

# Impact of Measles Vaccination on the Acquisition and Frequency of Measles Infection in Province of Sindh

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## Abstract

**Objective:** To determine the status of vaccination among confirmed measles cases and to determine the association of vaccination status with the occurrence of measles infection.

**Methods:** A cross-sectional survey was carried out in the province of Sindh from January 2016 to April 2016. The study included patients of both gender,  $\geq 9$  months of age, fulfilling the case definition of measles by World Health Organization (WHO), who were reported to and/or picked by the measles surveillance officers. A sample of 3-5 ml of blood was collected from each registered patient between day 4 and day 28 of the rash to test for measles IgM antibodies. The samples were labelled and sent to National Measles Laboratory, National Institute of Health (NIH) Islamabad in reverse cold chain. Patients who tested positive for IgM antibodies were grouped as confirmed measles while patients negative for measles IgM antibodies were grouped as suspected measles. Data of both the groups was analysed using windows SPSS 21 for vaccination status, for frequency of measles infection against the number of doses of measles vaccine received. Frequencies of vaccination among confirmed measles cases were compared with suspected measles for statistical significance using Chi-square. P-value of  $<0.05$  was taken as significant.

**Results:** A total of 572 out of 915 study subjects were confirmed measles cases, of which 258 (45%) were never vaccinated against the disease as compared to 72 (12.6%) who were completely vaccinated. Overall, 128 (37.3%) were fully vaccinated amongst suspected measles. Vaccination status was not known in a quarter of patients in both groups. A significant association was found between the vaccination status and measles infection with higher frequency of measles in unvaccinated as compared to the vaccinated ( $p < 0.001$ ).

**Conclusion:** We conclude that the vaccination rate among measles patients was significantly lower than among non-measles patients. A sizable 12.6% got the disease in spite of completing measles vaccination.

**Keywords:** Measles, immunization, children, vaccine, MMR vaccine.

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## Introduction

Measles is the most infectious disease known, affecting 30 million people annually and is associated with an infectivity rate of almost 100%<sup>1,2,3</sup>. It not only causes a lot of morbidity but is respon-

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sible for 50-60% of the 1.6 million deaths occurring globally each year caused by vaccine preventable diseases of childhood. Approximately 66% of these deaths occur in under-privileged countries including Pakistan in spite of the accessibility to an effective vaccine<sup>3,4</sup>. The case fatality rate of measles may stretch up to 10% in regions afflicted with prevalent malnutrition and dearth of sufficient health facilities<sup>4</sup>. In the absence of any specific treatment measles vaccine remains the only option to protect our children against this potentially fatal disease. The importance of vaccination is proven by the in-

interruption of endemic transmission of measles in many countries having a high vaccine coverage with consequent drop of 79% in measles deaths between 2000 and 2014<sup>1,4,5</sup>. The situation in Pakistan during those years was unfortunately contrary to these countries. With reporting of 5969 lab confirmed cases in 2013 as compared to the 2676 confirmed cases in 2012 Pakistan stood out as the highest measles reporting country in the Eastern Mediterranean region<sup>6,7</sup>. This raises the question if the measles vaccine is being administered at the wrong time or not at all or is ineffective due to some factors which need to be explored<sup>8</sup>. In Pakistan, measles vaccine used to be given as a single dose at nine months of age<sup>9</sup> but later, on recommendation by World Health Organisation (WHO) and United Nations International Children's Emergency Fund (UNICEF), a booster dose at 15 months was introduced in Expanded Program on Immunization (EPI) in 2009<sup>10,11</sup>. Regarding the age of vaccination, analysis of four months unpublished records of a single paediatric unit of Civil Hospital Karachi showed that 20 out of 100 children infected with measles were below the age of first inoculation against measles. The official estimate of measles vaccine coverage in Pakistan revealed a disappointing coverage of 80% and 53% in 2012 with the 1<sup>st</sup> and 2<sup>nd</sup> dose, respectively, while it was reported 63% in 2014<sup>12</sup>. These two factors are strong enough to explain the high surge in the measles cases contrary to the rapid decline witnessed by the rest of the world. But at the same time a study conducted in Karachi, during a measles epidemic, showed that 78% of the children had received at least a single dose of measles vaccine. However, the measles antibodies, which indicate immunity against measles, were found in only 55% of the children<sup>8</sup>. It was observed during the last few years that an increasing number of patients who were getting infected with measles had already received vaccine against measles. We decided to determine the frequency of measles cases that were already immunised against the disease. We also determined the relationship between the number of doses of measles vaccine received and the fre-

quency of infection and then will further analyse the data to determine an association between the numbers of doses of measles vaccine received with probability of acquiring measles infection by comparing the vaccination status in confirmed measles cases with that of suspected measles. Once shown that a substantial number of patients are getting infected with measles in spite of being immunised against the disease, we will move to carry out large scale, multicentre study at a national level to assess the factors responsible for the probable vaccine failure and take steps to remove or modify those factors on urgent basis. This will go a long way in decreasing a very high economic loss, morbidity and, above all, mortality associated with the disease.

## **Methods**

A cross-sectional survey was carried out in the province of Sindh over a period of four months from January 2016 to April 2016. Sample size of 317 cases was calculated using the formula  $n=(Z^2P(1P))/e^2$  for average measles prevalence of 71%, with margin of error 5%, on 95% confidence intervals. Although the minimum sample size required was 317, we increased the size to 915 to cover up for the probable drop outs during the survey and to increase the reliability of results. The study included all patients of both gender,  $\geq 9$  months of age, fulfilling the case definition of measles suggested by WHO and who were reported to and/or were picked by the measles surveillance officers. Suspected measles case was defined as 'any person with generalised maculopapular rash and fever plus one of the following: cough or coryza (runny nose) or conjunctivitis (red eyes)' or 'any person in whom a clinician suspects measles'. Cases where information such as age, vaccination status or epidemiology number (EPID number) was missing were excluded from the study.

This survey was carried out as a part of measles case-based surveillance and outbreak investigation EPI, province of Sindh. The surveillance officers regularly visited or were called at the health

facilities including all major tertiary care hospitals of the province to identify and register all the patients of suspected measles. Data was recorded on standard, predesigned pro forma including age, gender, vaccination status, address and reporting institute. Vaccination status was determined by vaccination cards if available or by verbal information from the parents. The data was then transferred to the line list of the EPI Sindh on regular basis. A sample of 3-5 ml of blood was collected in sterile syringe from each registered patient between day 4 and day 28 of the onset of rash to test for measles IgM antibodies as a confirmation of the diagnosis of measles. The samples were then labelled, allotted an EPID number and sent via EPI offices to National Measles Laboratory, NIH Islamabad in reverse cold chain with the maintenance of temperature between 2-8°C. Patients who tested positive for IgM antibodies in their blood were grouped as confirmed measles cases while patients whose blood specimens turned out to be negative for measles IgM antibodies were grouped as suspected measles. Since the age of first inoculation against measles in our country is nine months, to comply with our objective, data of the subjects  $\geq 9$  months of age in both the groups was analysed using windows SPSS version 21 for their vaccination status in order to determine the frequency of patients who developed measles when they were unvaccinated, partially vaccinated or completely vaccinated. Further analysis was done to determine the frequency of measles infection against the number of doses of measles vaccine received. Finally the analysis was done to determine the association of measles vaccination with the occurrence of measles infection by comparing the vaccination status of the confirmed measles cases with that of suspected measles. Statistical significance was checked by using Chi-square. P-value of  $< 0.05$  was taken as significant.

Other results including gender, IgM serology and status of vaccination were described in frequencies and percentages.

## **Results**

Case records of 1033 patients were analysed. Out of these 915 fulfilled our criteria of being  $\geq 9$  months of age. 464 out of these were males amounting to 51% while the rest of the 49% were females. Serum IgM antibodies against measles came out positive in 572 (62.51%) out of the 915 and thus were confirmed as measles cases. Fig.1 is showing the analysis of the study subjects as a flow chart. Analysis of vaccination status of these 572 measles IgM positive cases showed decreasing frequency of measles infection with increasing number of doses of measles vaccine. A total of 258 (45%) of the patients who had measles were those who had never been vaccinated against the disease as compared to 72 (12.6%) who had received both the doses of vaccine (Table 1). There is a large group of 146 (25.5%) whose vaccination status was not known. Vaccination status of  $\geq 9$  months old with measles IgM negative showed that 128 (37.3%) did not get measles were fully vaccinated against the disease while 96 (28%) were never vaccinated (Table 1). In this group also there were 70 ( $> 20\%$ ) whose vaccination status was not known. A significant association was found between the vaccination status and the occurrence of measles infection with higher frequency of measles detected in unvaccinated subjects as compared to the vaccinated ( $p < 0.001$ ) (Table 2).

## **Discussion**

In our study, we could assess the immunisation status in about 76% of all the patients who were initially recruited as measles. This frequency is comparable to or even better than those of several other countries including the well-developed ones. Studies from Ontario/Canada and Malaysia were able to gauge the immunisation status of their measles patients in 70%<sup>13</sup> and 69%<sup>14</sup>, respectively. The rate of the evaluation of the immunisation status was even lower in Mozambique and California/USA ranging from 29%-43%<sup>15</sup>. The highest numbers of vaccination records available for 95% of the cases were reported from

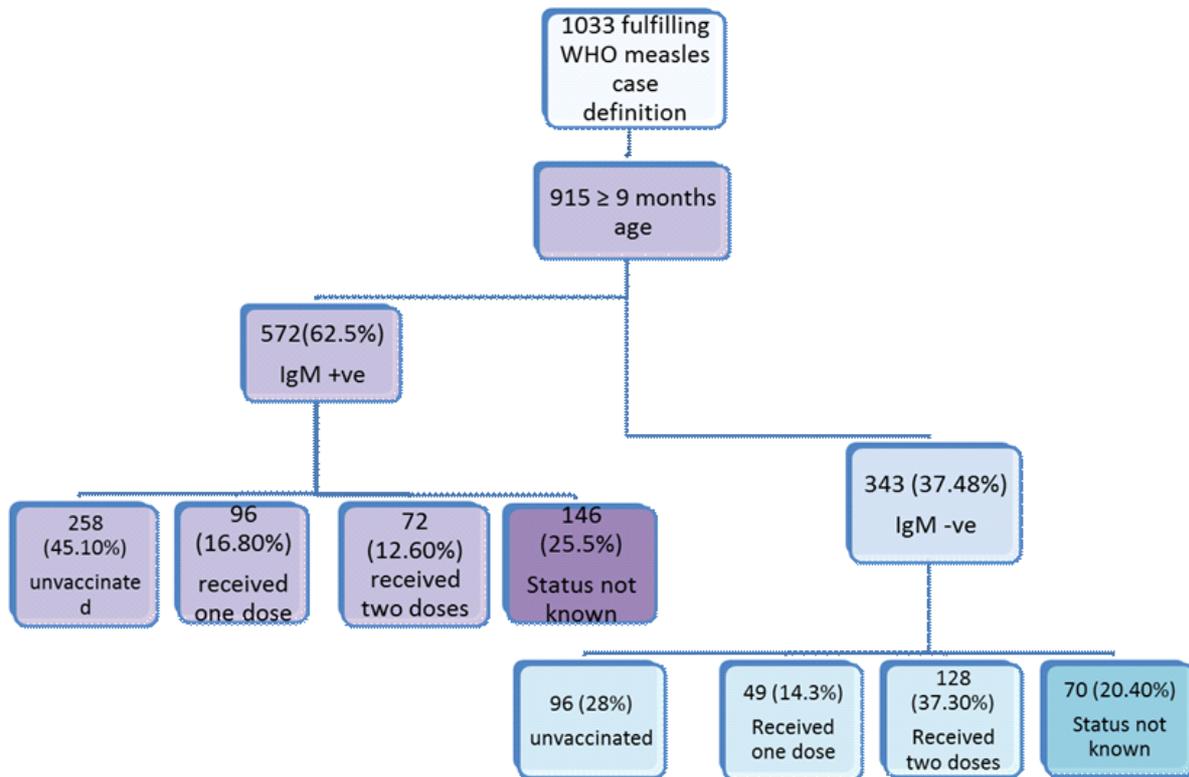
**Table 1.** Vaccination status among  $\geq 9$  months of age with confirmed and suspected measles (n= 915)

No. of doses of vaccine received	Children with measles IgM positive, n (%)	Children with measles IgM negative, n (%)
Two doses	72 (12.60)	128 (37.30)
One dose	96 (16.80)	49 (14.30)
None	258 (45.10)	96 (28.00)
Status not known	146 (25.50)	70 (20.40)
Total	572 (100)	343 (100)

**Table 2.** Association of vaccination status with frequency of measles infection (n= 699)

Vaccination status	Number of patients	Measles (IgM) positive, n (%)	Measles (IgM) negative, n (%)	p-value
vaccinated	345	168 (48.7)	177 (51.3)	<0.001*
Non vaccinated	354	258 (72.9)	96 (27.1)	
Total	699	426 (60.94)	273 (39.05)	

Chi-square test used for association



**Fig. 1.** Flow chart showing the analysis of study subjects

European Union (EU) & European Economic Area (EEA) countries<sup>16</sup>. This availability of the records reflects on the health awareness and education of the parents and the efficacy of their health and immunisation departments. The frequency of the records available in our series is unexpectedly high though it may not represent the true rate as a lot of patients may not have reported to the surveillance officers. Analysis of the vaccination status of confirmed measles cases in our study revealed that

45% were never vaccinated against measles. The frequency of unvaccinated among measles is similarly and globally high varying from 45%-83% as reported from California, Canada<sup>13</sup>, Mozambique<sup>15</sup> and EU/EEA countries<sup>16</sup>. USA reported that 63 out of 64 reported measles cases in one analysis were unimmunised. On the other hand in Malaysia 31.29% were not vaccinated<sup>14</sup>. This high frequency of unvaccinated in measles suggest a protective role of measles vaccine against the disease. To

confirm this positive correlation between the absences of vaccination with higher frequency of measles infection we compared the frequency of measles cases among unvaccinated with the frequency of measles among those who have received one or two doses of the vaccine and it turned out that increasing number of doses was associated with decreased frequency of measles infection. That is only 12.6% of the children who had received both doses of measles vaccines were affected by the disease as against 45% among those who received nil doses. One important fact that came up in this study is that an overall 30% of the cases got the measles even though they had received at least one dose of the vaccine against the disease. This included a little over 12% of patients who had received both the doses of the vaccine. These results of measles infection in the vaccinated population are again comparable to the reported frequency range of 9%-30% from other regions including Canada<sup>13</sup>, California, EU/EEA countries<sup>16</sup> and Malaysia<sup>14</sup>, This is inclusive of 1.8%-15% who had had their complete series of inoculation against measles. The proportion of unvaccinated cases was high among all age groups<sup>16</sup>. Pennsylvania and Virginia reported measles infection during an outbreak in 2009 in two physicians both of whom have been fully vaccinated against the disease<sup>17</sup>. This occurrence of measles infection in the vaccinated individuals rang the alarm bells about the efficacy of the vaccine and provides enough grounds to explore the reason for such phenomenon. Some of the studies done so far in this regard has shown reduced formation of IgG antibodies in response to measles vaccination in under developed countries including Pakistan where the seroconversion was reported in only 73.8% of the children vaccinated against the disease<sup>18</sup>. One positive observation made during the infection of the two American physicians was the absence of spread of the infection to others thus suggesting a very low infectivity potential as compared to fully symptomatic individuals<sup>17</sup>. While we need to check into the causes of measles infection in immunised individuals before it is too late, the more significant food for thought and

action is a high number of children remaining unvaccinated. The answer may lie within the domain of EPI including quality assurance of the information and surveillance system, accuracy of demographic data used by the program to calculate vaccination targets and vaccine coverage. In addition, it may also be affected by the availability of human resources, will, equipment and the political and professional commitment by the concerned personnel. It is extremely unfortunate that the province of Sindh which contributes most to the measles incidence and mortality is also a home to one of the most corrupt health departments as has been declared by the Transparency International<sup>19</sup>. The study is limited by the fact that this data does not include the patients who preferred private treatment or to remain at home. Furthermore, lack of knowledge of the vaccination status in almost quarter of the patients may result in false interpretation of the results although it can be presumed that absence of knowledge means no vaccination. We recommend that a strategy be devised and followed to increase the routine vaccine coverage to >95%. We also recommend that efforts be made to maintain the vaccination records of all children. There is a dire need to not only determine the factors responsible for the poor vaccine coverage and records but find a solution to the problems on urgent basis. Above all there is a need to educate the public regarding the importance and safety of vaccination via all means including media, mosques and school health services. Last, but not the least, we recommend large scale studies to determine the factors associated with measles infection in those already immunised against the disease.

### **Conclusion**

We conclude that there is a significant association between the vaccination against measles and acquisition of measles infection with higher frequency of measles occurring in unvaccinated as compared to the vaccinated. There is a sizable 12.6% who got the disease in spite of receiving both the doses of measles vaccine. In approximately quarter of the patients, vaccination status was not known.

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## Conflict of Interest

Authors have no conflict of interests and no grant/funding from any organisation for this study.

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