RESEARCH PAPER

Mumps Antibody Titer in MMR-Vaccinated and Vaccine Naïve Children at a Public Hospital in Delhi

Bhoomika Saxena,[1] VG Ramachandran,[1]Rumpa Saha[1] and Dheeraj Shah[2]

From Department of [1]Microbiology and [2]Pediatrics, University College of Medical Sciences and Guru TegBahadur Hospital, Delhi, India.

Correspondence to:
Dr Bhoomika Saxena,
105, Gaytri Nilaya, 12th B Main Road,
6th Block, Rajajinagar,
Bengaluru 560 010, Karnataka, India.
bhoomika286@gmail.com
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Objective: To compare the mumps antibody titers in Measles-Mumps-Rubella (MMR)-vaccinated and vaccine naive children. **Methods**: This cross-sectional study was conducted at a tertiary-care public hospital in Delhi from November, 2016 to April, 2018 among 78 healthy children (aged 16 month-12 years) attending the pediatric outpatient department. Serum IgG and IgM rubella antibodies were measured by ELISA for confirmation of MMR vaccination status. Qualitative determination of IgG mumps was done followed by quantitative determination in samples positive for IgG mumps antibodies. **Results:** IgG mumps was present in 69.2% of study population, with seroprotective titers in 32% taking endpoint titer as 1:4. Among MMR vaccinated children, 41.1% were sero-protected and in MMR vaccine naïve children 9.1% were seroprotected for mumps. **Conclusion:** Single dose of MMR vaccine does not provide effective (>90%) sero-conversion required for successful herd immunity to prevent mumps outbreak.

Keywords: *Immunization, Measles, Rubella, Seroprotection.*

Mumps is a vaccine preventable viral respiratory illness mainly in pediatric age group. Epididymo-orchitis is the most common complication and meningo-encephalitis is most common cause of mortality in mumps [1]. Sporadic outbreaks of mumps are reported from India and other countries indicating resurgence of disease in both vaccinated and unvaccinated population. Outbreaks in vaccinated young adults indicate waning of immunity with time. Outbreaks in India have been reported from various states [2-5].Integrated Disease Surveillance Programme data shows 475, 124, 92 and 447 cases from year 2015-18 [6].

In India, MMR vaccine is a part of State immunization program of Delhi, Goa, Puducherry and Sikkim, adminis-tered as a single dose at 15-18 months [7]. National Technical Advisory Group on Immunization in June 2014, in view of India's commitment to eliminate Measles by 2020, recommended Measles-Rubella (MR) vaccine in National immunization program (NIP).

The Indian Academy of Pediatrics, on the other hand, recommended continuation of MMR vaccine in India as mumps is still an important vaccine preventable disease [8]. Considering the paucity of data regarding seroprotectiveness in children against mumps, this study aims at comparing level of mumps specific antibodies in MMR vaccinated and vaccine naive healthy children.

METHODS

This cross-sectional study was conducted at the departments of Microbiology and Pediatrics, University College of Medical Sciences and Guru Teg Bahadur Hospital from November, 2016 to April, 2018. Inclusion criterion was healthy children aged 16 months to 12 years attending hospital as outpatients. Children with chronic infection and acute febrile illness were excluded. The study was approved by the institutional ethics committee. Informed and written consent was obtained from parents/ guardians of participating subjects, and assent obtained from children above seven years of age. Confidentiality was ensured by coding questionnaire and samples before data entry and analysis.

Blood samples were collected from healthy children attending pediatric OPD for routine checkup. Forty of the participants have received MMR vaccine and 38 were unvaccinated with MMR vaccine. The participant's details and history was noted in a case record form, which included age, MMR vaccination status, number of doses of MMR received, demographic details, past history of clinical mumps, history of exposure to any clinical mumps case in the past, maternal rubella history and antenatal history of mother. Vaccination history was

documented on basis the of immunization card. Data on history of rubella could not be collected as it was not recalled accurately by the family member.

All blood samples were centrifuged at 3000 RPM for 15 min and serum was extracted and stored at -20°C for further use. The samples were first subjected to IgG rubella ELISA test (Calbiotech Inc.) to confirm MMR vaccination status. To rule out any chance of recent vaccination, IgG rubella negative samples were also tested for IgM rubella (Calbiotech Inc). Samples were then subjected to IgG mumps ELISA test (Immunolab). The tests were performed and interpreted as per manufacturer's instructions. Due to resource constraints, only samples showing high optical density (2.0-3.5) were subjected to quantitative IgG Mumps ELISA for antibody titer calculation by standard reference graph plot method. Eleven samples were serially diluted from 1:5 to 1:40 and 15 samples were diluted from 1:2 to 1:8. End point titer was noted for each sample by extrapolation from standard graph obtained and antibody level was calculated for the undiluted and diluted samples showing optical density above cut off value as per kit instructions. Samples with OD in the grey zone were considered negative for statistical evaluation.

Statistical analyses: Data of subjects were categorized into two groups viz. MMR vaccinated and MMR-unvaccinated. Only children who tested positive for either IgG or IgM Rubella were considered as MMR vaccinated. Based on previous studies that correlated results of MuV PRNT and ELISA, end point titer of ≥4 was considered as sero-protective for mumps [9]. Chi-square test was used to find out *P* value between vaccination status and IgG Mumps antibody presence. Fischer's exact test was used to compare significance between vaccination status and sero-protective antibody titer. *P* value less than 0.05 was considered as significant.

RESULTS

Fifty-six of total 78 samples i.e., 71.7% (95% CI: 0.61, 0.81) were positive for IgG rubella and were designated as MMR vaccinated. Mean (SD) age of vaccinated children was 6.7 (3) years. Eighteen of the 78 samples were negative for IgG rubella, and four samples gave indeterminate results and were considered as negative test result. Mean age of unvaccinated children was 5.6 (2.6) years. None of the sample tested positive for IgM rubella.

Fifty four of total 78 samples [69.2% (95% CI: 0.58-0.78%)] were positive for IgG mumps antibody. Among MMR-vaccinated children, 45 (80.3%) had concurrent antibodies against both mumps and rubella. The mean age of these children was 6.8 (3) years. End point titre of ≥4, indicating sero-protection against mumps was seen in 41.1 % (95% CI: 0.29, 0.58), children, with mean (SD) age of was 7.3 (2.9) years. Nine samples showed qualitative presence of IgG mumps antibody even in the absence of IgG rubella Ab; only two had seroprotective levels. Correlation between IgG mumps antibody presence and seroprotection was insignicant (*P*=0.46).

DISCUSSION

In this study, 32.5% of total study population (41.1% of vaccinated and 9.1% of unvaccinated children) were found to be seroprotected for mumps. Low rate of seroprotection among MMR vaccinated children can be attributed to failure of development of immunity with a single dose of vaccine or failure of vaccine uptake. Rate of subclinical infection and atypical presentation in mumps are known to be very high. In a country like India, diagnosis is mainly clinical and laboratory confirmation is not routinely requested. Thus, seroconversion may arise as a result of clinical or subclinical infection as well as successful vaccination regardless of laboratory confirmation of the etiology.Sudden shift in age group of mumps affection from 5-9 years to 19-20 years made the Advisory Committee on Immunisation Practices (ACIP) to include a second dose of mumps vaccine at the age of 4 to 6 years [10]. Some of the countries are considering an adult third dose at 15-19 years of age as recent outbreaks are in this age group [11].

Host factors like immunological dysfunction, chronic diseases impacting the immune system, though rare are significant causes of vaccine failure. It may be pointed out that, of the 18 subjects who were seronegative for rubella, some could be due to primary or secondary vaccine failure. Moreover, indeterminate IgG rubella results for four subjects could be a consequence of waning IgG levels over time to levels below the threshold of the detection system.

There were limitations to our study including a small sample size whose results cannot be generalized to the entire population. Date of vaccination and time of blood sampling post vaccination could not be recorded for all participants as most of the participants did not carry vaccination card with them. MMR vaccination confirmation was done only by the presence of IgG or IgM Rubella estimation. Lastly, end point serial dilution was not done for all the samples seropositive for IgG mumps antibodies. Antigen used in ELISA was whole cell virus and not HN protein, which is the target against for neutralizing antibody production [12]. Thus, the antibodies detected in our study may not necessarily confer protection even with high end point dilution titers.

WHAT THIS STUDY ADDS?

- A large proportion of single dose recipients of MMR vaccine do not develop seroprotective titers against mumps.

Further, apparently seroprotective levels of mumps antibodies may also possibly arise due to antigenic cross-reactivity among paramyxoviruses.

Results of this study matches with previous reports that a single dose is not sufficient to prevent clinical mumps and natural immunity in Indian children is not sufficient to offer protection upon exposure [13]. In view of these results, decision of GOI and NTAGI on replacing MMR with MR vaccine may require reconsideration. Removing Mumps vaccine from states with <70% of MMR vaccine coverage can lead to potential outbreaks in future. Additionally poor efficacy in vaccinated indivi-duals causes a rightward shift in epidemiology, resulting in affliction of older age group children and young adults. This phenomenon changes the epidemiology and also increases clinical severity of disease.

Blanket withdrawal of mumps component of MMR should not be a decision without a strong backup of long term epidemiological data. In a developing country like ours, with complex urban-rural divide and a varied spectrum of economic and social status with very variable healthcare access in different regions, a one-time decision to withdraw a vaccine can at best be an interim measure, which should be accompanied by regular sentinel surveillance of the status of protection of potentially vulnerable population.

Ethics clearance: Institutional Ethics Committee, UCMS; No. IEC-HR/130/18.10.2016 dated November 25, 2016.
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