data from clinical trials and case-control studies because there is no serologic test to measure immunity to tuberculosis or the immune response after BCG vaccination.

Most experts speculate that protection declines over time and is probably nonexistent 10 to 20 years after vaccination. However, a 60 year follow up study from one of the original placebo controlled trials in American Indians and Alaska Natives estimated 52% protective efficacy in patients 50 to 60 years after a single dose of BCG vaccine [42].

In a review of 10 randomized BCG trials, the average efficacy more than 10 years after vaccination was 14% [43]. A meta-analysis of BCG in neonates and infants in 3 controlled trials and 6 case control studies indicated that BCG vaccine efficacy in this age group may persist through 10 years after vaccination [44].

New vaccines against TB

In recent years, there has been a dramatic increase in the number of candidate TB vaccines evaluated in research laboratories. Better understanding of the immunological deficits of BCG and impressive progress in knowledge of mycobacterial genomics have paved the way for promising new products. The main vaccine targets are prevention of infection in naïve individuals, prevention of reactivation of latent infection and therapeutic vaccines to prevent relapses in TB patients. Currently, the most favoured research strategies include recombinant modified BCG vaccines, attenuated strains of Mtb, subunit vaccines and DNA vaccines.

Immunization policy in different countries

1. **WHO BCG policy:** The WHO recommends that BCG be given to all children born in countries highly endemic for TB because it protects against miliary TB and TB meningitis [45].

2. **United States:** The US has never used mass immunization of BCG, relying instead on the detection and treatment of latent tuberculosis.

3. **United Kingdom:** The UK introduced universal BCG immunization in 1953 and until 2005, the UK policy was to immunize all school children at the age of 13, and all neonates born into high risk groups. BCG was also given to protect people who had been exposed to tuberculosis. The peak of tuberculosis incidence is in adolescence and early adulthood, and the evidence from the MRC trial was that efficacy lasted only 15 years at most. Styblo and Meijer argued that neonatal immunization protected against miliary TB and other non-contagious forms of TB and not pulmonary TB which was a disease of adults, and that mass immunization campaigns with BCG would therefore not be expected to have a significant public health impact [46]. For these and other reasons, BCG was therefore given to time with the peak incidence of pulmonary disease. Routine immunization with BCG was withdrawn in 2005 because of falling cost-effectiveness: whereas in 1953, 94 children would have to be immunized to prevent one case of TB, by 1988, the annual incidence of TB in the UK had fallen so much that 12,000 children would have to be immunized to prevent one case of TB.

4. **India:** India introduced BCG mass immunization in 1948, the first non-European country to do so [47].

5. **Brazil:** Brazil introduced universal BCG immunization in 1967-1968, and the practice continues until the present day. According to Brazilian law, BCG is given again to professionals of the health sector and to people close to patients with tuberculosis or leprosy.

6. **Other countries:** In the UK, BCG was only ever given once (as there is no evidence of additional protection from more than one vaccination), but in some countries such as the former USSR, BCG was given regularly throughout life. In South Korea, Singapore, Taiwan and Malaysia, BCG was given at birth and again at the age of 12. But in Malaysia and Singapore, from 2001, this policy was changed to once only at birth and it was discontinued in South Korea.

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