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Safety profile of BCG revaccination for COVID prevention among elderly individuals in India

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ABSTRACT

BCG vaccination is known to be safe in infants and a part of immunization schedule in high tuberculosis (TB) burden countries. In the conquest to bring down the severity of the COVID 19 pandemic, many drugs were repurposed in research mode including BCG vaccination/revaccination in various populations. We did a study among the elderly population (>60 years of age) to assess the role of BCG revaccination in preventing the severity of COVID 19 disease. Live attenuated BCG vaccine was given to the willing participants and were followed up for 6 months to estimate COVID19 incidence, understand severity and immunogenicity profile. A total of 48 serious adverse events (SAE) were reported among 1566 elders, none of them had more than one SAE. None of the SAEs were related to the BCG revaccination. Among the 372 adverse events reported, 96% were local reactions at the vaccine site and resolved on its own. BCG revaccination appeared to be safe and could be explored further if repurposing studies were planned for other diseases.

1. Introduction

The Bacillus Calmette-Guérin (BCG) vaccination is given at birth in high tuberculosis (TB) disease burden countries for prevention of severe forms of TB. BCG has been widely used in children from early 20th century; proven to be safe and implemented as a part of the immunization schedule for children in many countries. BCG vaccination is also considered for protection against leprosy, buruli ulcer and treatment of specific urinary bladder carcinoma.[1] The role of BCG in immunomodulation, prevention and reducing the severity was studied extensively during the COVID 19 pandemic.

A prospective study by Glynn et al. showed that there was no detrimental effect among BCG revaccinated in a wider age group from pediatric to geriatric population and in the long term. There was no difference between the BCG and placebo vaccinated on all-cause mortality.[2] The safety profile including serious adverse events (SAEs) among an elderly population who were revaccinated with BCG to assess its effectiveness in reducing the COVID 19 morbidity, mortality and understand the immunogenicity profile is being presented here.

2. Methods

Elders between 60 and 80 years of age willing to participate in a multi centric prospective study in India were vaccinated with a single dose of 0.1 ml of BCG vaccine administered intradermally after ruling out COVID 19 infection. The vaccine composition was live, attenuated Bacillus Calmette-Guerin Strain. Each ml of the vaccine contained between 2×10^6 and 8×10^6 Colony Forming Units (C.F.U.) (Freeze-dried, manufactured by Serum Institute of India, Pune.) The study was conducted during the first and second wave of Covid 19 pandemic (Wave 1) when specific vaccines were not readily available for this group during the study period. The participants were followed up for 6 months over telephonic calls in view of pandemic related restrictions and in person at specified time intervals (weekly telephonic calls during the first 2 months and then monthly in person visits for the next 4 months). They were reviewed for COVID 19 symptoms, testing as well as any adverse events to the vaccine. The protocol was approved by Institutional Ethics Committee of all centres.

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3. Safety assessments

The Adverse Event (AE) was defined as any untoward medical occurrence in a patient which did not necessarily have a causal relationship with BCG revaccination. An AE included an abnormal laboratory finding, symptom, or disease whether or not related to the vaccination which was not present earlier, or worsening after vaccination. SAEs included any untoward medical occurrence that resulted in death, life threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity.

4. Results

A total of 1566 elders consented and were vaccinated with BCG vaccine. The complete demographic profile and comorbidities of this study population is presented elsewhere.[3] Total of 372 adverse events (AE) had been reported among 268 participants. Among them, BCG scar was present among 51 (19%) and scar was absent among 216 (81%) participants. Most of them (96%) were local reactions at the vaccine site including redness, pain, ulcer, swelling, scab formation etc. and 4% had fever which resolved with symptomatic management. Almost 1298 (83%) participants did not have any AE. None of the participants were diagnosed with TB disease in the post vaccination follow up. Among the adverse events (AE), the median duration (IQR) for fever was 3[1–7] days, pain in the injection site 10 (5–15), redness 42 (9–49), blister/swelling 14 (7–21), ulcer and scab formation was 8 (7–14). None of the vaccinated individuals developed any disseminated BCGosis.

During the follow up period of 6 months, 48 SAEs were reported including 32 hospitalizations and 16 deaths. Among the hospitalizations, 20 were due to COVID 19, five elective planned surgeries, one each for dengue fever, viral pneumonia, chronic obstructive pulmonary disease, and complication of Hepatitis C viral infection, supraventricular tachycardia, tonic clonic seizure, and accidental consumption of antihypertensive medication. None of the participants were hospitalized due to more than one SAE. Regarding deaths reported in the follow up period, four were due to COVID 19 infection, nine due to cardiac arrests and one each due to accident, renal disease and chronic obstructive airway disease etc. None of the 48 SAEs were related to BCG revaccination. Clinicodemographic characteristics of the vaccinated individuals who had those SAEs were presented in Table 1.

5. Discussion

BCG revaccination is known to be safe and induces nonspecific adaptive immune responses thereby boosting immunity in elderly individuals. Most of the AEs observed in our cohort were local reactions at the vaccination site which had resolved on its own. There were no major systemic effects. Redness at the injection site occurred in almost 30% of the study population.

A placebo control randomized trial for COVID 19 among elderly in Netherlands irrespective of previous BCG vaccination showed that it is safer in the elderly. There was no significant difference between the BCG vaccinated and placebo groups in the incidence of SAEs.[4] In another similar study ACTIVATE 2, number of hospitalizations due to COVID 19 were higher among the placebo vaccinated compared to BCG vaccinated and deaths were reported only among the placebo group. Erythema was the commonest adverse event among the vaccinated.[5] In our cohort, men had more SAEs including hospitalizations than women and more deaths were reported among them. Comorbidities such as hypertension, diabetes etc, were shown to be risk factors of COVID 19. Our study showed that number of hospitalizations and deaths were more among the diabetics and hypertensives than those without. Almost half of the SAEs that occurred in our population was due to COVID 19. Rest of them were age related, admissions for planned procedures or other infections. BCG revaccination is not causal in any of these vaccinations.

Interim analysis of ACTIVATE study showed that BCG vaccination protects elderly against respiratory infections and safe. SAEs noted in the BCG vaccinated group were lower than the placebo group. None of the BCG vaccinated participants developed TB in this study. [6] Safety and immune modulating potency of BCG vaccine in the elderly population turns the spotlight on considering its revaccination for prevention of respiratory infections. BCG revaccination among various age groups in a community showed that TB was significantly among the BCG vaccinated group compared to the placebo arm over a period of 15 years. [7]

Limitations are multifactorial analysis was not done to look for factors associated with those SAEs due to limited information of other age related risk factors and lesser number of events. Also the safety of BCG revaccination in one age group is being reported here and may not be generalizable to all age groups.

Repurposing BCG revaccination during COVID 19 pandemic was studied extensively for prevention and reducing the disease severity in different populations. These studies have shown that revaccination is relatively safe. With the deadline for TB elimination fast approaching and the lack of other effective preventive vaccines, revaccination with BCG in wider age groups could be studied as an option for TB prevention. However, larger studies are needed to understand the safety of BCG revaccination in various age groups and its role in prevention of other diseases such as TB.

Table 1
Clinical and demographic characteristics of elderly individuals who were BCG revaccinated and had serious adverse events (n = 48) during 6 months post vaccination.

DEMOGRAPHIC	Total n (%)	HOSPITALIZATION n (%)	Death n = 16 (%)
Gender	n (%)	**n = 32(100)**	**n = 16(100)**
Male	39(81)	25(78)	14(88)
Female	9(19)	7(22)	2(12)
Age Median(IQR)	**70(65–73)**	**n = 32(100)**	**n = 16(100)**
<70 years	23(48)	18(56)	5(31)
≥70 years	25(52)	14(44)	11(69)
BMI Median (IQR)	**24.70 (22.1–29.1)**	**n = 32(100)**	**n = 16(100)**
<25 kg/m^2	19(40)	11(34)	8(50)
≥25 kg/m^2	29(60)	21(66)	8(50)
Diabetic	**n=30(62.50)**	**n=25(83)**	**n = 5(17)**
Yes	15(50)	11(44)	4(80)
No	15(50)	14(56)	1(20)
Hypertension	**n=32(67)**	**n=25(78)**	**n = 7(22)**
Yes	20(63	14(56)	6(86)
No	12(38)	11(44)	1(14)

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Author's contribution

Bella Devaleenal Daniel:(a) design and/or analysis and interpretation of data and to (b) drafting the article or revising it critically for important intellectual content and on (c) final approval of the version to be published; Mythily Venkatesan, (a) Analysis and interpretation of data and to (b) drafting the article, revising it critically for important intellectual content (c) final approval of the version to be published; C. Padmapriyadarsini:(a) conception, design and/or analysis and interpretation of data and to (b) drafting the article or revising it critically for important intellectual content and on (c) final approval of the version to be published.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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