RESEARCH PAPER

Vaccination With Routine Childhood Vaccines and Severity of COVID-19 Among Children in Delhi

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Objective: To study the association between routine childhood vaccination and the severity of COVID-19 among children. **Methods:** A cross-sectional study was undertaken among 141 children (aged ≤15 years), tested positive for SARS-CoV-2 infection. **Results:** COVID-19 severity (combined moderate and severe) was significantly more in males (14.5%) than females (3.8%), and in those who did not receive first and second dose of MR vaccine (57.1%, and 40%, respectively) than who received (6.3%, and 6.1%, respectively). Disease severity was more in partially immunized children (16.7%) as compared to fully immunized children (7.0%). **Conclusions:** Children who did not receive both doses of MR vaccine had a severe infection when compared to those who were vaccinated.

Keywords: *Measles vaccine, SARS-CoV-2 infections*.

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SARS-CoV-2 infection among children manifests with mild to moderate disease [1]. The reasons why children have relatively low severity of COVID-19 remains unclear. Low infection rate and mild form of the disease in children are expected to be due to childhood vaccinations [2]. Measles containing vaccine has been suggested to reduce incidence of SARS-CoV-2 infection in children [3]. Measles-mumps-rubella (MMR) vaccine may provide strong protection from COVID-19 spread and mortality [4,5]. BCG vaccination may lessen the severity of COVID-19 among children [6]. This study was conducted to examine the association between routine childhood vaccinations and the severity of COVID-19.

METHODS

This observational study was conducted over six months among children of age group up to 15 years who tested positive for SARS-CoV-2 by rapid antigen test (RAT) or reverse transcriptase-polymerase chain reaction test (RT-PCR) in Central district, Delhi. Considering the prevalence of COVID-19 disease among children to be 2%, with a 95% confidence interval and with a permissible error of 2% (absolute), a minimum of 188 participants were required [7]. The final sample size was calculated to be 210 taking a non-response rate of 10%.

Out of 903 children up to 15 years with COVID-19, 210 were selected by simple computer generated random sampling. Auxiliary nurse midwives (ANMs) providing immunization services to the children were identified by the District Immunization Officer (DIO) and they were asked to provide data related to immunization and demographic characteristics of the study subjects on a semi-structured questionnaire. ANMs visited the concerned children and interviewed the mother or caregiver after obtaining informed written consent, and verbal assent where applicable. Among them, 141 (67.1%) completed responses were included in the final analysis. Children, who received one dose of BCG, three doses of OPV, three doses of Rotavirus, three doses of (Penta/DPT/HepB), two doses of fractional IPV, and one dose of MR vaccine, before completion of age of 1 year, were considered as fully immunized.

Data related to disease severity was obtained from the CDMO office, Central District, New Delhi. The disease status of the individual patients was maintained at the office of CDMO office and classified as per the guidelines of Government of India [8].

Statistical analysis: The analysis of data was done by SPSS Statistics for Windows, version 25 (IBM Corp.). Chi-square test and Fisher exact test were used for inferential purpose. A P value <0.05 was taken as statistically significant.

RESULT

Of the 141 children with SARS-COV-2 infection, 100 (70.9%) were symptomatic, with mild, moderate and severe disease in 88 (62.4%), 9 (6.4%) and 3 (2.1%), respectively. Among

those with moderate and severe disease, there was significantly higher proportion of boys (14.5%) ($P<0.01$). Age, religion, type of family, and socioeconomic status (SES) were comparable (**Table I**).

Among the participants, 114 (80.8%) were fully immunized, 24 (17.1%) partially immunized and 3 (2.1%) children were not immunized at all. Symptomatic infection was more in the case of partially immunized children as compared to the fully immunized children (75% vs 69.7%; $P=0.60$). In partially immunized children, combined moderate and severe disease was more (16.7%) as compared to fully immunized children (7.0%) ($P=0.26$). Among the recipients of the measles/MR (measles and rubella) vaccine (first dose as well as second dose), disease severity was significantly less as compared to those who did not receive [6.3% vs 57.1%; $P=0.001$] for first dose, and [6.1% vs 40%; $P=0.005$] for second dose. However, no such association was observed with other vaccines (**Web Table I**). The odds of having combined moderate and severe disease was 19.6 times higher (for the first dose) [OR (95% CI) 19.6 (3.74-103.4); $P=0.001$] and 10.2 times higher (for the second dose) [OR (95%CI) 10.2 (2.34-45.1); $P=0.01$] among those who did not receive measles/MR vaccine as compared to the recipient of the vaccine.

DISCUSSION

We found COVID-19 severity (moderate and severe) more among boys and those who did not receive measles/MR vaccine. A plausible explanation for the gender difference could be based on their immunological responses to foreign and self-antigens, and differences in innate and adaptive immune responses [9], or differences in their immunization status.

More symptomatic infections and higher disease severity in partially immunized might be due to the cross-reactivity of the components of the childhood vaccination to the SARS-CoV-2 virus. Contrary to this, in a mouse model, Kandeil, et al. [10], reported that none of the childhood vaccines provided antibodies capable of neutralizing SARS-CoV-2 up to seven weeks after vaccination. The low infection rate and mild form of disease presentations in children >1 year of age have been reported previously also, and suggested to be due to childhood vaccinations [2]. Salman, et al. [11] suggested that children were spared by COVID-19 disease owing to the low immunity in childhood that does not exaggerate the immune response against the virus as in an adult. In the present study, the severity of disease was significantly less in the recipients of the MR vaccine. This might be due to the cross-reactivity of measles or rubella components of the vaccine with the SARS-CoV-2 virus and the development of neutralizing antibodies towards the SARS-CoV-2 virus. MMR vaccine may provide strong protection from COVID-19 spread and mortality [4,5]. A significant negative correlation was observed between mumps virus titre and severity of COVID-19 disease [4]. More directly, there is also evidence that the rubella virus has a 29% sequence homology with a SARS-CoV-2 surface protein. Accordingly, the rubella component of the MMR vaccine may confer specific protection against COVID-19 [5,12].

MMR had previously been used to induce bystander immunity against other virus strains e.g., warts caused by human papillomavirus could be ameliorated using an intralesional MMR vaccine [11]. Sidiq, et al. [12] found that 30 amino acid residues homology between the Spike (S) glycoprotein of the SARS-CoV-2 virus including Fusion (F1) glycoprotein of measles virus (residues R389 to K419) as well as with the envelope (E1) glycoprotein of the rubella virus (residues A444 to K473). Thus, they believed that humoral immunity created through the MMR vaccination provides children with advantageous protection against COVID-19 as well. A recent case-control study in Sweden [14], on MMR vaccination in health care workers (adults) and COVID-19 did not support a substantial protective effect of the MMR vaccine in the whole study population. However, they concluded that there may be a protective effect of the MMR vaccine against SARS-CoV-2 in males but not in females [14]. Several researchers have reported that BCG vaccination may also lessen the severity of SARS-CoV-2 infection [6]. However, in the current study, such association could not be observed.

In conclusion, those who received the measles/MR

Table I Sociodemographic Profile of the Participants ($N=141$)

Characteristics	*Disease outcome* (*COVID-19*)		
	Asymptomatic	*Mild*	*Moderate and severe*
Males[a]	11 (17.7)	42 (67.8)	9 (14.5)
Hindu religion	35 (33.1)	61 (57.5)	10 (9.4)
Joint family	18 (27.7)	42 (64.6)	5 (7.7)
Age group (COVID-19)			
3-60 mo	15 (30.6)	29 (59.2)	5 (10.2)
6-10 y	8 (18.6)	33 (76.7)	2 (4.7)
11-15 y	18 (36.7)	26 (53.1)	5 (10.2)
Socioeconomic status[b,c]			
Class I	25 (32.5)	46 (59.7)	6 (7.8)
Class II	11 (20.4)	37 (68.5)	6 (11.1)
Class III	5 (50.0)	5 (50.0)	0

Values in no. (%). [a]P<0.01. [b]As per modified BG Prasad classification [15]. [c]None of the participants belonged to Class IV and V.

WHAT THIS STUDY ADDS?

- Children who did not receive measles/MR vaccine had a severe form of COVID-19 disease as compared to those who were vaccinated.

vaccine had a less severe form of COVID-19 disease as compared to those who were not vaccinated. Though this study is limited by small sample size, and non-estimation of antibody titters to corroborate the findings, this study suggests that the COVID-19 disease manifests in a less severe form among the recipient of measles/MR vaccine.

Ethics clearance: Institutional ethics committee, Maulana Azad Medical College, New Delhi; No. F.1/IEC/MAMC/80/08/2020/ No-246 dated October 01, 2020.

Contributors: MMM: data interpretation, data analysis, manuscript preparation; ALB: manuscript review, manuscript editing and definition of intellectual content; PL: concept, design, definition of intellectual content and manuscript review; MM: collection and assembling of data; KVR: facilitation of data collection and availability of data. All authors approved the final version of manuscript and are accountable for all aspects related to the study.

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Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

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Web Table I Disease Outcome and Vaccination Status of Study Participants (*N*=141)

Received vaccine	*Disease Outcome* (*COVID-19*)		
	Asymptomatic	*Mild*	*Moderate & Severe*
BCG (n=137)	41 (29.9)	84 (61.3)	12 (8.8)
OPV-0 (n=120)	37 (30.8)	74 (61.7)	09 (7.5)
HepB (n=106)	30 (28.3)	68 (64.2)	08 (7.5)
OPV-1 (n=137)	41 (29.9)	84 (61.3)	12 (8.8)
OPV-2 (n=135)	41 (30.4)	82 (60.7)	12 (8.9)
OPV- 3 (n=133)	40 (30.1)	81 (60.9)	12 (9.0)
f-IPV-1 (n=34)	10 (29.4)	22 (64.7)	02 (5.9)
f-IPV-2 (n=30)	09 (30.0)	19 (63.3)	02 (6.7)
ROTA-1 (n=32)	10 (31.2)	20 (62.5)	02 (6.3)
ROTA-2 (n=30)	10 (33.3)	18 (60.0)	02 (6.7)
ROTA-3 (n=29)	09 (31.0)	18 (62.1)	02 (6.9)
DPT-1 (n=70)	22 (31.4)	42 (60.0)	06 (8.6)
DPT-2 (n=69)	22 (31.9)	41 (59.4)	06 (8.7)
DPT-3 (n=66)	21 (31.8)	39 (59.1)	06 (9.1)
HepB-1 (n=70)	21 (30.0)	43 (61.4)	06 (8.6)
HepB-2 (n=69)	21 (30.4)	42 (60.9)	06 (8.7)
HepB-3 (n=64)	20 (31.2)	40 (62.5)	04 (6.3)
PENTA-1 (n=69)	19 (29.7)	39 (60.9)	06 (9.4)
PENTA-2 (n=63)	19 (30.2)	38 (60.3)	06 (9.5)
PENTA-3 (n=62)	18 (29.0)	38 (61.3)	06 (9.7)
Measles/MR-1 (n=126)[a]	38 (30.2)	80 (63.5)	08 (6.3)
Measles/MR-2 (n=115)[a]	34 (29.6)	74 (64.3)	07 (6.1)
OPV-Booster (n=118)	36 (30.5)	73 (61.9)	09 (7.6)
DPT-Booster-1 (n=109)	35 (32.1)	66 (60.6)	08 (7.3)
DPT-Booster-2 (n=77)	25 (32.5)	46 (59.7)	06 (7.8)
TT-1st dose (n=21)	07 (33.3)	10 (47.6)	04 (19.1)

Values in no. (%), [a]P<0.01, BCG- Bacillus Calmette Guerin, OPV- Oral polio vaccine, HepB-Hepatitis B vaccine, f-IPV- Fractional inactivated polio vaccine, ROTA- Rotavirus vaccine, DPT- Diphtheria pertussis tetanus, PENTA- Pentavalent vaccine, MR-Measles Rubella vaccine, TT-Tetanus toxoid vaccine.