BCG REVISITED

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History

Ever since Koch discovered the tubercle bacillus in 1882, numerous workers tried to attenuate the bacillus with the hope of producing a vaccine for the prevention of tuberculosis(l).

In 1921, after a total of 231 transplants Calmette and Guerin attenuated a highly virulent *Mycobacteriutn bovis* strain to a completely harmless strain whose antigenicity was unimpaired. This strain was named *Bacillus Calmette* and *Guerin (BCG)*. In 1924 Calmette declared the bacillus incapable of reverting to virulent form. In 1928, the League of Nations also declared the *BCG* strains to be harmless to animals and man(2,3).

In India the BCG vaccination programme started in 1948 in Madanpalle (Tamil Nadu) and the BCG Vaccine Laboratory was established in the same year in Madras. By 1960, the first round of mass BCG vaccination was completed in all states with about 254 million persons having been vaccinated by 1979. Yet BCG is one of the most controversial vaccines. This review aims to discuss operational details of BCG.

Constitution

The freeze-dried vaccine is used in all countries now. This attenuated Calmette-Guerin strain of bovine *M. tuberculosis* is present in a concentration of 0.1 to 0.4 million viable bacilli per dose(4). The WHO recommends the "Danish 1331" strain for the production of BCG vaccine, which has been used by the BCG Laboratory, Guindy, Madras since 1967. Quality control is ensured by the International Reference Centre at Copenhagen(5).

Storage

If stored at sub-zero temperatures (-20°C) the vaccine remains potent for 2 years. Normally, the undiluted vaccine should be stored in the middle of the main compartment of the refrigerator (2° to 4°C) without loss of potency upto 6 months(4). At the peripheral level, at 2° to 8°C it is good for use up to one week. Strict attention should be paid to maintenance of the cold chain and it should be transported in thermos flasks with ice to the outreach immunization clinics. As the vaccine deteriorates

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on exposure to light it is usually supplied in dark colored ampoules and wrapped in black paper/cloth(5).

Reconstitution

Ampoules of freeze-dried BCG vaccine are long and are sealed under vacuum. They have to be opened carefully by gradually filing at the junction of the neck and the body of the ampoule so that air does not rush in, causing spillage(4). The vaccine is then reconstituted by dissolving it in normal saline as distilled water acts as an irritant(5). The diluent should always be kept with the vaccine in the main compartment of the refrigerator/cold box/vaccine carrier to ensure that it is cold enough when one needs it. Reconstituted BCG vaccine should be used within 3 hours and separate needle should be used for each child. The standard dose of BCG vaccine is 0.1 mg in 0.1 ml volume. Hence the same dose (0.1 mg) should be given at all ages(4). Most studies have shown good sensitization when BCG has been given at birth(6-10) though tuberculin-conversion rates are slightly higher when it is given a little later say at 1 or 3 months of age(ll). However, since it is difficult to get children back for immunization and BCG immunization at birth produces adequate cell-mediated immune response (CMIR) (11) it is recommended that BCG be given either at birth or at the time of earliest contact with the child preferably before 5 months of age and definitely by the time he is an year old(4).

BCG can be easily given to newborns weighing above 2000g(4) and has been found to be effective in preterm infants also having appropriate weight for gestation. However, 'small-for-gestational age' babies show poor post-vaccination conversion(12). Policies differ from country to country; a single dose of BCG is given at 13 months in United Kingdom(13).

Administration

Conventionally, BCG is given on the left upper arm. No special preparation of the skin is necessary before its administration, clearing with sterile water is enough. Ideally use of separate disposable or autoclaved needles should be adhered to for intradermal injection though the same syringe may be used for multiple administrations. When 0.1 ml of the vaccine is injected intradermally it raises a wheal of 8 mm in diameter over the injection site. Hair follicles are seen as small pits on the wheal produced. The wheal is absorbed in 20-30 minutes. No rubbing or hot fermentation at the injection site is recommended. By the 3rd or 4th week induration is felt at the vaccination site which becomes a lump of 6-10 mm by the 6th week. This is not painful but tender to touch. This lump may soften with pus formation and discharge, leaving a tiny ulcer which heals by itself. Sometimes this cycle of ulceration and healing may repeat 2-3 times over a period of 2-3 months. Healing is usually complete by 10-12 weeks and the site is marked by a small hypopigmented scar 5-7 mm in size(4). *Table I* summarizes the contraindications to BCG vaccination. According to the updated WHO recommendations BCG should be given only to asymptomatic HIV positive individuals but it should not be given to HIV positive children with clinical AIDS(14-16). However, a recent study has shown no difference in immune response between patients with clinical AIDS and those who were only HIV positive. Hence, the previous recommendation that BCG is contraindicated in children with AIDS does not hold true presently. Isoniazid chemoprophylaxis in a dose of 5 mg/kg/day

TABLE I—*Contraindications to BCG Vaccination*

A.	*Immunodeficiency*	
	1. Congenital : Cellular, immunoglobulin deficiency	
	2. Acquired	: AIDS
		: Leukemia, lymphoma
		: Disseminated malignancy
B.	*Depressed immune system*	
	1. Steroid use, alkylating agents, antimetabolites	
	2. Radiation	
	3. Recent viral infection, *viz.*, measles, chickenpox and hepatitis (in previous 6 weeks)	
	4. Immunoglobulin use in preceding 4-6 weeks	
C.	Congenital infection (TORCH group)	

should be administered to children who develop measles or whooping cough within 4-6 weeks of BCG administration(4). BCG should also be avoided in neonates with congenital (TORCH) infections as the intrauterine growth retardation and secondary immunosuppression would make BCG uptake questionable in these cases(4).

Protective Efficacy of BCG

Protective efficacy is defined as the percentage reduction in the risk of getting the disease in vaccine recipients when compared with similarly exposed nonimmunized individuals. Well conducted randomized trials, and less desirable alternatives like case control or household contact designs have yielded an extraordinary range of results from no protection to 80% protective efficacy (*TableII*)(17,18). The report of the Madras Tuberculosis Prevention Trial conducted in the Chingleput district of Western Tamil Nadu has been widely misinterpreted as showing that BCG offers no protection against tuberculosis under any epidemiological condition(19). However, since extrapulmonary forms of tuberculosis and children under 10 years of age were not included in the assessment, the results of this study cannot be extrapolated on to the pediatric population. Data from observation case-control, historical cohort and cross-sectional studies in areas where vaccination is performed at birth indicates that the incidence of tuberculous meningitis and miliary tuberculosis is 52-100% lower and that of pulmonary tuberculosis 2-80% lower in vaccinated children less than 15 years of age than in unvaccinated controls (20-24). This fact was pointed out by Wallgren way back in 1948(25) and confirmed by Dahlstrom in 1954(26). Other explanations such as genetic and physiological differences between the trial populations, or geographic differences in *M. tuberculosis* or *M. leprae* have not been substantiated. It seems highly likely that several factors have conspired together(13). Evaluation of BCG efficacy would have been facilitated if an immunological assay to measure protective immunity was available. Hart(23) and Comstock(24) found tuberculin skin sensitivity to be a poor indicator of efficacy contrary to popular belief.

TABLE II– *Efficacy of BCG in Various Controlled Trials*

Area	Efficacy (95% confidence intervals)
Haite	50-93%
British school children	65-82%
N. American Indians	66-80%
USA (Chicago infants)	50-85%
Puerto-Rico	10-40%
S. India (Madanpalle)	–50-+50%
USA (Georgia + Alabama)	–75-+40%
S. India (Chingleput)	–100-+45%
USA (Illinois children)	–300-+45%
USA (Georgia children)	–900-+70%

Adapted from Fine PEM. Rev Infect Dis 1989, 2 (Suppl): 354.

Various reasons have been suggested to explain the variable protective efficacy. The more popular explanations such as differences between the potency of BCG strains and the role of regional difference in prevalence of infections with environmental mycobacteria are discussed subsequently. The third explanation is based on the hypothesis that various immune mechanisms act against different stages of mycobacterial infection and disease. BCG, however, acts only against some of these. It seems that BCG appears to protect against tuberculosis by inhibiting *the bacilletnic phase of primary infection with virulent mycobacteria.* Therefore, such vaccines can be expected to provide protection against tuberculosis developing via the endogenous reactivation pathway and that in the progressive primary disease. BCG can not be expected to protect against disease developing via the exogenous reinfection pathway or the primary tubercular infection itself(27). The protect against disease developing by the latter pathway, it would seem that such vaccines shall have to inhibit the implantation of bacilli at the portal of entry into the lungs(28).

The evaluation of the impact of BCG at a community level is also beset with difficulties. It is reasonably clear that BCG vaccination has reduced the incidence of childhood tuberculosis. A six-fold increase in childhood tuberculosis was noticed in Sweden following cessation of BCG(16). However, its effect on adult tuberculosis needs to be still demonstrated. Therefore, BCG vaccines which are cheap, stable, safe and widely used are still judged worthwhile.

Variables Affecting Protective Efficacy

(i) ***Age***

BCG vaccination in the newbom and in infants, confers valuable protection against tuberculosis(l 1,21,22,29-32). This immunity is often equated with tuberculin in skin sensitivity as it is believed that tuberculin skin testing gives information about the duration of protection provided by BCG. Contrary to tins belief, Spirer *et al.* (33) reported persistence of lymphoblast transformation in skin test negative children immunized with BCG in infancy. Seth *et al.* (34) also demonstrated positive. CMIR elicited by leucocyte migration inhibition test (LMIT) in 36.1% of cases, with negative tuberculin test. Seth *et al.* (34,35) have also reported waning of CMIR with time; maximum waning occurred in the first three years. Kathipari *et al.* (11) also reported that BCG given at birth or at 3 months of age in a group of 120 newborns showed comparable CMIR hence, the practice of giving BCG at birth in our country should be continued.

(ii) Nutrition

Seth and co-workers(35) reported that Mantoux conversion rate after BCG vaccination in children with mild to moderate degree of protein energy malnutrition (PEM) was comparable to that in the normally nourished group but was poor in children with severe PEM. Though there was no relationship between Mantoux conversion and age in the case of normally nourished children, a significantly higher proportion in the l-<3 year age-group had positive Mantoux test (induration >10 mm) as compared to 3-6 year age-group in the undernourished group. Another study by Seth *et al.* (36) shows that though malnourished children can evoke CMIR after 8 weeks of BCG, retention of CMIR is poor in malnourished children. Waning of CMIR was also observed to be less in children with normal nutrition as compared to the malnourished group.

(iii) *Potency of Vaccine*

BCG vaccines currently used in humans have varying degrees of potency-low, inter' mediate, or high. Usually the Danish strain is of high potency and the French strain of intermediate potency. In animal studies, BCG vaccination inhibited hematogenous spread of virulent bacilli. This retardation or reduction of hematogenous spread to the lungs appears to be a function of the potency of the vaccine(36).

(iv) *Exposure to Nontuberculous Environmental Mycobacteria*

Exposure to these organisms favours the development of nonspecific tuberculin sensitivity which may be protective (Listeria type) or deleterious (Koch type). Koch type nonspecific sensitivity favors the occurrence of reinfection type of tuberculosis which is not prevented by BCG. This explains how tuberculosis continues to occur in areas where non-specific tuberculin sensitivity is highly prevalent, or (as in the case of Listeria type sensitivity) that a low risk of disease does not necessarily result from a low risk of infection(37). Regional differences in prevalence of infection with atypical mycobacteria like *M. xenopi* and *M. avium* can account for variable efficacy of BCG. In the Chingleput trial(19), 95% of the population over the age of 10 years was sensitized by previous infection with environmental mycobacteria which would itself induce a high prevalence of heterologous protection. This fact combined with the observation that relatively small number of cases of tuberculosis were observed in the first $7^{1/2}$ years of the trial suggests that this intense exposure may have induced a protective effect in the placebo group equal to that of BCG. It is likely that there was no true placebo group in the Chingleput trial(28).

Since BCG induces a level of protection similar to, natural primary infection, it is of no benefit to those already infected. Also, repeated insults of exogenous reinfection can also overcome BCG-induced anti-tubercular immunity and cause disease. This is the reason why BCG vaccination is not effective in areas of high prevalence of tuberculosis; as retrospective surveys showing a favourable effect of BCG were invariably conducted under conditions where the role of exogenous reinfection was not significant(37). However, BCG was definitely effective in preventing serious manifestations of hematogenous spread, namely miliary and meningeal forms of disease, especially in children(26,27).

Revaccination

In India and abroad it was observed that both natural and BCG-induced tuberculin

sensitivity tends to wane in the course of time(36,37). This waning could also be associated with some degree of loss of protection against exogenous superinfection. Seth *et al*.(36) showed that only 26.3% of children were Mantoux positive after 3-<6 years of BCG vaccination compared to 35.7% at l-<3 years of age, though LMIT positivity did not change significantly. These factors do suggest the need to consider revaccination. Though opinions again vary on the optimum age for booster BCG revaccination it would be logical to consider giving BCG in Mantoux negative children at school entry, *i.e.,* at 5 years of age(37). In certain East European countries, repeated doses are given throughout childhood(13).

Untoward Reactions with BCG Vaccination

Complications with intradermal BCG vaccination can be categorized as follows(38):

(a) Side effects associated with normal evaluation of BCG

(i) Simple local reactions-swelling, pain at site

(ii) Temporary swelling of regional lymph nodes

(b) Abnormal BCG primary complex
(Loco-regional complications)

(i) Ulcer, abscess
(ii) Regional suppurative lymphadenitis
(iii) Osteomyelitis (very rare)

(c) *Complications of dissemination (non-fatal/localized lesions rare)*

Otitis, retropharyngeal abscesses, cutaneous lesions, metastatic subcutaneous or intramuscular abscesses, lesions of bones, joints and synovia; renal and urogenital lesions, mesenteric adenitis, multiple adenitis/ hepatosplenomegaly/other localizations.

(d) Generalized dissemination (fatal cases)

(e) Post-BCG syndrome

Local chronic cutaneous lesions (keloids, histiocytoma), acute cutaneous eruptions (erythema nodosum, rashes), ocular lesions

(f) Other syndromes

In a large study by International Union Against Tuberculosis and Lung Disease (IUATLD) on complications induced by intradermal BCG vaccination loco-regional complications(25,26) formed the target group with a risk of 0.0387 per 1000 vaccinated cases in children <1 year of age and 0.025 per 1000 in 1-20 year age-group. In newborns the risk of persisting and disseminated BCG infection and hypersensitivity manifestations ranged from 3.46 to 5.59 per 1 million vaccinated subjects in the 6 European countries under study. In all age groups the risk ranged from 0.98 to 13.60 per 1 million vaccinated subjects. Such precise estimates are not available from our country. However, the general impression is that the incidence of complications in the newborn is almost negligible. Once in a while, change in the strain of BCG may produce higher incidence of BCG adenitis.

Serious complications remain a rarity though loco-regional complications may be seen in the first 6 months of vaccination in children less than one year of age. Tardieu *et al.* (39) have described two cases of tuberculous meningitis in children after vaccination with BCG of *M. bovis* strain. They investigated the immune status of the children; both quantitative and quantitative functions of polymorphs, B cells and T cells. With great difficulty they could isolate the organisms from CSF. TBM induced after BCG as a complication responds to

antitubercular drugs very well. Both the children recovered subsequently inspite of 6 months' delay in starting the therapy. Hence, it is clear that BCG vaccination rarely induces serious complication(40).

Seth has also seen TBM cases following BCG vaccination rather less infrequently than what is reported in the literature; however, she did not attempt any extensive study to isolate the BCG strain from CSF nor did she screen the cases for immunodeficiency as was done by Tardieu *et al.*(39). The general impression is that almost all these children recover with the antitubercular therapy and management of raised intracranial tension requires mostly conservative approach and very few need a shunt.

BCG as a Diagnostic Modality: The BCG Test

Though direct BCG vaccination (without prior tuberculin testing) has been recommended by the WHO's Expert Committee on Tuberculosis(41) and Udani *et al.* (42) and is followed in our country, the importance of BCG as a diagnostic modality needs to be evaluated as explained by Seth *et al.* (2):

(i) A higher antigen load with BCG may give rise to false positive reactions.

(ii) Once BCG is given, the tuberculin test can not be given to judge recent conversion in areas of high prevalence of tuberculosis which is a major handicap. However, it is not immunologically a sound test because the antigen used is the total bacillus and has many components which can act as non-specific antigens. Hence, Seth(2) does not recommend it as a specific diagnostic test. The only advantage is that BCG vaccine is given to the child. However, if it is given immediately after an attack of measles, it can precipitate fatal tuberculosis. Hence, the use of BCG test is only recommended on a restricted basis.

Other Uses of BCG

BCG has also been used as an immune-modulating agent in diseases like nephrotic syndrome and urinary bladder cancer in developed countries. Many controlled trials have shown evidence for BCG induced protection in leprosy. However, BCG is rarely given to prevent leprosy, *e.g.,* the household contacts of leprosy patients in Cuba, Venzuela, *etc.*

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