Original Research Paper

Volume - 12 | Issue - 03 | March - 2022 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Paediatrics

TO EVALUATE CORRELATION OF BACILLUS CALMETTE GUERIN (BCG) VACCINATION STATUS WITH SEVERITY OF COVID 19 DIAGNOSED PEDIATRIC PATIENTS ADMITTED AT TERTIARY CARE CENTRE OF SOUTH GUJARAT OF WESTERN INDIA.

Dr. Jigisha Patadia	M. D. Pediatrics, Professor (Additional), Department of Pediatrics, Government Medical College, Surat, India.
Dr. Vijay Shah	M. D. Pediatrics, Professor & Head, Department of Pediatrics, Government Medical College, Surat, India.
Dr.Praful Bambharoliya*	M. D. Pediatrics, Assistant Professor, Department of Pediatrics, Government Medical College, Surat, India. *Corresponding Author
Dr.Tushar Bambharoliya	PHD, Research Assistant, Department of Pediatrics, Government Medical College, Surat, India.

ABSTRACT **Background:** Several studies have documented that BCG vaccine which is a part of Primary Immunization in certain countries not only prevent occurrence of Tuberculosis in children but also have numbers of heterologus protective effects which subsequently decreases the chances of occurrence of sepsis and various respiratory infections during childhood. In the present pandemic of SARS-Cov2 it is observed worldwide that Pediatric patients neither show severity nor adverse outcome of COVID 19 as compare to Adult population. **Objectives:** 1. To find out the proportion of BCG vaccination among COVID 19 positive paediatric patients admitted in a tertiary care centre. 2. To document the progress of the COVID 19 disease between BCG vaccinated COVID 19 patients and BCG non-vaccinated COVID 19 patients admitted in the tertiary care centre. **Methods:** It is a cross sectional study conducted in All COVID 19 positive patients admitted in the department of Paediatrics of the tertiary care centre during the study period shall be included. **Results:** All 57 COVID 19 positive children were BCG vaccinated. Majority of children (98.2%) recovered from COVID 19 and discharge from hospital, only 1.8% death occurred due to COVID 19 in children. **Conclusion:** we conclude that BCG vaccination has a protective effect against severity of COVID-19 in childhood. The main limitation of study, there were not any unvaccinated covid-19 positive children admitted in hospital during study period.

KEYWORDS : BCG; Children; Respiratory infections

INTRODUCTION

Several studies have documented that BCG vaccine which is a part of Primary Immunization in certain countries not only prevent occurrence of Tuberculosis in children but also have numbers of heterologus protective effects which subsequently decreases the chances of occurrence of sepsis and various respiratory infections during childhood. In the present pandemic of SARS-Cov2 it is observed worldwide that Pediatric patients neither show severity nor adverse outcome of COVID 19 as compare to Adult population.

Efforts for developing vaccines for novel coronavirus disease (COVID-19) are ongoing, but it is unlikely to be available in the immediate future.[1] In the absence of specific therapy, the researchers are exploring other potential preventive and therapeutic options. Recently, there has been a buzz about the protective effect of Bacille Calmette-Guérin (BCG) vaccine in COVID-19. Based on epidemiological correlations, many unpublished preprints hypothesized that the BCG vaccine may offer protection against COVID-19. It gained so much popularity that within 20 days three randomized controlled trials (RCTs) were registered, and many more are in the pipeline.[2] To make an informed decision, we must understand the mechanism of action of BCG, and appraise the robustness of the evidence.

The basis of the possible use of the BCG vaccine against COVID-19 lies in its non-specific effects (NSEs) over the immune system.[3] The NSEs of BCG are mainly mediated by potentiating innate immune response through epigenetic mechanisms. These epigenetic changes within the innate cells act as de novo enhancers to boost the immune response against a secondary challenge.[3,4,5] This enhancing response is popularly known as 'trained immunity' and is very characteristic of BCG. This trained immunity also offers protection against a variety of pathogens (Salmonella, Shigella, malaria, respiratory viruses, etc.) other than Mycobacterium tuberculosis, and forms the basis of its use in bladder cancer, melanoma etc. However, this non-specific effect is mostly short-lived and wanes soon after the primary BCG stimulus is cleared from the body. By virtue of the NSEs, BCG vaccine has shown to decrease all-cause mortality in children. Though a few observational studies suggest that the NSEs may last till adulthood, but the overall evidence is still inadequate and is of low quality.[3,6,7]

On critical appraisal of the non-peer reviewed pre-print evidence, at the relationship between BCG and COVID-19 is being proven by looking at correlation/ association among two data set (BCG vaccine coverage and COVID-19), without acknowledging the confounders. The variables like the difference in testing strategies, reporting bias, demographics, nation's ability to respond to the pandemic, prevalence of co-morbidities, and different stages of the pandemic across various countries might have a significant impact on these associations/ correlations and must be interpreted carefully. Therefore, at this stage, this association should be considered as a hypothesis only and should be tested through appropriately designed studies.

Though the epidemiological association between BCG and COVID-19 is striking, it does not prove causal relationship unless tested in well-designed clinical trials. Also, we should not forget that the NSEs of the BCG vaccine has not been well-studied in human beings and their clinical relevance is unknown.[2,3]

So putting above facts in to consideration, we can expect less chances of occurrence of SARS-Cov2 infection in children & in case if infection occurs due to certain factors then it may not lead to severe COVID 19. By conducting such studies, we can learn about BCG vaccination status with correlation of age of occurrence with course of disease & associated risk factors.

AIMS AND OBJECTIVES

1. To find out the proportion of BCG vaccination among COVID 19 positive paediatric patients admitted in a tertiary care centre.
2. To document the progress of the COVID 19 disease between BCG vaccinated COVID 19 patients and BCG non-vaccinated COVID 19 patients admitted in the tertiary care centre.

METHODOLOGY

Study Design: Cross Sectional Study

Sample size: Data was accessed from the case papers of all the COVID 19 positive pediatric patients admitted between 1st April 2020 and 30th June 2020.

Sampling Technique & Site:

Purposive sampling. All COVID 19 positive patients admitted in the department of Paediatrics of the tertiary care centre during the study period shall be included.

Inclusion Criteria:
All COVID 19 positive pediatric patients aged from 2 months to 12 years admitted in the pediatric wards in the tertiary care centre.

Exclusion Criteria:
Incomplete case papers from the Medical Record Section

Method of data collection:
All case record of patients admitted in the Paediatric ward and positive for COVID 19 (positive report (RT-PCR) were accessed from the medical record section. From the case records, complete history, immunization history with Anthropometry, general & systemic examination was noted in the questionnaire. Confirmation of BCG vaccination status would be done as per the status of BCG scar as noted in the case record as per protocol. Data was entered in SPSS version 23 and appropriate tests of significance shall be applied.

Statistical Analysis:
The data entry was done using Microsoft Office Excel 2016 and appropriate tests of significance shall be applied in Microsoft Office Excel 2016 and IBM SPSS version 23.

Ethical Clearance:
Ethical approval was taken before the commencement of the study from the ethical committee of the concerned institution.

RESULTS

Total 57 COVID 19 positive (positive report by RT-PCR) pediatric patients were enrolled in study. All 57 COVID 19 positive children were BCG vaccinated.

Table 1: Demographic Profile of COVID 19 positive children

Demographic Profile		Frequency (N=57)	Percent (%)
Age (years)	< 1	5	8.8
	1 to 5	19	33.3
	6 to 12	33	57.9
Gender	Male	29	50.9
	Female	28	49.1
Location	Rural	11	19.3
	Urban	46	80.7

Above table shows that 57.9% children were between 6 to 12 years old, 33.3% children were between 1 to 5 years old and only 8.8% children were below 1-year-old. Almost half of (50.9%) children were male and 49.1% children were female. Four fifth (80.7%) children were coming from urban area and remaining (19.3%) children were coming from rural area.

Table 2: Distribution of COVID 19 positive children according to symptoms

Symptoms	Frequency (N=57)	Percent (%)
Asymptomatic	19	33.3
Cough	23	40.4
Fever	20	35.1
Sore Throat	9	15.9
Rhinorrhoea	10	17.5
Others	9	15.8
Total	57	100.0

Above table shows that 33.3% children were asymptomatic, 40.4% children were present with cough, 35.1% children were present with fever, 15.9% children were present with sore throat, 17.5% children were present with rhinorrhoea and 15.8% children were present with other symptoms.

Table 3: Distribution of COVID 19 positive children according to contact and past history

History		Frequency (N=57)	Percent (%)
Contact History	Present	27	47.4
	Absent	30	52.6
	Total	57	100.0
Past History	Present	2	3.6
	Absent	55	96.4
	Total	57	100.0

As per the above table 47.4%, children had History of contact with COVID 19 positive patient and 52.6% children had no History of contact with COVID 19 positive patient. Majority of children (96.4%) had no past history of any chronic diseases, only 1.8% of children had history of chronic diseases like asthma and dengue each.

Table 4: Distribution of COVID 19 positive children according to General Examination

General Examination		Frequency (N=57)	Percent (%)
Weight for Age	Normal	23	40.4
	Mild	18	31.6
	Moderate	9	15.8
	Severe	7	12.3
Respiratory Rate	Fast	8	14.0
	Normal	49	86.0
SpO2 (%)	85 - 95	8	14.0
	>95	49	86.0

In General Examination, we observed malnutrition as per weight for Age, Respiratory Rate and SPO2 (%). Two fifth of children (40.4%) were normal as per weight for age, 31.6% of children were mild malnutrition, 15.8% of children were moderate malnutrition and 12.3% of children were severe malnutrition. Majority of children (86.0%) had normal respiratory rate and 14.0% of children had fast breathing. Around one fifth of children (14.0%) had SpO2 level between 85 to 95 and 50.9% of children had SpO2 level more than 95.

Table 5: Distribution of COVID 19 positive children according to outcome

Outcome	Frequency	Percent
Discharge	56	98.2
Death	1	1.8
Total	57	100.0

Above table shows that majority of children (98.2%) recovered from COVID 19 and discharge from hospital, only 1.8% death occurred due to COVID 19 in children.

DISCUSSION

On 11 April 2020, WHO updated its ongoing evidence review of the major scientific databases and clinical trial repositories for COVID-19 and BCG. The review yielded three preprints, in which the authors compared the incidence of COVID-19 cases in countries where the BCG vaccine is used with countries where it is not used and observed that countries that routinely used the vaccine in neonates had less reported cases of COVID-19 to date.[8]

In present study, all COVID 19 positive children admitted during study period were BCG vaccinated. Among them, majority of children were with normal respiratory rate and SpO2 level more than 95% during admission in the hospital. Majority of children recovered from COVID 19 and discharge from hospital with only one death occurred in COVID 19 positive admitted children. Suggesting less severity and mortality among BCG vaccinated COVID 19 positive children.

Paul K. Hegarty et al.[9] findings show that; incidence of Covid-19 was 38.4 per million in countries with BCG vaccination compared to 358.4 per million in the absence of such a program. The death rate was 4.28/million in countries with BCG programs compared to 40/million in countries without such a program. They Interpreted that countries with national program of whole population BCG vaccination appear to have a lower incidence and death rate from Covid-19. This may be due to the known immunological benefits of BCG vaccination. In the absence of a specific vaccination against Covid-19, population-based BCG vaccination may have a role in reducing the impact of this disease.

Furthermore, a study by Hensel et al.[10] also showed a lack of significance when comparing COVID-19 incidence in countries with a BCG vaccine policy and countries without a current BCG vaccine regimen. They concluded that the observation of incident differences could be connected to population density, age, incidence of TB, regional population, COVID-19 testing rates interlinked with BCG protocols causing confounding effects. While a study conducted by Gursel and Gursel[11] showed that COVID-19 case numbers in countries that have BCG vaccination programs were significantly less than those without a BCG vaccination program.

Hegarty et al.[9] and Mahase et al.[12] considered a link between national BCG vaccine protocols and mortality rates. They concluded

that nations with a population-wide BCG program appear to show a lower number of cases and deaths due to COVID-19 infection, possibly due to the confirmed immunological benefits of the vaccination. Shet et al.[13] also reported a pattern of COVID19-related mortality amidst BCG-employed nations that was 5.8 times lower (95% CI 1.8-19.0) compared to countries without a vaccination program.

In general, a vaccine will provide its protection from distinct pathogens by its effector mechanism. A live attenuated vaccine such as BCG, an attenuated strain of Mycobacterium bovis, provides protection to pathogens causing respiratory infections.[14] There is enduring evidence that this vaccine induces unspecified mortality protection, the most commonly administered vaccine worldwide, enticing approximately 38%-45% reduction in fatality rates.[15] Developed to combat TB, its mortality benefits stem from a reduction in neonatal sepsis and respiratory infections. The underlying mechanism for this defence caused by the BCG vaccination is thought to be mediated through the activation of innate immune memory, or trained immunity.[16] In a randomized placebo controlled human study conducted by Arts et al.[17], it was evident that BCG vaccine induces genetic reprogramming of monocytes and shown protection against few experimental viral infections with an underlying key role of interleukin-1 beta (IL-1) as a trained immune response.

CONCLUSION

From our study we conclude that BCG vaccination has a protective effect against severity of COVID-19 in childhood. The main limitation of study, there were not any unvaccinated covid-19 positive children admitted in hospital during study period. Furthermore, there was very small sample size and few severe cases in our study, so we do not clearly conclude.

REFERENCES

1) Ella KM, Mohan KV. Coronavirus vaccines: Light at the end of the tunnel. Indian Pediatrics. 2020 April.
2) World Health Organization. [Online].; 2020 [cited 2020 APRIL. Available from: https://www.who.int/news-room/commentaries/detail/bacille-calmette-gu% C3 % A 9 rin-(bcg)-vaccination-and-covid-19
3) Secretariat TSWGoBVaW. World Health Organization. [Online].; 2017 [cited 2020 APRIL Available from: https://www.who.int/immunization/sage/meetings/2017/ october/ 1,BCG_report_revised_version_online.pdf.
4) Moorlag SJCFM, Arts RJW, van Crevel R, Netea MG. Non-specific effects of BCG vaccine on viral infections. Clin Microbiol Infect. 2019 December; 25(12,:1473-1478. doi: 10.1016/j.cmi.2019.04.020. Epub 2019 May 2. PMID: 31055165.).
5) Arts RJW, Moorlag SJCFM, Novakovic B, Li Y, Wang SY, Oosting M, et al. BCG Vaccination Protects against Experimental Viral Infection in Humans through the Induction of Cytokines Associated with Trained Immunity. Cell Host & Microbe. 2018 january; (23, 89–100).
6) Usher NT, Chang S, Howard RS, Martinez A, Harrison LH, Santosham M, et al. Associationof BCG vaccination in childhood with subsequent cancer diagnoses: A 60-Year Follow-up ofa clinical trial. JAMA Network Open. 2019; 2(:e1912014).
7) Abbott S, Christensen H, Lalor MK, Zenner D, Campbell C, Ramsay ME, et al. Exploring theeffects of BCG vaccination in patients diagnosed with tuberculosis: Observational study usingthe Enhanced Tuberculosis Surveillance system. Vaccine. 2019; 37(:5067-72).
8) WHO: Bacille Calmette-Guérin (BCG) vaccination and COVID-19, Accessed: April 24, 2020:https://apps.who.int/iris/bitstream/handle/10665/331745/WHO-2019 ,CoV,Sci_BriefBCGvaccination-2020.1-eng.pdf
9) Paul K. Hegarty, Ashish Kamat, Helen Zafirakis, Andrew DiNardo; BCG vaccination may be protective against Covid-19, March 2020; DOI: 10.13140/RG.2.2.35948.10880
10) Hensel J, McAndrews JM, McGrail DJ, Dowlatshahi DP, LeBleu VS, Kalluri R: Exercising caution in correlating COVID-19 incidence and mortality rates with BCG vaccination policies due to variable rates of SARS CoV-2 testing. MedRxiv. 2020, 10. 1101/2020.04.08.20056051
11) Gursel M, Gursel I: WITHDRAWN: Is global BCG vaccination coverage relevant to the progression of SARS-CoV-2 pandemic? Med Hypotheses. 2020, 10.1016/j. mehy. 2020. 109707
12) Mahase E: Covid- 19: what treatments are being investigated? BMJ. 2020, 368:m1252. 10.1136/bmj.m1252.
13) Shet A, Ray D, Malavige N, Santosham M, Bar-Zeev N: Differential COVID-19-attributable mortality and BCG vaccine use in countries. MedRxiv. 2020, 10.1101/ 2020.04.01.20049478
14) Hollm-Delgado MG, Stuart EA, Black RE: Acute lower respiratory infection among Bacille CalmetteGuérin (BCG)-vaccinated children. Pediatrics. 2014, 133:e73-e81. https://doi.org/10.1542/peds.2013-2218
15) Garly ML, Martins CL, Balé C, et al.: BCG scar and positive tuberculin reaction associated with reduced child mortality in West Africa: a non-specific beneficial effect of BCG? Vaccine. 2003, 21:2782-2790. 10.1016/s0264-410x(03)00181-6.
16) Netea MG, Quintin J, van der Meer JW: Trained immunity: a memory for innate host defense. Cell Host Microbe. 2011, 9:355-361. 10.1016/j.chom.2011.04.006
17) Arts RJW, Moorlag SJCFM, Novakovic B, et al.: BCG vaccination protects against experimental viral infection in humans through the induction of cytokines associated with trained immunity. Cell Host Microbe. 2018, 23:89-100. 10.1016/j.chom.2017.12.010