

## RISK FACTORS ASSOCIATED WITH MEASLES PNEUMONIA

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### ABSTRACT

**Objective:** To identify risk factors that will predict the occurrence of measles pneumonia among children with measles.

**Method.** This study utilized a retrospective cohort design. The study population consisted of all the measles patients admitted at the National Children's Hospital from June 1, 1998 to June 30, 2000. Patients who developed pneumonia during their hospital stay were considered as cases while those who did not develop pneumonia served as controls. Absence of the outcome of interest ( pneumonia ) was ascertained by reviewing the admitting history. All subjects' medical records were reviewed for the presence of the following variables: age, sex, immunization status, nutritional status, and the presence of previous infection. The chi square t-test were used to determine association for the nominal and continuous variables respectively. All tests used to analyze the data were two-tailed with level of significance set at 0.05. Logistic regression was done to determine the simultaneous effects of the factors. All variables with a p value a p value of less than 0.05 were considered significant.

**Results.** There were 425 patients admitted for measles during the stated period. Of this total, 77% (329) developed pneumonia while the remaining 33% (96) did not. The proportion of males and females who had measles pneumonia did not differ significantly (  $p = 0.363$  ). The mean age of children who had measles pneumonia was significantly lower compared to those who just had measles only. The distribution of measles pneumonia patients between the age groups differed significantly (  $p < 0.001$  ) Majority of the subjects who were in the lower age groups had pneumonia . Wasting and stunting were both more common in those children who had pneumonia compared to those who only had measles. There was no significant difference in the frequency of measles pneumonia between the groups with previous infection against that which had none. The proportion of children not given measles vaccine at 9 months of age and developed measles pneumonia was higher than those given the vaccine. All five variables were then included in the logistic regression modeling. The procedure showed that only age, wasting, and stunting were associated with an increased risk for measles pneumonia.

**Conclusion:** Young age, wasting, and stunting are factors that predict the occurrence of pneumonia among children with measles.

### INTRODUCTION

Measles causes more than a million deaths a year, of which most are children under five years of age who die of pneumonia<sup>1,2</sup>.

In a retrospective study done by Castillo, reviewed the medical records of 126 patients who died of measles at the National Children's Hospital. He found out that the highest number of death belongs to the 9-12 months age groups and the most common complication seen was pneumonia<sup>3</sup>.

There were studies done in the past to determine factors or conditions that may be associated with mortality or the development of complications among patients with measles. One such study was done in Red Cross War Memorial Children's Hospital, Cape Town, from 1976-1982. In this study they reviewed the records for factors associated with fatal cases of measles. They found out that pneumonia, supervening infections (both viral and bacterial), peripheral lymphopenia, and severe malnutrition were almost always present among those who died measles but were less commonly found among the survivors<sup>4</sup>. In another retrospective study done at the Department of Pediatrics, De La Salle University Medical Center in Dasmarias, Cavite, Philippines, young age (under 2 years) and stay in the service ward (as opposed to the private ward) were significantly related to complicated measles. Malnutrition and the presence of other associated illness were not significantly related to measles complication. The study concluded that malnutrition possibly contributed less to severity of the disease than environmental factors such as hygiene and social class. More severe complications were seen at an early age than in industrialized countries where frequency appears to increase with age<sup>5</sup>.

Measles pneumonia is a life-threatening complication in children infected with the measles virus<sup>6</sup>. The increased number of reported cases over last several years<sup>3</sup> suggests a need for heightened awareness of the factors leading to its development. This study was done to identify risk factors that would be predictive of the development of pneumonia among measles patients. When such factors are identified, then greater care can be given to those patients possessing the risk factors. Fatal consequences could then be anticipated and managed effectively. Moreover, a more improved

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system of prophylactic measures can be designed and can be implemented with more zeal for those patients with risk factors for measles pneumonia.

## OBJECTIVES

### GENERAL OBJECTIVE

To determine factors that will predict the occurrence of measles pneumonia among children with measles.

### SPECIFIC OBJECTIVES

1. To describe the clinico-epidemiologic profile of the measles patients admitted at the National Children's Hospital from June 1, 1998 to June 30, 2000.
2. To compare the age, sex, immunization status, nutritional status (wasting and stunting), and history of previous infection of patients that developed measles pneumonia to those who did not develop pneumonia.
3. To identify factors associated with measles pneumonia.

### DEFINITION OF TERMS

1. Measles – was diagnosed clinically when the following clinical manifestations are noted: (1) acute febrile illness with temperature ranging from 38.3°C or more [ $> = 101$ °F]; (2) cough, coryza, conjunctivitis, an erythematous maculopapular rash, and/or a pathognomonic enanthem [Koplik's spots]<sup>4</sup>
2. Measles pneumonia- measles with persistence of fever after the 4<sup>th</sup> day of the exanthem<sup>11</sup>, coarse and/or fine crackles akin to the picture of bronchiolitis<sup>11</sup> and respiratory distress usually in the expiratory phase.
3. Nutritional status – assessment of the degree of malnutrition was based on the revised Waterlowe classification.
4. Previous infection – infection which occurred within six months from the onset of measles.

### METHODOLOGY

#### Patient population and study design.

This study utilized a retrospective cohort design. The study population consisted of all the measles patients (who did not have pneumonia on admission) admitted to the National Children's Hospital from June 1, 1998 to June 30, 2001. Patients who developed pneumonia during the hospital stay were considered as cases while those who did not develop pneumonia were controls.

Review of the monthly discharge summary of the records section of the National Children's Hospital revealed 425 patients were admitted for uncomplicated measles from June 1, 1998 to June 30, 2000. Absence of the outcome of interest (pneumonia) was ascertained by reviewing the admitting history. Only patients who did not reveal auscultatory findings, fine crepitant rales, on admission were included in the study. Three hundred twenty nine (329) patients developed pneumonia during the hospital stay while 96 patients did not develop pneumonia.

The following variables were obtained from the review of the hospital records: age, sex, immunization status, nutritional status, and the presence of previous infection. To assure the accuracy of the data collected, the medical records were reviewed and data collected by the main investigator. The data obtained was then verified by a senior pediatric resident of the hospital.

### STATISTICAL ANALYSIS

#### Descriptive analysis

Data was encoded using excel and was analyzed using SPSS version 10 and EPI info 6.0. The chi square test and independent t-test were used to determine association for the nominal and continuous variables respectively. All test used to analyze the were two-tailed with 0.5 level of significance.

#### Logistic regression

To determine the simultaneous effects of the factors, logistic regression was done. Backward logistic regression modeling was performed. All variables with a p value of less than 0.05 were considered significant.

### RESULTS

This study shows that majority of the four hundred and twenty five (425) measles cases seen from June 1, 1998 to June 30, 2000 at the National Children's Hospital were less than 24 months of age (70%), with malnutrition (wasting 52%, stunting 26%), and without history of previous infection (96%). There were slightly more males (52%) than females (48%). Very few of the population had measles immunization. Only 18% had measles vaccine at 9 months, 1.6% had MMR at 15 months, and 0.2% had MMR at 4-6 years old. Seventy seven (77) percent of the admitted patients eventually had pneumonia.

The proportion of males and females who had measles pneumonia did not differ significantly ( $p=0.363$ ) from those who did not have measles. The mean age

of children who had measles pneumonia (7-12 months) was significantly lower compared to those who just had measles only. The distribution of measles pneumonia patients between the age groups differed significantly ( $p < 0.001$ ). Majority of the subjects who were in the younger age group (less than 24 months old) had pneumonia.

Mild to severe wasting was more common in those children who had pneumonia compared to those who only had measles. Among children with wasting 57% had measles pneumonia while 32% had uncomplicated measles. Stunting was significantly higher in the measles pneumonia group (31%) compared to the nine percent (9%) of the measles group ( $< 0.001$ ).

There was also significant difference in the frequency of measles pneumonia between the groups that were positive for previous infection against those who had none.

**Table 1. General characteristics of participating patients**

Variables	Measles Pneumonia N = 329		Measles N = 96		P value
	Frequency	%	Frequency	%	
Sex					
Male	175	53.20	46	47.91	0.36
Female	154	46.8	50	52.09	
Age (mean + SD)	18.71(16.84)		37.4(40.88)		<0.001
0-6 months	48	14.59	7	7.29	
7-12 months	111	33.73	26	27.08	
13-23 months	93	28.26	16	16.67	
2-5 years	67	20.36	33	34.38	
6-12 years	10	3.05	11	11.45	
> 12 years			3	3.13	
Nutritional Status Wasting					<0.001
No wasting	141	42.86	65	67.71	
Mild wasting	93	28.26	14	14.58	
Moderate wasting	53	16.11	11	11.46	
Severe wasting	42	12.77	6	6.25	
Stunting					<0.001
No stunting	227	68.99	87	90.63	
Mild stunting	69	20.97	5	5.21	
Moderate stunting	31	9.43	3	3.12	
Severe stunting	2	0.61	1	1.04	
History of infection					0.48
Present	8	2.43	4	4.17	
Absent	318	96.96	91	94.79	
Unknown*	3	0.61	1	1.04	

\* Excluded from statistical analysis

The proportion of children not given measles vaccine at 9 months of age but developed measles pneumonia is higher than those who were given the vaccine. There was statistically significant difference

in the proportion of children who received measles vaccine at 9 months who developed measles pneumonia compared to those who did not develop measles pneumonia. Only five (5) children who were given MMR at 15 months had measles pneumonia against 142 who did not receive the vaccine but had measles pneumonia ( $p = 1.00$ ). No child received MMR at 4-6 years in the measles pneumonia group. One child who received MMR at 4-6 years of age developed measles but did not have pneumonia.

**Table 3. Immunization status of patients with measles and measles pneumonia**

Immunization status	Measles Pneumonia N = 329		Measles N = 96		P value
	Frequency	%	Frequency	%	
Measles vaccine at 9 months					
Positive	50	16.1	25	26.3	0.03
Negative	260	83.9	70	73.7	
MMR at 15 months					
Positive	5	3.4	2	3.3	1.00 <sup>a</sup>
Negative	142	96.6	58	96.7	
MMR at 4-6 years					
Positive			1	3.6	1.00 <sup>a</sup>
Negative	24	100	27	96.4	

<sup>a</sup> Fisher's exact test performed

All variables were included in the logistic regression modeling (age, sex, nutritional status, immunization status and history of infection). The procedure revealed that only age, wasting, and stunting were associated with occurrence of measles pneumonia.

Wasting and stunting significantly increases the risk of developing measles pneumonia by 2.85 and 3.85 times respectively. All levels of nutritional wasting showed increased risk of developing measles pneumonia, however only mild wasting was statistically significant.

**Table 5. Logistic regression**

Factors	Beta coefficient	RR (95% C.I)	p value
Age (months)	-.025	0.98 (0.97, 0.99)	<0.0001
Wasting			0.02
No wasting		1.00	
Mild	1.01	2.76 (1.39,5.45)	0.004
Moderate	0.54	1.72 (0.81,3.68)	0.16
Severe	0.63	1.87 (0.71,4.92)	0.20
Stunting			0.01
No stunting		1.000	
Mild	1.47	4.34 (1.66,11.37)	0.003
Moderate	1.10	3.00 (0.84,10.63)	0.09
Severe	0.53	1.69 (0.12,24.90)	0.70
Constant	1.25		

## DISCUSSION

The measles virus causes a distinct illness characterized by fever ranging from 38.3° C and above, cough, coryza, conjunctivitis, an erythematous maculopapular confluent rash, and a pathognomonic enanthem "Koplik's spots"<sup>14</sup>. Its primary clinical manifestation and complication often involves the pulmonary system<sup>11</sup>. Measles pneumonia then is a frequent manifestation and in most cases it is fatal. In this study the risk factors that predisposes some patients to develop pneumonia during a bout with measles are identified. Factors were reviewed such as sex, age history of previous infection, immunization status, and nutritional status.

Among these patients, young age, malnutrition (stunting and wasting) were identified as risk factors. On the other hand gender, stunting, history of previous infection and immunization status add no risk for having measles pneumonia. It was found out however that measles immunization does have protective effect for measles pneumonia.

In the pre-vaccine era during the 20<sup>th</sup> century, the highest measles attack rate occurred in children 5 to 9 years of age<sup>11</sup>. It is assumed that the infants especially those in the 0-15 months of age are protected from measles by the transplacentally transferred maternal measles antibodies<sup>10</sup>. In the U.S., it was seen that most infants become seronegative at about the age of 15 months and this become the basis for the American Academy of Pediatrics recommendation that measles vaccine be given at 15 months<sup>10</sup>. However, in some developing countries like ours, the approximate age of seroconversion is at an earlier age of nine months<sup>10,7</sup>. Consequently, the EPI program, prescribes measles immunization at 9 months. Recent studies done in the Philippines show that at four months old almost fifty percent of the infants are already negative for maternal measles antibodies and this rises to eighty seven percent (87%) at the age of six months<sup>7,8</sup>. The results of this study confirms the above results: the measles attack rate occurs at 7-12 months of age with several cases identified at the 0-6 months age group. In fact, there were four (4) cases of measles pneumonia at 4 months of age and below. The youngest recorded rate occurred at 3 months. One explanation that can be offered is that the mother never had measles and therefore could not pass on measles antibodies to her child. Another is that the mother had only one dose of measles vaccine at nine months and because of the

waning antibodies<sup>11</sup>. that occur at the age of 5-12 years old, a very low of antibodies must have been passed on her child which is not protected enough against measles. There are even newer evidences claiming that there is an increased susceptibility to measles among infants born to mothers vaccinated against measles. According to this study, vaccinated mothers have fewer antibodies to pass on to their infants. If the infants of these mothers are not immunized as scheduled they have a 33% greater chance of developing measles<sup>21</sup>.

It is also shown in this study that measles occurring at a young age are more often complicated with measles pneumonia. Older age at infection seems protective from measles pneumonia. This could be explained by the copious secretions of the measles infection. Being young, they are also characterized by being weaker and underdeveloped immune defenses.

A high percentage of those patients with measles pneumonia were noted to have wasting and/or stunting compared with those who had measles only. Malnutrition was present among those patients who developed pneumonia but was significantly less common in those patients who had measles only. Malnutrition may play a part in the development of complications (like pneumonia) among measles patients through suppression of the immune system<sup>23</sup>. Another explanation offered is that malnutrition also involves Vitamin A deficiency and both conditions are found among children less than five years of age. An association between vitamin A status and immune function has been suggested by community studies and animal experiments<sup>17</sup>. Mortality and morbidity and Vitamin A deficiency is strongest in children with measles because of the rapid destruction of epithelial cells which in turn increases the body's utilization of Vitamin A. Vitamin A also causes a defect in the immune system due to alterations in the glycoproteins of the lymphocyte membrane, an adverse effect on helper T-cell function, the effect on epithelial tissue, or some other mechanism. In young patients with waning measles antibodies, with malnutrition, and significant Vitamin A deficiency, the likelihood of a complicated measles increases.

Among the measles pneumonia group, only 16% had measles vaccine at nine months of age, three-



fourth had MMR at 15 months, and none MMR at 4-6 months. Comparatively, the group, who did not develop measles pneumonia. Showed better immunization status: 26% had measles vaccine at nine months, 3.3% had MMR at 15 months, and 3.6% had MMR at 4-6 years of age. Initially, there was a statistically significant difference in the proportion of children with measles vaccine at nine months who developed measles pneumonia compared to those who did not develop measles pneumonia. However, when logistic regression was done, status of immunization did not appear as a risk factor measles pneumonia. The result could have been affected by the lack of subjects with immunization among the higher age group. This an avoidable selection bias because 90-95% of our patients belong to the lower income group of our society. Not only were they unable to afford the MMR but they were also unaware of its significance. Even if there was failure of immunization, the vaccine is able to confer some protective effect from the complications of measles.

The raw data showed that there were slightly more males (53%) than females (46.8%) among the measles pneumonia group compared with the measles only group. However the difference was not found to be statistically significant. There are some studies suggesting that complications are higher in males than in females<sup>11</sup>. This study shows that gender poses no greater risk for measles pneumonia.

It is expected that a history of previous infection would have lowered a child's resistance or immune response making him more susceptible to infections. In this study, ninety-seven percent (97%) of those who had measles pneumonia did not have any other infection within six months prior to contracting measles. This being a retrospective study, we could only assume that perhaps, some information regarding previous infection prior to contracting measles were missed during the time the illness occurred.

## CONCLUSION

In conclusion, the four hundred and twenty five measles cases seen from June 1, 1998 to June 30, 2000 at the National Children's Hospital were equally distributed between male and female. Majority of the population are found to be less than twenty-four (24) months of age, with wasting and stunting, and without any history of previous infections. Very few of the population had measles immunization.

Most of the admitted patients that eventually had pneumonia are younger in age and malnourished (wasted and/or stunted) compared to those that had measles only. By logistic regression, only young age and malnutrition (wasting and stunting) were identified as risk factors for measles pneumonia. Gender, stunting, and history of previous infection add no risk for having measles pneumonia. Measles immunization status was found to have protective effect for developing pneumonia.

## RECOMMENDATIONS

It was learned through this study that there are indeed factors that predict the occurrence of pneumonia among measles patients. However, being a retrospective study, there were only a few variables that we were able to use from the data available in the medical records. A prospective study may be able to identify additional risk factors which may be directly asked and verified from the subjects or their parents such as use of antibiotics prior to consultation, administration of Vitamin A in previous consultation, or even the nature of mother's immunity (whether it was natural or acquired immunity).

Secondly, in as much as young age (less than 24 months old), stunting and/or wasting predict the occurrence of pneumonia among measles patients, it is recommended then that those possessing the risk factors identified above would be placed under close watch during a bout with measles in order to catch the early signs of life-threatening complications.

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