Role of BCG and Measles vaccination in protection against COVID-19 infection and severity of the disease: A pilot case-control study

Alok Ranjan[1], Purushottam Kumar[2], Manisha Verma[3], Chandramani Singh[4], Sanjay Pandey[5], Bijaya Nanda Naik[6], Santosh Kumar Nirala[7], Rajath Rao[8]

[1]Assistant Professor, Department of Community and Family Medicine, AIIMS, Patna
[2]Senior Resident, Department of Community and Family Medicine, AIIMS, Patna
[3]Senior Resident, Department of Community and Family Medicine, AIIMS, Patna
[4]Professor & Head, Department of Community and Family Medicine, AIIMS, Patna
[5]Professor, Department of Community and Family Medicine, AIIMS, Patna
[6]Assistant Professor, Department of Community and Family Medicine, AIIMS, Patna
[7]Assistant Professor, Department of Community and Family Medicine, AIIMS, Patna
[8]Senior Resident, Department of Community and Family Medicine, AIIMS, Patna

ABSTRACT

Background: The role of BCG and MMR/Measles vaccination in reducing the burden of COVID-19 has been based on ecological data mostly. We planned this explorative pilot case-control study to understand the role of vaccination with Bacillus Calmette–Guerin (BCG) and measles administered as part of MMR vaccine on COVID 19.

Methodology: A case-control study was conducted in AIIMS Patna during December 2020 and January 2021. A total of 100 COVID-19 patients confirmed by RT-PCR test were taken as cases, and for each case, age and gender-matched SARS-COV-2 negative individual was taken as control. A study tool containing a pre-tested semi-structured questionnaire was used.

Results: The unadjusted odds of COVID-19 were found to be significantly higher among BCG vaccinated [1.88(1.03-4.4)] and MMR vaccinated individuals [5.06(2.34-10.90)]. BCG vaccine was not found to have an independent effect on COVID-19 after adjusting for tobacco use, MMR vaccination status, unprotected contact with SARS-COV-2 positive patients, and co-morbidities. But Measles vaccine was found to independently increase the risk of COVID-19 [AOR: 4.505(1.8-11.3)].

Conclusion: BCG vaccination status was not found to be an independent predictor of COVID-19. Further studies with large sample size and better study design (cohort, randomized trials) need to be conducted.

Keywords: BCG, Measles, Vaccination, COVID-19 protection

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a severe acute respiratory syndrome caused by Coronavirus 2 (SARS-CoV-2). As of 31 January 2021, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected 102,691,967 patients, with 2,222,403 deaths across 215 countries. By this date in India

SARS-CoV-2 has infected 10,746,174 patients, with 1,54,274 deaths. In the light of its rapid global spreading, on 11 March 2020, the World Health Organization has declared it a pandemic.[1]

The global spread of COVID-19 is not uniform as some countries are relatively less affected. The reason(s) for such anomalous behaviour is still not fully

understood but distinct hypotheses have been proposed.[2] Many studies hypothesize that the countries having BCG & MMR vaccination in their universal immunization program were less affected by COVID-19.[3] There is mounting evidence that live attenuated vaccines provide nonspecific protection against lethal infections unrelated to the target pathogen of the vaccine by inducing "trained" nonspecific innate immune cells for improved host responses against subsequent infections. Mortality in COVID-19 cases is strongly associated with progressive lung inflammation and eventual sepsis. Vaccination with MMR in immunocompetent individuals has no contraindications and may be especially effective for health care workers who can easily be exposed to COVID-19.[4] Epidemiological studies and randomized trials have shown that BCG vaccination reduces all-cause infant mortality by diminishing deaths due to infections other than tuberculosis. The observation that BCG vaccination could protect against viral infection was strengthened by a study in Guinea-Bissau showing that BCG reduced the incidence of respiratory syncytial virus infection.[5]

In contrast, Cecilia S et al believe that current mortality rates of the COVID-19 pandemic do not support a clear negative correlation with Bacillus Calmette–Guerin coverage and that there are alternative explanations for the differences observed between Western and Eastern Germany states. Ongoing randomized controlled trials will provide answers to whether Bacillus Calmette–Guerin reduces the incidence and severity of COVID-19 through its heterologous effects.[6]

All the published literature, so far, on the role of BCG and MMR vaccination in reducing the burden of COVID-19 has been based on ecological data. None of the studies has been carried out on individual-level information. Hence, the ecological fallacy could not be ruled out. In this background, we planned this explorative pilot case-control study to understand the role of vaccination with Bacillus Calmette–Guerin (BCG) and Measles on COVID 19 infectivity and severity.

OBJECTIVES

The present study was conducted to understand the role of vaccination with BCG and measles administered as part of MMR vaccine on COVID 19. The study also aimed to find out independent risk factors of COVID 19.

MATERIAL AND METHODS

Study design, duration, and ethics: This explorative pilot case-control study was carried out during December 2020 and January 2021. The ethical approval for this study has been obtained from Institute Ethics Committee, AIIMS, Patna.

Study setting: AIIMS, Patna is one of the Institute of National Importance and is providing dedicated health care during the COVID-19 pandemic. The study was conducted in the Flu clinic and OPD area of AIIMS Patna.

Study population: The study population included all the COVID-19 patients attending the Flu Clinic at AIIMS, Patna with positive documentation (RT-PCR or Rapid Antigen Test/RAT Positive) during the study period and satisfied the inclusion and exclusion criteria as cases. Controls were selected from the patients attending the OPDs with negative documentation of COVID.

Sampling population

Cases: COVID-19 patient with positive documentation who has attended the Flu Clinic, AIIMS, Patna.

Control: One age (±5years) and gender-matched control was identified among the patients attending the various OPDs. Control should have documented the negative report (RT-PCR or Rapid Antigen Test/RAT Negative) of COVID-19.

Sample size: Due to lack of prior literature on the association of BCG and COVID-19, 100 reported and documented COVID-19 patients at Flu clinic AIIMS, Patna were considered as cases. One control per case as per the operational definition cited above was selected.

Sampling technique: A total of 100 COVID-19 cases satisfying inclusion and exclusion criteria were selected purposively from the Flu Clinic. After obtaining written informed consent they were included in the study. One control per case was enrolled from the OPD area conveniently matching the age and gender satisfying inclusion and exclusion criteria.

Inclusion and exclusion criteria:

For Cases, we included the COVID-19 positive patients of age ≥18 years, attending the Flu clinic, AIIMS, Patna. We excluded the seriously ill patients not able to communicate. For controls we took documented COVID-19 negative person of age ≥18 years, attending the other OPD clinic at AIIMS, Patna. Seriously, ill patients not able to communicate were excluded.

Study tool The information was collected using a pre-tested semi-structured interview schedule. The study tool has three sections. The first section contains the general characteristics of the study participants. Section two has basic knowledge of the out prevention and control of COVID-19. Section three contains the information on BCG and Measles vaccination status. The BCG vaccination was ascertained by history and examining the presence of the BCG scar. The measles vaccination was ascertained by history.

Bio-statistical analysis: The information collected was entered in MS Excel and analysis was done using the SPSS version20. The categorical variables were

expressed as proportions and percentages. Multivariate binomial logistic regression was performed to ascertain the independent influence status of BCG and Measles vaccination. ODDs ratio was calculated to determine the risk of COVID-19 among non-vaccinated persons. The p-value of 0.05 was considered statistically significant.

RESULTS

Sociodemographic details of participants: The sociodemographic details of the participants are shown in Table 1. Males (70%) outnumbered females. The maximum number of participants aged more than 60 years.

Sociodemographic Predictors of COVID 19: The adjusted odds of COVID-19 was found to be significantly higher among individuals having higher educational qualification [5.736(1.8-18.2)]**,** un/semi-skilled worker**s** [0.336(0.139-0.816)] and Clerical/ semiprofessional/ professional individuals [0.355(-.140-0.9)]. The above-mentioned factors were found to have an independent effect on COVID-19 after adjusting for gender, age, and socioeconomic status, type of family, religion, and caste.

Behavioral details of participants: The behavioral details of participants are shown in Table 2. About 73% of cases and 59% controls were vaccinated with BCG**.** 10% of control and 36% of cases were vaccinated with MMR**.** Nearly 22% and 9% of cases and controls respectively had a history of unprotected contact with COVID-19 patients. About 76% of cases and 34% of controls suffered from various co-morbidities.

Behavioral Predictors of COVID 19: The unadjusted odds of COVID-19 were found to be significantly higher among BCG vaccinated [1.88(1.03-4.4)] and MMR vaccinated individuals [5.06(2.34-10.90]. However, the BCG vaccine was not found to have an independent effect on COVID-19 after adjusting for tobacco use, MMR vaccination status unprotected contact with SARS-COV-2 positive patients, and co-morbidities. But Measles vaccine was found to independently increase the risk of COVID-19 [AOR: 4.505(1.8-11.3)].

Co-morbidity Profile of Participants: Out of 200 participants, 110 suffered from various co-morbidities such as Diabetes Mellitus, Hypertension, Cardiovascular Diseases, etc. as shown in the pie chart.

Table 1: Socio-demographic predictors of COVID 19 (N= 100)

Variable	Cases (%)	Controls (%)	Unadjusted OR with 95% CI	Adjusted OR with 95% CI
Gender				
Male	70	71	0.95(0.5-1.7)	
Female	30	29	1	
Age				
18-30 years	19	14	1	
31-60 years	38	47	0.59(0.26-1.34)	
>60 years	43	39	0.812(0.36-1.83)	
Education*				
Illiterate	11	17	1	1
Up to class 10	21	55	0.5(0.2-1.46)	0.883(0.32-2.4)
>class 10	68	28	3.75(1.5-9.02)	5.736(1.8-18.2)**
Occupation*				
Unemployed	35	29	1	1
Un/semi-skilled worker	17	37	0.38(0.17-0.811)	0.336(0.139-0.816)**
Clerical/semiprofessional/professional	48	34	1.17(0.6-2.26)	0.355(-.140-0.9)**
Socioeconomic *status				
Upper	40	20	4.66(1.08-19.997)	3.07(0.561-16.82)
Middle	57	73	1.82(0.4-7.3)	1.77(0.3-7.95)
Lower	3	7	1	1
Type of family*				
Nuclear	41	51	0.668(0.382-1.1168)	0.524(0.265-1.039)
Joint	59	49	1	1
Religion				
Hindu	90	96	1	
Muslim	6	3	2.13(0.5-8.7)	
Sikh	1	0	0	
Christian	3	1	3.2(0.3-31.32)	
Caste				
General	55	47	1	
OBC	41	33	1.062(0.582-1.937)	
SC	4	11	0.31(0.09-1.04)	
ST	0	9	0	

*Variables considered for Multivariable Binominal logistic regression;
**P-value is <0.05 and is statistically significant

Table 2: Behavioural predictors of COVID 19 (N=100)

Variable	Cases (%)	Controls (%)	Unadjusted OR with 95% CI	Adjusted OR with 95% CI
Tobacco use*				
Yes	21	29	0.651(0.3-1.24)	0.784(0.369-1.666)
No	79	71	1	1
BCG vaccination status*				
Vaccinated	73	59	1.879(1.03-3.405)**	1.446(0.696-3.004)
Not vaccinated	27	41	1	1
MMR vaccination status*				
Vaccinated	36	10	5.062(2.343-10.938)**	4.505(1.793-11.317)**
Not vaccinated	64	90	1	1
Travel history				
Yes	11	11	1(0.4-2.4)	
No	89	89	1	
Unprotected contact with COVID positive patients*				
Present	22	9	2.889(1.256-6.644)**	2.091(0.803-5.447)
Absent	77	91	1	1
Co morbidities*				
Present	76	34	6.147(3.314-11.403)**	6.576(3.333-12.974)**
Absent	24	66	1	1

*Variables considered for Multivariable Binominal logistic regression
**P-value is <0.05 and is statistically significant

Figure 1: Symptoms in COVID 19 Cases (N=100)
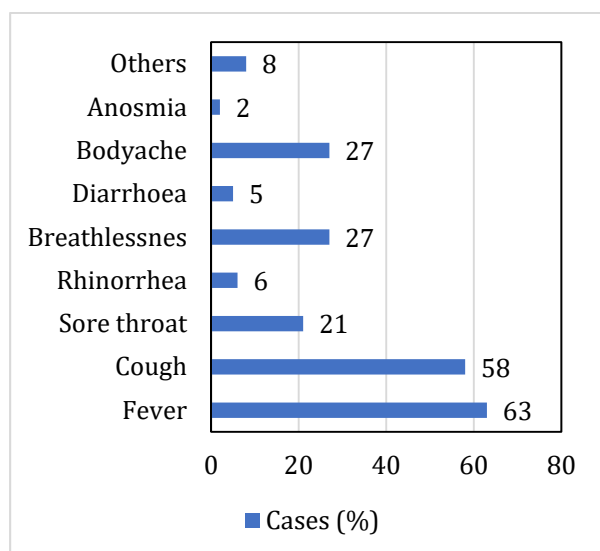
Duration of hospital stay, symptoms, and severity of cases: The majority of cases (62%) were hospitalized for less than 5 days. 68% of cases were categorized as asymptomatic and mild cases and 32% were categorized as moderate and severe cases. This grading was done based on saturation and oxygen requirement at the time of admission.

Majority of cases in our study presented with fever (63%) followed by cough (58%) as shown in figure 1.

DISCUSSION

The role of BCG and MMR vaccination in reducing the burden of COVID-19 has been based on ecological data mostly. Hence, the ecological fallacy could not be ruled out. We planned this explorative pilot case-control study to understand the role of vaccination with Bacillus Calmette–Guerin (BCG) and measles administered as part of MMR vaccine on COVID 19. A case-control study was conducted in AIIMS Patna during December 2020 and January 2021. The objectives of our study were to understand the role of vaccination with BCG and measles administered as part of MMR vaccine on COVID 19 and to find out independent risk factors of COVID 19. A total of 100 COVID-19 patients confirmed by RT-PCR test were taken as cases, and for each case, age and gender-matched SARS-COV-2 negative individuals were taken as control. A study tool containing a pre-tested semi-structured questionnaire was used to collect information on socio-demographic characteristics, knowledge about prevention and control of COVID-19, and vaccination status of BCG & Measles.

In this study, we found that about 59% of controls and 73% cases were BCG vaccinated. 10% of controls and 36% of cases were MMR vaccinated. The unadjusted odds of COVID-19 were found to be significantly higher among BCG vaccinated [1.88(1.03-4.4)] and MMR vaccinated individuals [5.06(2.34-10.90)]. About 22% and 9% of cases and controls respectively had a history of unprotected contact with COVID-19 patients. However, the BCG vaccine was not found to have an independent effect on COVID-19 after adjusting for tobacco use, MMR vaccination status unprotected contact with SARS-COV-2 positive patients, and co-morbidities. But Measles vaccine was found to independently increase the risk of COVID-19 [AOR: 4.505 (1.8-11.3)].

BCG Vaccine: Potential Protection against COVID-19?

Many articles published in recent years suggest that Childhood BCG vaccination may be protective for COVID 19 severity. Paul K et al, in their study report that out of 178 countries; current national programs

of BCG vaccination exist in 131 countries; 21 countries have no current program of national BCG vaccination, and for 26 countries status is unknown. They interpret that countries with the 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 and is being studied in a prospective trial.[7–14]

In our study, we found that about 59% of controls and 73% cases were BCG vaccinated (Table 2). The unadjusted odds of COVID-19 were found to be significantly higher among BCG-vaccinated individuals [1.88(1.03-4.4)]. Nearly 22% and 9% of cases and controls respectively had a history of unprotected contact with COVID-19 patients. However, the BCG vaccine was not found to have an independent effect on COVID-19 after adjusting for tobacco use, MMR vaccination status, unprotected contact with SARS-COV-2 positive patients, and co-morbidities (Table 2).

Our study results are in accordance with many researches including World Health Organization where they strongly deny the claim that BCG vaccination is protective against COVID 19 infection. Such ecological studies are prone to significant bias from many confounders, including differences in national demographics and disease burden, testing rates for COVID-19 virus infections, and the stage of the pandemic in each country.[15]

Could MMR / Measles Vaccine Serve as a Preventive Measure To Dampen Severity Associated with COVID-19 Infection?

Paul L et al propose the concept that administration of an unrelated live attenuated vaccine, such as MMR (measles, mumps, rubella), could serve as a preventive measure against the worst sequel of corona virus disease 2019 (COVID-19). There is mounting evidence that live attenuated vaccines provide nonspecific protection against lethal infections unrelated to the target pathogen of the vaccine by inducing "trained" nonspecific innate immune cells for improved host responses against subsequent infections. Mortality in COVID-19 cases is strongly associated with progressive lung inflammation and eventual sepsis. Vaccination with MMR in immunocompetent individuals has no contraindications and may be especially effective for health care workers who can easily be exposed to COVID-19. Following the lead of other countries conducting clinical trials with the live attenuated Mycobacterium bovis BCG (BCG) vaccine under a similar concept, a clinical trial with MMR in high-risk populations may provide a "low-risk–high-reward" preventive measure in saving lives during this unprecedented COVID-19 pandemic.[14]

Desiree E. Larenas-Linnemann reported his clinical observations in 255 subjects, vaccinated in their Centre since the start of the Corona virus disease-2019 (COVID-19) pandemic, with the mumps-measles-rubella (MMR) vaccine and of who thirty-six have presented COVID- 19, all with a remarkably mild course. Among the 255 vaccinated subjects, there are 24 confirmed and 12 (highly) probable COVID-19 cases, thirteen of them with hypertension, diabetes, obesity, smoker, or uncontrolled asthma as possible risk factors. With the presented cases he supported that MMR vaccination, as a preventive measure, might reduce the severity of COVID-19, although he differs in his view on the mechanisms by which he hypothesizes this happens.[16]

In contrast to the above findings, in our study, we found that about 10% of controls and 36% of cases were Measles vaccinated. The unadjusted odds of COVID-19 were found to be significantly higher among Measles vaccinated individuals [5.06(2.34-10.90]. Nearly 22% and 9 % of cases and controls respectively had a history of unprotected contact with COVID-19 patients. The measles vaccine was found to independently increase the risk of COVID-19 [AOR: 4.505(1.8-11.3)]. As the Measles vaccine started late in Bihar in 1990 under the Universal Immunization Programme and coverage of the Measles vaccine is also very low. As the coverage of the Measles vaccine is very low so it is very difficult to comment about its effect on COVID 19.

CONCLUSION

BCG vaccination status was not found to be an independent predictor of COVID-19 in our study. Due to low coverage, the role of measles vaccine was difficult to conclude, further research with more sample size required. We also recommend further studies with better study design (cohort, randomized trials) to substantiate the effect of BCG and Measles vaccine on COVID-19. Till then COVID-19 appropriate behaviour has to be followed by all to prevent the spread of SARS-COV-2 infection.

Conflicts of Interest Statement: None

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