IJPSR (2019), Volume 10, Issue 4 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 07 August 2018; received in revised form, 13 October 2018; accepted, 23 October 2018; published 01 April 2019

PREVALENCE OF MEASLES VIRUS INFECTION AMONG VACCINATED AND NON-VACCINATED CHILDREN IN NORTHERN INDIA

Ankita Pandey [1, 2], Nidhi Tejan [1], Rambha Tripathi [1], Rachna Chaturvedi [* 2] and Tapan N. Dhole [1]

Department of Microbiology [1], Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow - 226014, Uttar Pradesh, India.
Amity Institute of Biotechnology [2], Amity University, Lucknow - 226028, Uttar Pradesh, India.

Keywords:

Measles, Maculopapular rash, Vaccination, MMR, ELISA, IgM antibody

Correspondence to Author:
Dr. Rachna Chaturvedi

Assistant Professor,
Department of Biotechnology,
Amity Institute of Biotechnology,
Amity University, Lucknow - 226028,
Uttar Pradesh, India.

E-mail: rchaturvedi1@lko.amity.edu

ABSTRACT: Introduction: Measles virus (MeV) is still a common acute illness caused by viruses belonging to the family Paramyxoviridae and genus *Morbillivirus*. The objective of this study was to determine the prevalence of MeV in both vaccinated and unvaccinated children and consecutively, testing the efficacy of MeV vaccination among children in north India. **Materials and Methods:** A total of 323 blood samples were collected along with measles mumps rubella (MMR) vaccination history from children (0-15 years) manifesting fever and rashes. In serum samples, we employed the enzyme-linked immunosorbent assay (ELISA) to quantify the presence of IgM antibodies against measles virus infection. **Results:** Out of 323 serum samples 148 (45.8%) were found to be positive for MeV infections. Expectedly, In the vaccinated group we found the prevalence of MeV is 70 (47.3%), while in unvaccinated children occurrence of MeV infection is 78 (52.7%), showing a statistical significance between vaccination history and measles infection (P<0.0001*). In this study, 0-5 years old children have 93 (62.8%) MeV infection conversely, >5 years old age of children have 55 (37.2%) MeV infection. **Conclusion:** The children, who have not achieved the MMR vaccine for the elimination of MeV infection and we found 47.3% of children are still being infected with MeV that have MMR vaccination history. Therefore, there is a need to identify the reason for the low protective efficacy of the vaccine as well as long-term follow-up studies are needed for getting insight to longevity and persistence of immunity induced by this vaccine.

INTRODUCTION: Measles is an acute, highly contagious human disease caused by a Measles virus (MeV); it belongs to the family of Paramyxovirus and genus *Morbillivirus* [1]. These are enveloped, single-stranded and negative-sense RNA viruses; its genome size is 100-200 nm in diameter, and two membrane envelope proteins are important in pathogenesis [2, 3].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.10(4).1953-58

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.10(4).1953-58

Up to now, at least MeV has identified eight groups (A-H) and subdivided into 24 genotypes (A, B1-B3, C1 and C2, D1-D11, E, F, G1-G3, and H1–H2) [4, 5, 6]. MeV infection is commonly transmitted by aerosolized secretions deposited on upper respiratory tract mucosal surfaces [7]. Although large proportions of the MeV disease cases are self-limiting still mortality rates are higher.

The symptom of disease includes high-grade fever, conjunctivitis, coryza, cough and maculopapular rashes in the body. Despite global vaccination programs, it was observed that at least 2 million children still die every year because of treatable vaccine infections. Among these, measles, rubella

and mumps are the most common viral infections which attribute significantly to the global mortality and morbidity in the population of India [8, 9]. The Indian government has launched an immunization programme from the past 50 years which includes free vaccination for children against measles, rubella and mumps infection.

This MMR vaccine has live-attenuated Edmonston-Zagreb strain which is present in lyophilized form and stored at 4 °C after dilution. Under this programme, the first dose of MMR vaccine was recommended for the children at 9 months of age while the second dose is given to the children at 15 months of age and both doses given to the children up to 5 years of age if any child missed the 1st and 2nd dose [10, 11]. Before the introduction of the MMR vaccine in the 1960s, it was reported that mortality among children was around 7-135 million while in lower economic countries it was much higher. But after the introduction of the MMR vaccine, there is a substantial decrease in the mortality rate worldwide and accounts for 78% drop in measles cases globally between 2000 and 2012.

In India, a substantial decrease in measles cases was reported from 1987 to 2007 (the number of cases falls from 252,000 cases to 36,900. [12, 13, 14] By 1996, it was observed that 87% decline in measles case; however, in the urban slums effective control of measles infection was hampered due to low vaccination coverage. Despite this success, still, measles disease is a global threat. In 2005, measles virus infection reported causing 92,000 deaths in India which were predominant in children below 5 years old. In the WHO SEAR, the mortality observed globally due to measles was 77% in the year 2008 and the number of cases was found in India against this infection [15, 16].

In 2012, 122,000 deaths were found from MeV infection alone, the majority of these being from developing countries, mainly Africa and Southeast Asia. On the other side, a significant change has been observed in mortality and morbidity rate in the population of those regions where the vaccination step is improved while in some region death rate still higher in children due to the failure to deliver of even one dose of MMR vaccine. During outbreaks, there have been so many reports in the southern and northern parts of India on the frequency and incidence of measles infection [12, 17]. Thus, it was clear from the data discussed above that there is variability in the implementation of measles mortality reduction across the states. However, there is limited information on the vaccination status and level of severity of measles infection in the country. To get insight into the level of severity of measles infection in the country, we investigated the prevalence of measles infection among vaccinated and unvaccinated children. Our study also aims to find vaccine effectiveness in infected children who have already received vaccination and the result obtained from of this study will provide a platform to initiate appropriate measures against measles virus infection and to reduce morbidity and mortality in North Indian children.

MATERIALS AND METHODS:

Study Design and Study Population: In this study children presenting with fever, Maculopapular rash, conjunctivitis, and cough were selected. Immuno-compromised children were excluded from the study. Total 323 children aged 0-15 years were recruited for this study comes in general hospital of Sanjay Gandhi Postgraduate Institute of Medical Sciences.

Sample Collection: 2 ml blood sample were collected from each child by syringe into the sterile and labeled plain vial. Vaccination history and other information of children regarding symptoms were obtained from their parents using questionnaires.

Laboratory Analysis by ELISA: A single set of blood samples collected from the suspected cases and serum was separated by centrifugation at 3000 rpm for 10 min and finally stored in 2 ml cryovials tube at -20 °C until processing. The serum was then tested for anti-MeV-IgM antibody using enzyme-linked immunosorbent assay test kit (Siemens, Germany) according to the manufacturer's instructions. Positive and negative control from the kit used in each ELISA plate. The optical density of the wells was read by an ELISA reader (Finstruments, Multiskan Model, Lab systems Finland, Type-347) at 450/620 nm having positive and negative control reading also. Results were calculated according to the manufacturer's instructions.

Statistical Analysis: The data obtained from the children's parent were grouped and tabulated. Graph Pad Prism 5 statistical software used for data analysis and group comparisons were performed using the chi-square test, and the level of statistical significance was set at P values < 0.05.

Ethics Statement: Ethical approval for the use of blood specimens was granted by the Ethics Committee of Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, IEC code-2018-76-PhD-103 and written informed consents were obtained from all patients.

RESULTS: A total of 323 blood samples were collected from 0-15 years children, in which 178 males and 145 females were present. The children age ranged from 0-15 years and divided into two groups, 0-5 years and >5 years. Out of 323, 193 (59.8%) children had vaccinated, whereas 130 (40.2%) children had not vaccinated and the history of Measles Mumps Rubella (MMR) vaccination obtained from their parents. Out of the total screened 323 samples, 148 (45.8%) subjects were positive for Measles IgM antibodies. Among the positive cases, 89 (60.1%) were male, and 59 (39.9%) were female, and male/female (M/F) ratio was 1.51:1. There was no significant difference in the prevalence of measles virus among male and female children (P>0.25) shown in **Table 1**. Children between 0-5 years old represented the highest positive rate of measles antibodies 93 (62.8%), whereas >5 years old children had represented 55 (37.2%) infection, which is statistically non significant association in age group and measles virus infection (P>0.46), which is depicted in **Table 1** and **Fig. 1**.

TABLE.1: DEMOGRAPHICAL CHARACTERISTICS IN FEVER RASH LIKE ILL CHILDREN POSITIVE FOR MEASLES VIRUS INFECTION

Characteristics of fever-rash ill children	Fever–rash ill children with Measles virus infection N=148	Fever–rash ill children without Measles virus infection N=175	P-value
Gender			
Male	89 (60.1%)	89 (50.9%)	0.25
Female	59 (39.9%)	86 (49.1%)	
Age group in year			
0-5 years	93 (62.8%)	98 (56.0%)	
>5 years	55 (37.2%)	77 (44.0%)	0.46

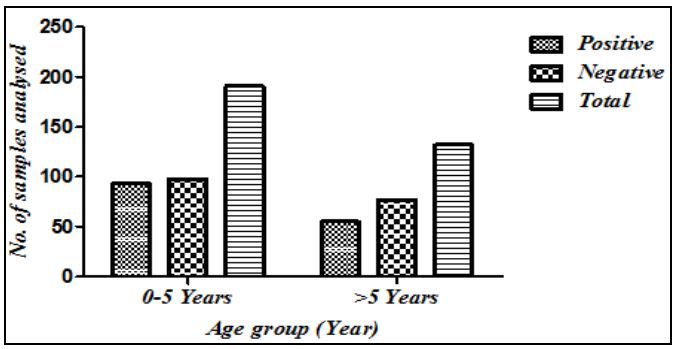

FIG. 1: AGE-WISE DISTRIBUTION OF MEASLES VIRUS INFECTION

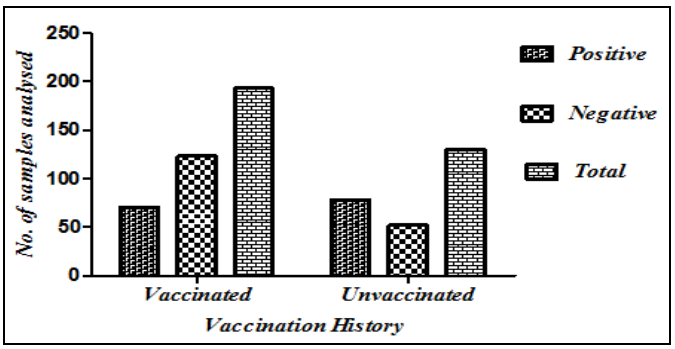

FIG. 2: THE PREVALENCE OF MEASLES VIRUS INFECTION AMONG VACCINATED AND UNVACCINATED CHILDREN

TABLE 2: COMPARISON OF VACCINATED AND UNVACCINATED CHILDREN FOR MEASLES VIRUS INFECTION AMONG FEVER RASH LIKE ILL CHILDREN

Children suffered from fever rash-like illness	Measles virus positive N=148	Measles virus negative N=175	P-value
Vaccinated children	70 (47.3%)	123 (70.3%)	<0.0001*
Unvaccinated children	78 (52.7%)	52 (29.7%)	

Out of 193 vaccinated children, the prevalence of measles infection is 70 (47.3%) even as in 130 unvaccinated children, the frequency of measles infection is 78 (52.7%) having a statically significance between vaccination history and measles infection (P<0.0001*) showed in **Table 2** and **Fig. 2**. The occurrence of measles infection more in 0-5 years old children and less in >5 years

old children. Also, vaccinated children who were tested positive for measles virus infections had a grave matter compared with unvaccinated children.

DISCUSSION: In this study, we investigated measles infection among vaccinated and unvaccinated children presenting with fever, maculopapular rash, conjunctivitis and cough in North Indian children using a measles-specific IgM detection ELISA test kit. As recommended by the WHO, detection of measles IgM remains the gold standard for diagnosing of measles virus [18].

In India, measles is known as Captain of the killer team. Even though the incidence of measles cases have reduced, it continues to occur both sporadically and as outbreaks. Scientific evidence strongly suggests that measles is preventable with vaccination. We observed the high incidence of measles infection in children. The probable reasons for this are two folds. Firstly, the reduced MMR vaccine efficacy and secondly logistic limitations in the vaccination programme. Measles infection positivity in MMR vaccinated children demonstrates the high burden of the disease in North India [19, 20, 21, 22].

Dengue virus, parvovirus B19, and herpes virus 6 also cause rash infections which should be investigated because they cause much serious complication in children. Many children had not vaccinated may be due to poor economic status, illiteracy, etc. and other workers also found similar findings. Measles infection which occurs in vaccinated children may be due to vaccine failure whether primary or secondary vaccine failure and the reason of vaccine failure due to cold-chain maintenance systems, insufficient viral dose, and presence of other diseases such as malaria [18, 23, 24, 25, 26]. Hence, further studies will be required on the interactions between other disease treatment and MMR vaccination in the population. The occurrence of measles virus infection were 148 (45.8%), out of 323 screened samples recorded in this study from north India, and the results are supported by the previous study from that the burden of the disease in the country Belarus and Nigeria, is still very high [20, 21, 27, 28]. Gender distribution was statistically non-significant (P> 0.25) although a higher percentage of males were infected compared to females, so male/female (M/F) ratio was 1.51:1, and like other studies this difference was not statistically significant. The frequency of measles infection in children decreased as the age increases and also in other studies it was found that measles infection mostly affects children less than 5 years of age. Due to the endemic nature of measles virus children younger than 5 years of age have the high chance of being exposed while children older than 5 years of age, lifelong immunity would have been conferred [9, 19, 29, 30, 31, 32, 33, 34, 35].

In this study, some children younger than 9 months old also found to be infected which is the age for MMR vaccination, and this may be due to the early warning of maternal antibodies. When the comparison occurs between vaccination status and measles infection, it was observed that unvaccinated children had more infection. Previous studies showed that MMR vaccination might not prevent the progression of symptoms with wild type measles virus, but might protects children of endemic areas from severe measles virus infection, therefore reducing the measles-related mortality rate. In India, many studies reported that after vaccination low protective antibodies found in the target population while these reports may not give true information about immune memory and readiness after re-infection. There is a need to consider the protective roles of cell-mediated immune response and other antibodies against measles infection at the time of vaccine efficacy measuring where other infections are likely to be present [36, 37, 38, 39, 40, 41]. Attack rates of measles infection by vaccination status and age among vaccinated and unvaccinated children have been recognized to vaccine failure.

CONCLUSION: The results of this study indicate that the burden of measles infection is still high among vaccinated and unvaccinated children in North Indian population. This study familiar with age, gender and vaccination history of children shows the demographic risk factors for Measles Virus (MeV) infection in children. The findings of this study confirm the high prevalence of MeV in 0-5 years old children in north India comparable with the occurrence of MeV obtained in other parts of India. MeV positivity 62.8% obtained in 0-5 years old children as compare to positivity rate of MeV in >5 years old children was 37.2%, which

indicates that measles is endemic in north India and still poses a public health problem, despite the availability of an effective and safe vaccine.

Therefore, there is need to identify the reason for the low protective efficacy of vaccine as well as long-term follow-up studies are needed for getting insight to longevity and persistence of immunity induced by this vaccine and also essential to review the vaccination age of infants and intensify vaccination campaign programs.

Therefore, the development of a sustainable framework for achieving high vaccination coverage among children younger than 5 years of age in the country is therefore recommended.

ACKNOWLEDGEMENT: We thank the Parents for giving us the permission and consent to collect the samples from children's and also acknowledge the help of V. K. Misra (Senior technician) and Hemant Verma in the laboratory work.

CONFLICT OF INTEREST: The authors declare that there is no conflict of interest regarding the publication of this paper

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How to cite this article:
Pandey A, Tejan N, Tripathi R, Chaturvedi R and Dhole TN: Prevalence of measles virus infection among vaccinated and non-vaccinated children in Northern India. Int J Pharm Sci & Res 2019; 10(4): 1953-58. doi: 10.13040/IJPSR.0975-8232.10(4).1953-58.