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Revisiting the Chingleput BCG vaccination trial for the impact of BCG revaccination on the incidence of tuberculosis disease

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***Background & objectives*: Vaccines play a crucial role in the prevention of tuberculosis (TB). Revaccination with Bacille Calmette–Guerin (BCG) for the prevention of TB is an important strategy that is currently gaining interest. The objective of this study was to reanalyze the community-based Chingleput BCG vaccination trial for protective efficacy of BCG revaccination against incident TB disease.**

***Methods*: A retrospective analysis of the Chingleput BCG vaccination trial (conducted in 1968) data was carried out. Data on participants with evidence of prior BCG vaccination at trial intake and randomized to BCG vaccine [low dose (0.01 mg), high dose (0.1 mg)] and placebo arms were analyzed. The incidence of TB disease, which was based on sputum culture and/or chest X-ray was compared between the BCG and placebo arms over a 15 yr follow up period.**

***Results*: Of the 269,727 individuals randomized in the trial; 263,158 had no evidence of TB at baseline, of which 4436 (1.68%) had evidence of BCG vaccination at trial intake (2890 in the BCG vaccine and 1546 in the placebo arms, respectively). There were 77 (190 per 100,000) and 64 (296 per 100,000) incident TB cases in the BCG and placebo arm, respectively, at 15 yr post-vaccination. The incidence of TB disease was significantly lower in the BCG arm [Hazard ratio of BCG arm (95% confidence interval): 0.64 (0.46-0.89)].**

***Interpretation & conclusions*: Retrospective data analysis of this community-based trial revealed that BCG revaccination in a community offered modest protection against the development of TB disease at the end of 15 years which, however, requires further evaluation.**

Key words BCG revaccination - Chingleput trial - protective efficacy - TB incidence - tuberculosis

Prevention of tuberculosis (TB) is crucial to attain the end TB targets and vaccines play a major role in this initiative. Research towards the development of vaccines for TB has paved the way for many newer TB vaccines in the pipeline, which are in various stages of development[1,2]. Under the Universal Immunization Programme (UIP) of India, single-dose intradermal Bacille Calmette–Guerin (BCG) vaccination is administered to newborns at birth for the prevention of TB. The 15 yr follow up of the Chingleput BCG

vaccination trial concluded that BCG offered no overall protection in adults and a low level of protection in children against TB[3]. A systematic review and meta-analysis reported that BCG vaccination protects against pulmonary and extrapulmonary TB for up to 10 years[4]. In this context, revaccination with BCG may constitute an important strategy that is currently gaining interest[2]. Studies on the protective efficacy of BCG revaccination against TB are varied as reported from countries including Brazil, Sweden, Finland, Honk Kong and Malawi[5-10]. However, there is a lack of evidence on the effect of BCG revaccination in the prevention of TB from India, except for a study which reported that BCG revaccination is significantly immunogenic[11]. In this context the large-scale Chingleput BCG vaccination trial involving more than 0.25 million individuals provides an opportunity to explore existing evidence pertaining to BCG revaccination (*i.e*. amongst those with prior BCG vaccination) on incident TB.

So, the objective of this retrospective data analysis was to explore the evidence for protective efficacy of BCG revaccination against incident TB in comparison to those who were not revaccinated. In addition, the impact of age, sex and latent TB infection (LTBI) on the incidence of TB in BCG revaccination compared to those not revaccinated was examined.

Material & Methods

The present study was a retrospective analysis of the Chingleput BCG vaccination trial data[3]. In 1968, a large-scale double-blind, placebo-controlled BCG vaccination community trial was initiated in Chingleput district in the State of Tamil Nadu, South India, covering 209 villages and nine town blocks. At intake, all individuals aged ≥1 yr undertook a tuberculin test with 3 IU of purified protein derivative (PPD) of mammalian tuberculin (PPD-S) and 10 units of PPD-B (prepared using *Mycobacterium intracellulare* from the Battey strain). The population was randomized at the individual level into 0.1 mg BCG dose, 0.01 mg BCG dose and placebo arms, respectively. The Danish and French strains of BCG were used at 0.1 mg/0.1 ml and 0.01 mg/0.1 ml, respectively. The methodology of the trial, including the fieldwork, has been described earlier[12].

All individuals aged 10 yr or more underwent chest radiographs once in 2.5 years which were read independently by two expert readers. For individuals whose radiographs were classified as abnormal, especially those with probable or possible active TB, attempts were made to collect two sputum specimens. These were examined by fluorescence microscopy and cultured on Löwenstein-Jensen medium. Individuals in the age group <10 yr were considered as those with normal chest radiograph.

The case finding was continuous with periodic repeat surveys every 2.5 years, selective case finding (every 10 months) and passive case detection through existing health facilities over a 15 yr period.

Study population: Individuals with evidence of prior BCG vaccination at trial intake and randomized in the Chingleput BCG vaccination trial into BCG vaccine [low dose (0.01 mg), high dose (0.1 mg)] and placebo arms were considered for this analysis. In the BCG trial, the study participants were examined for the presence of BCG scar on the left shoulder at trial intake. The responses were stated as scar, no scar, doubtful scar, keloid and fresh BCG lesion. Of these scar, keloid, fresh BCG lesion were considered as evidence of prior BCG vaccination at trial intake for the present analysis. Additional inclusion criteria were as follows: no evidence of TB disease at trial intake (normal or abnormal X-ray not suggestive of TB and negative sputum culture report). Census status at survey time points indicated as present or absent and chest X-ray done at trial intake (age group <10 yr was considered as those with normal X-ray).

Operational definitions:

Incident TB disease: Those individuals diagnosed with TB based on at least one positive sputum culture and or abnormal chest X-ray, as mentioned by two independent chest X-ray readers, classified as possible/probable TB at follow up survey time points.

LTBI – Positive: Tuberculin skin test (TST) reaction of ≥12 mm by PPD-S; negative: TST reaction of <12 mm by PPD-S.

Data analysis: Data were verified for completeness and consistency and analyzed using the STATA software version 16.0 (StataCorp., Texas, USA). Proportions were computed for the variables of interest. The subgroups were compared using the Log-rank test. Hazard's ratio (HR) with 95 per cent confidence interval (95% CI) was calculated using the Cox proportional hazards model. The protective efficacy of the BCG vaccine was calculated in comparison with the placebo

as 100 × (1-hazards ratio); $P<0.05$ was considered statistically significant.

A formal sample size was not calculated for this study. As this was a retrospective analysis, all the individuals with the evidence of prior BCG vaccination at the time of enrolment into the Chingleput BCG vaccination trial were considered. A power calculation using the STATA 'power stcox' command with the overall estimation of the Hazards ratio between the BCG and placebo arms using the Cox proportional hazards model was performed.

Results

A total of 269,727 individuals were randomized in the BCG vaccination trial: BCG high dose (n=89,507), BCG low dose (n=89,710) and placebo (n=90,510) arm. Of the 269,727 individuals, 263,158 had no evidence of TB at baseline. Of these, 4436 (1.68%) had evidence of BCG vaccination at trial intake and were randomized to receive BCG high dose (n=1439), BCG low dose (n=1451) and placebo (n=1546) arm, respectively (Fig. 1). The analysis was done to determine the difference in TB incidence between low dose (0.01 mg) and high dose (0.1 mg) BCG, however, no difference was observed in TB incidence between the two. Hence, both doses of BCG arms were combined to be treated as a single group (BCG vaccine arm). There were 2890 individuals in total who received BCG revaccination in this analysis.

Baseline characteristics: Of the 4436 individuals, males constituted 58.5 per cent (n=2594) (Table I). About 31.9 per cent of the individuals were aged ≤15 yr (n=1416), 56.6 per cent aged from 16 to 30 yr (n=2514) and 11.4 per cent were aged >30 yr (n=506) at the time of trial intake. There were 2494 (56.2%) with LTBI-positive status. The distribution by age, sex and LTBI status was similar across the randomization arms.

Incidence of tuberculosis (TB) in the randomized arms: There were a total of 2890 individuals in the BCG vaccine arm and 1546 in the placebo arm. There were 77 [incidence rate of 190/100,000 population (95% CI: 150-237/100,000)] and 64 [incidence rate of 296/100,000 population (range 228-378/100,000)] incident TB cases in the BCG vaccine and placebo arms, respectively (Table II). The incidence of TB was significantly lower in the BCG vaccine arm over the follow up period of 15 years [HR BCG arm (95% CI):0.64 (0.46-0.89) (P=0.008)] (Fig. 2).

Table II shows data on the protective efficacy of BCG vaccine based on the follow up survey period post-vaccination. The protective efficacy of BCG vaccine against incident TB was evident at the end of 15 years of post-vaccination follow up [36% (95% CI: 11 to 54%)] but not at 5 or 10 yr follow up. 59 (76.6%) of the 77 incident TB cases in the BCG vaccine arm, and 46 (71.8%) of the 64 incident TB cases in the placebo arm were found to occur at the 10 yr post-vaccination follow up. There were 20 out of 64 and 23 out of 77 incident TB cases in the placebo and BCG vaccine arm, respectively, who were sputum culture positive.

Impact of age, sex and latent TB infection on the incidence of TB: The incidence of TB in the 31-40 yr age group at trial intake was significantly lower in the BCG vaccine arm [HR (95% CI): 0.2 (0.07-0.57), P=0.002; Table III]. The protective efficacy of BCG vaccine in this age group at trial intake was 80 per cent (95% CI: 43-93; Table III). The difference in the incidence of TB in the other age groups observed in BCG vaccine and placebo arms was not significant. The incidence of TB in males was significantly lower in the BCG vaccine arm [HR (95% CI): 0.57 (0.38-0.84), P=0.005; Table III]. The BCG vaccine protective efficacy against TB in males was found to be 43 per cent (95% CI: 16-62%), while in females, it was 21 per cent (95% CI: −48 to 58%; Table III).

There was no significant difference in the incidence of TB according to the LTBI status in the BCG vaccine and placebo arms (Table III).

Discussion

The present analysis of 4436 individuals at the end of the 15 yr follow up period post-vaccination revealed that BCG revaccination offered 36 per cent protection against TB. The power was computed as >90 per cent for the population available for the comparison of the outcome analysis (*i.e.* incident TB) in the BCG *vs.* placebo arms. Earlier studies on BCG revaccination reported no beneficial effect against the development of TB[5,8,9]. A systematic review on BCG revaccination against TB observed no statistically significant difference in the incidence rate ratio (0.57-1.74), relative risk [0.39 (0.31-0.59)] and HR [1.20 (0.77-1.89)] in the BCG revaccinated group compared to non-revaccinated group[13]. The evidence available so far suggests a lack of protective efficacy of BCG revaccination against TB which is, however, contrary to our present observations.

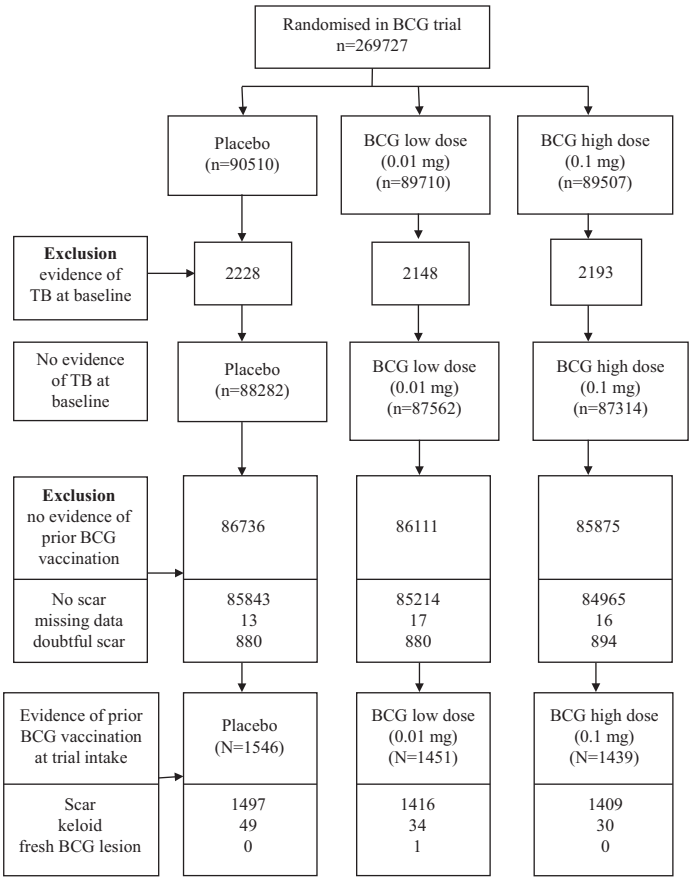


Fig. 1. Individuals with evidence of prior BCG vaccination at trial intake.

The present retrospective analysis showed that BCG revaccination had a protective effect in males but not in females. This sex-differential effect of BCG had been reported in earlier studies as well[14,15]. A study conducted in 303 healthy volunteers from the Netherlands reported an enhanced cytokine response to restimulation[14]. Furthermore, a reduction in inflammatory proteins after BCG vaccination was also reported more in men than in women[14]. Randomized trials have suggested a sex-specific effect in all-cause mortality and morbidity after neonatal BCG vaccination with a strong protective effect in males within the first week of vaccination and in females beyond two weeks[15]. However, animal studies have documented a weaker protection in BCG vaccinated male mice compared to female[16]. Research is, however, warranted for insights and factors on the sex-differential protective efficacy of BCG revaccination on TB in addition to correlates of protection. Nevertheless, the observation that BCG revaccination offers protection in males against TB is encouraging since pulmonary TB is more common among males and there may be scope for protection from this condition[17].

A protective effect from TB with BCG revaccination was observed in individuals who were aged 31-40 yr at the time of intake into the trial but not in the other age groups. This provides evidence for the time period for BCG revaccination for protection against TB, which, however, warrants further evaluation.

The immunological response to BCG revaccination seems promising as evident from earlier studies[7,11,18]. The study from India reported that BCG revaccination boosts adaptive polyfunctional Th1/Th17 and innate effectors irrespective of TB infection in adults[11]. A recent phase II clinical trial on the prevention of TB infection in adolescents from South Africa reported that BCG revaccination had 45.4 per cent efficacy in reducing the rate of sustained quantiferon TB (QFT) conversion[7]. This offers scope for BCG revaccination to be further explored for the prevention of progression of TB infection. Moreover, boosting immunity with BCG revaccination observed in the South African study[7] and its correlation with protection against the development of TB needs to be explored further[18].

Table I. Baseline characteristics of individuals with prior BCG vaccination at trial intake according to randomization arms

Characteristics	Placebo (n=1546), n (%)	BCG vaccine (n=2890), n (%)	Total (n=4436), n (%)
Age (yr)			
<1	46 (3)	75 (2.6)	121 (2.7)
1-5	88 (5.7)	135 (4.7)	223 (5)
6-10	110 (7.1)	243 (8.4)	353 (8)
11-15	244 (15.8)	475 (16.4)	719 (16.2)
16-20	354 (22.9)	686 (23.7)	1040 (23.4)
21-25	330 (21.3)	590 (20.4)	920 (20.7)
26-30	184 (11.9)	370 (12.8)	554 (12.5)
31-35	78 (5)	134 (4.6)	212 (4.8)
36-40	51 (3.3)	84 (2.9)	135 (3)
41-45	28 (1.8)	49 (1.7)	77 (1.7)
46-50	19 (1.2)	33 (1.1)	52 (1.2)
>50	14 (0.9)	16 (0.6)	30 (0.7)
Sex			
Female	680 (44)	1162 (40.2)	1842 (41.5)
Male	866 (56)	1728 (59.8)	2594 (58.5)
Latent TB infection			
Negative	562 (36.4)	1151 (39.8)	1713 (38.6)
Positive	891 (57.6)	1603 (55.5)	2494 (56.2)
Not available	93 (6)	136 (4.7)	229 (5.2)

TB, tuberculosis

Table II. Incident tuberculosis cases in the BCG vaccine and placebo arm over the period of 15 yr post-vaccination and the corresponding protective efficacy in individuals with prior BCG vaccination at trial intake

Follow up period post-vaccination	Placebo (n=1546)			BCG vaccine (n=2890)			Protective efficacy (%; 95% CI)
	Person-years	Incident TB cases (n)	Rate/100,000	Person-years	Incident TB cases (n)	Rate/100,000	
Upto 5 yr	10,713	30	280 (189-400)	20,048	39	195 (138-266)	31 (−12-57)
Upto 10 yr	16,311	46	282 (207-376)	30,594	59	193 (147-249)	32 (0-54)
Upto 15 yr	21,588	64	296 (228-378)	40,626	77	190 (150-237)	36 (11-54)

CI, confidence interval

The variable protection offered by a single dose of BCG could be attributed to pre-sensitization with environmental mycobacteria, variations in BCG strain, geographic location and route of administration[19]. A systematic review documented the absence of prior *Mycobacterium tuberculosis* infection or sensitization with environmental mycobacteria to be associated with higher BCG efficacy against TB while the efficacy was not associated with the strain of BCG[20]. In the present study no significant difference was observed in the incidence of TB according to LTBI status in the BCG vaccine and placebo arms which, however, needs to be confirmed in future studies.

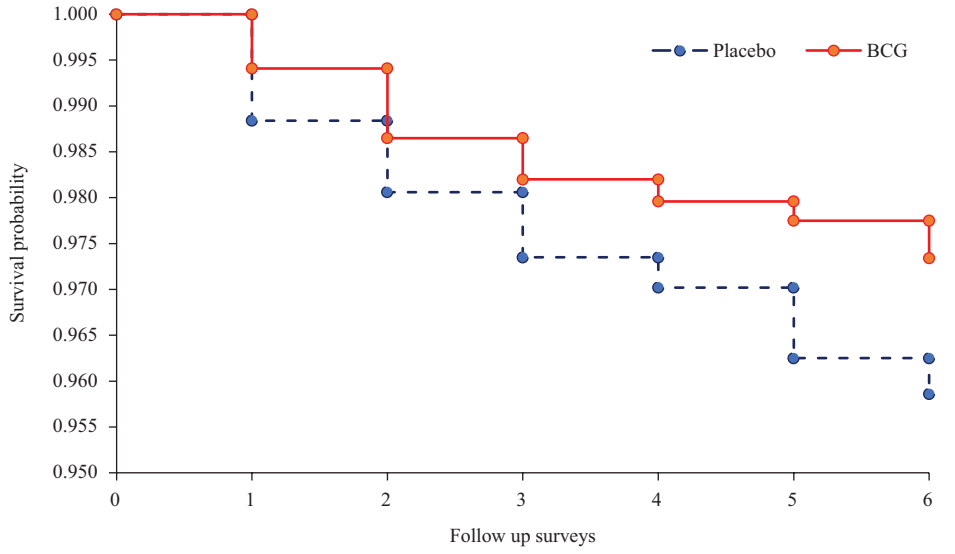
BCG has inherent advantages over the new vaccine candidates since it has been used over many decades, and the health system is optimized for vaccine administration. A systematic review on the safety of BCG revaccination concluded that there was minimal risk[21], while a study from Australia among adults observed an increased risk of abscess and lymphadenopathy among the revaccinated, which resolved within a month without intervention[22]. In this context, detailed documentation of adverse events

Table III. Incidence of tuberculosis disease and protective efficacy of BCG vaccine according to age at trial intake, sex and latent tuberculosis infection status in individuals with prior BCG vaccination at trial intake

Characteristics	Total (n)	Incident TB cases, n (%)	Hazard ratio (95% CI)	*P*	Protective efficacy % (95% CI)
Age (yr)					
<10					
Placebo	244	5 (2)	Reference		
BCG	453	9 (2)	0.96 (0.32-2.88)	0.948	4 (−188-68)
11-20					
Placebo	598	21 (3.5)	Reference		
BCG	1161	25 (2.2)	0.61 (0.34-1.09)	0.093	39 (−9-66)
21-30					
Placebo	514	24 (4.7)	Reference		
BCG	960	32 (3.3)	0.71 (0.42-1.21)	0.208	29 (−21-58)
31-40					
Placebo	129	14 (10.9)	Reference		
BCG	218	5 (2.3)	0.2 (0.07-0.57)	0.002	80 (43-93)
>40					
Placebo	61	0	-	-	-
BCG	98	6 (6.1)			
Sex					
Female					
Placebo	680	17 (2.5)	Reference		
BCG	1162	23 (2)	0.79 (0.42-1.48)	0.466	21 (−48-58)
Male					
Placebo	866	47 (5.4)	Reference		
BCG	1728	54 (3.1)	0.57 (0.38-0.84)	0.005	43 (16-62)
Latent TB infection					
Negative					
Placebo	562	18 (3.2)	Reference		
BCG	1151	20 (1.7)	0.54 (0.29-1.02)	0.058	46 (−2-71)
Positive					
Placebo	891	42 (4.7)	Reference		
BCG	1603	52 (3.2)	0.68 (0.46-1.03)	0.066	32 (−3-54)
Unknown					
Placebo	93	4 (4.3)	Reference		
BCG	136	5 (3.7)	0.85 (0.23-3.16)	0.807	15 (−216-77)
Overall					
Placebo	1546	64 (4.1)	Reference		
BCG	2890	77 (2.7)	0.64 (0.46-0.89)	0.008	36 (11-54)

following immunization in those with prior BCG vaccination is essential.

We tried to explore the difference in the period of TB breakdown in the BCG and placebo arms.



No. at risk (event)	Survey-0	Survey-1	Survey-2	Survey-3	Survey-4	Survey-5	Survey-6
Placebo	1546 (0)	1546 (18)	1528 (12)	1516 (11)	1505 (5)	1500 (12)	1488
BCG	2890 (0)	2890 (17)	2873 (22)	2851 (13)	2838 (7)	2831 (6)	2825

Fig. 2. TB disease-free survival in individuals with prior BCG vaccination at trail intake in those randomized to the BCG vaccine (n=2890) and placebo arm (n=1546).

However, the observations were not significant up to five or 10 yr of post-vaccination follow up period, which could be attributed to an insufficient number of individuals. It is suggested that this observation requires further evaluation and should be considered in future prospective studies.

BCG vaccine has gained importance in the context of COVID-19 due to its non-specific cross-protection against other infectious diseases through the mechanism of trained immunity[23-25]. Multiple studies across the world evaluated the protection of BCG against COVID-19[23,25]. In a TB endemic country like India, wherein BCG is given at birth, revaccination for COVID-19 showed reduced morbidity, less cytokine storm with COVID-19 and enhanced dendritic cells, interleukins-28A and 29 in elderly individuals who received BCG revaccination demonstrating the ability of BCG to induce non-specific innate immune responses as well in this population[26,27].

Despite its findings, this retrospective analysis is not without some inherent limitations. This was a post hoc analysis of a study done more than 50 years ago. The observation from this analysis has to be interpreted with caution since the numbers are not sufficient to make valid conclusions for a sub-group analysis which include age, sex, LTBI status and duration of follow up. The findings are useful for generation of hypothesis which, however, needs to be evaluated further in prospective studies. Data were not available on potential confounders such as nutritional, socio-economic and TB exposure status to analyze factors associated protective effect of BCG revaccination against TB. The data on the time interval between possible prior BCG vaccination and the BCG dose given at trial intake were also not available.

Overall, our reanalysis of data from a community-based vaccine trial revealed that BCG revaccination in a community suggestively offers 36 per cent protection against development of TB at the end of 15 years of post-vaccination follow up period. However, protection from TB with BCG revaccination, which was observed based on age, sex and LTBI status, needs to be further evaluated in future studies. The observation from this analysis offers scope for further evaluation of BCG revaccination in India.

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***Conflicts of Interest*:** None.

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