Risk Factors of Developing Pneumonia Among Confirmed Measles Cases

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ABSTRACT

Background. Deaths may occur due to complications of measles. The most common measles complication is pneumonia and accounts for most measles-related deaths.

Objective. The study aimed to identify risk factors for developing pneumonia among measles cases.

Methodology. A cross-sectional study was conducted using measles surveillance data from an outbreak in the Philippines from January 2013 to December 2014. Data on age, sex, area of residence, clinical manifestations, receipt of measles vaccine, and other exposure variables were obtained and analyzed using logistic regression.

Results. Approximately 25,166 confirmed measles cases were included in the study where 16% had pneumonia. Potential risk factors identified in the development of pneumonia among confirmed measles cases were younger age (<5 years = OR 2.49, 95% CI: 1.81,3.42; 5-14 years = OR 2.34, 95% CI: 1.64,3.33), resident of Mindanao (OR 2.18, 95% CI: 1.74,2.74), presence of cough (OR 5.51, 95% CI: 2.04,14.86), presence of conjunctivitis (OR 1.31, 95% CI: 1.11,1.55), and being admitted to hospital (OR 3.16, 95% CI: 2.57,3.90). Confirmed measles cases with receipt of measles containing vaccine (MCV) (OR 0.74, 95% CI: 0.63,0.87) were found to be less likely to have pneumonia.

Conclusion. These risk factors help identify cases requiring prompt management to reduce morbidity and mortality in any future measles outbreaks.

Key Words: measles, Philippines, pneumonia

INTRODUCTION

Most measles-related deaths are caused by complications associated with the disease.[1,2] Complications of measles occur in as many as 40% of all cases and the risk of complication is increased by extremes of age and underlying conditions including malnutrition.[3] Pneumonia is the most common fatal complication of measles, occurring in 56 to 86% of measles-related deaths. Pneumonia has been reported in 2 to 27% of measles cases among communities in developing countries and in 16 to 77% of children admitted to hospitals.[3] Pneumonia occurring in measles cases may be caused by secondary viral or bacterial infections or by the measles virus itself.[4]

The control of measles is centered on vaccination. The World Health Organization (WHO) has established a target in five WHO Regions for measles elimination by 2020 through measles vaccination.[5,6] Between 2000 and 2013, measles vaccination has decreased measles-related deaths globally by 75% and it is still considered as the best means of preventing measles.[4,7] In the Philippines, the case fatality rate for confirmed measles has decreased from 0.51%

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in 2014 to 0% in 2016.[8,9] However in 2017, case fatality rate among confirmed measles cases was 1.92%.[10] Although a safe and cost-effective vaccine has been available for several years, measles remains a major cause of death among young children.[7]

Several studies have explored the risk factors on contracting severe measles. One study identified overcrowding, exposure intensity, prior respiratory infection, and intercurrent infection as factors affecting measles severity.[11] A retrospective study by Samsi et al showed a model of variable risk factors for developing severe measles involving malnutrition, patient demographic composition, and socio-economic and socio-cultural conditions including availability and utilization of health facilities. The paper also mentioned that the most frequent cause of mortality was the combination of bronchopneumonia-encephalopathy (59.3%) and bronchopneumonia-encephalopathy-diarrhea (24.1%) and that most deaths occurred during the first 24 hours of hospitalization.[12]

Literature on risk factors for pneumonia in community-based studies has been sparse. A prospective study in South India revealed that among 401 cases who had measles complications, 288 had measles-related pneumonia.[13] A hospital-based study in the Philippines noted that the majority of those with measles-related pneumonia were aged less than 24 months. Malnutrition has been found to be associated with the occurrence of measles pneumonia.[14] The studies on risk factors for the development of pneumonia among measles cases mentioned above were all hospital-based.

A measles outbreak occurred in the Philippines from 2013-2014 affecting the whole country. All measles cases were reported to the Philippine Integrated Disease Surveillance and Response (PIDSR) system through the Epidemiology Bureau of the Department of Health. All suspected measles cases reported to the PIDSR were investigated and specimen collected to confirm measles cases.[15] This paper provides assessment of risk factors associated with developing pneumonia among confirmed measles cases using routine measles surveillance data.

MATERIALS AND METHODS

A cross-sectional study of measles-related pneumonia cases compared to measles cases without pneumonia was assessed. Potential risk factors for development of pneumonia among confirmed measles cases based on the January 2013 to 20 December 2014 measles surveillance data from the Department of Health. Characteristics of confirmed measles cases included in the analysis were age, sex, area of residence, receipt of MCV, presence of colds/runny nose, fever, red eye/conjunctivitis, cough, rash, hospital admission, history of travel to an area with known measles transmission, place of probable exposure, and exposure to other measles cases. Confirmed measles cases were defined according to the new classification adapted in 2013.[15]

Case ascertainment

Cases were defined as individuals classified as measles confirmed in the PIDSR system with a diagnosis of pneumonia during the 2013 to 2014 measles outbreak. Non-cases were defined as measles confirmed cases without pneumonia reported to PIDSR during the same outbreak. All measles confirmed cases were included in the analysis.

Outcome ascertainment

A confirmed measles case was ascertained to have the outcome if pneumonia was present in the final diagnosis or listed as a complication in the surveillance data.

Statistical analysis

All statistical analyses were conducted using Stata 13.1. Univariate analysis on all variables was performed to define the characteristics of the study population. A Chi-square test was used to assess the association of each variable to having pneumonia. Logistic regression was used to assess the risk factors for development of pneumonia among measles confirmed cases. Variables whose effect sizes were significant at $p < 0.05$ were included in the final multiple logistic regression model.

RESULTS

Data were obtained from the Epidemiology Bureau on reported measles cases to the PIDSR from 2013 to 2014. A total of 67,029 suspected measles cases were reported for both years. More than half (52%) of suspected cases were males and the highest number of suspected measles notifications came from NCR (26%), Region 4A (16%) and Region 3 (10%).

Suspected measles cases were classified according to discarded / non-measles cases; confirmed measles cases; and rubella-confirmed, measles compatible, and pending cases as shown in Figure 1. A total of 25,166 (37%)
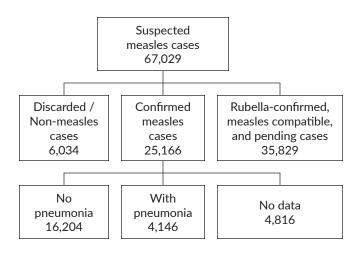

Figure 1. Classification of suspected measles cases and occurrence of pneumonia among confirmed measles cases, Jan 2013 - 20 Dec 2014, Philippines.

confirmed measles cases were reported to PIDSR. More than half (53%) of suspected cases were classified as measles compatible, rubella-confirmed, and pending cases while 9% were classified as discarded/non-measles cases. A total of 4,146 (16%) confirmed measles cases were reported to have pneumonia.

Children aged 1-5 years old had the highest proportion of confirmed measles cases (29%), followed by children <1 year of age at 27% while those who were aged 16-20 years old comprised 12% of confirmed cases (Figure 2). The highest proportion of reported confirmed measles cases were from Region 4A (22%), NCR (31%), and Region 3 (12%) (Table 1).
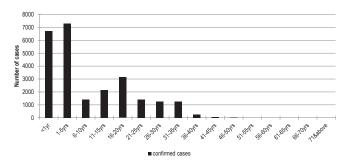

Figure 2. Number of reported confirmed measles cases by age, Jan 2013 to 20 Dec2014, Philippines.

Table 1. Age, sex and area of residence of reported measles cases according to case classification from January 2013 to 20 December 2014, Philippines

	Confirmed Number (%)	Discarded Number (%)	Rubella confirmed/ Measles compatible Number (%)	Total (%)
Age				
<1 year	6,733 (27)	1,005 (17)	9,565 (27)	17,303 (26)
1-5 years	7,291 (29)	1,059 (18)	9,135 (26)	17,485 (26)
6-10 years	1,422 (6)	513 (9)	2,022 (6)	3,957 (6)
11-15 years	2,134 (8)	615 (10)	3,201 (9)	5,950 (9)
16-20 years	3,135 (12)	813 (13)	4,711 (13)	8,659 (13)
21-25 years	1,404 (6)	635 (11)	2,399 (7)	4,438 (7)
26-30 years	1,271 (5)	432 (7)	1,953 (5)	3,656 (5)
31-35 years	1,251 (5)	377 (6)	1,879 (5)	3,507 (5)
36-40 years	234 (1)	191 (3)	449 (1)	874 (1)
41-45 years	62 (0)	137 (2)	142 (0)	341 (1)
46-50 years	25 (0)	70 (1)	81 (0)	176 (0)
51-55 years	9 (0)	56 (1)	46 (0)	111 (0)
56-60 years	13 (0)	40 (1)	31 (0)	84 (0)
61-65 years	9 (0)	34 (1)	26 (0)	69 (0)
66-70 years	2 (0)	11 (0)	10 (0)	23 (0)
71 & above	2 (0)	13 (0)	8 (0)	23 (0)
Missing	169 (1)	33 (1)	171 (0)	373 (1)
Total	25,166 (100)	6,034 (100)	35,829 (100)	67,029 (100)
Sex				
Male	13,340 (53)	2,968 (49)	18,589 (52)	34,897 (48)
Female	11,826 (47)	3,066 (51)	17,240 (48)	32,132 (52)
Total	25,166 (100)	6,034 (100)	35,829 (100)	67,029 (100)
Area of residence (Region)				
I	796 (3)	267 (4)	1,570 (4)	2,633 (4)
II	620 (2)	203 (3)	1,415 (4)	2,238 (3)
III	2,939 (12)	685 (11)	3,408 (10)	7,032 (10)
IVA	5,551 (22)	1,066 (18)	4,289 (12)	10,906 (16)
IVB	323 (1)	210 (3)	1,441 (4)	1,974 (3)
V	665 (3)	176 (3)	1,343 (4)	2,184 (3)
VI	1,046 (4)	782 (13)	1,457 (4)	3,285 (5)
VII	914 (4)	277 (5)	1,015 (3)	2,206 (3)
VIII	247 (1)	62 (1)	1,186 (3)	1,495 (2)
IX	241 (1)	113 (2)	561 (2)	915 (1)
X	740 (3)	126 (2)	1,633 (5)	2,499 (4)
XI	1,257 (5)	337 (6)	1,950 (5)	3,544 (5)
XII	857 (3)	208 (3)	3,192 (9)	4,257 (6)
ARMM	314 (1)	45 (1)	1,198 (3)	1,557 (2)
CAR	255 (1)	185 (3)	410 (1)	850 (1)
CARAGA	592 (2)	147 (2)	1,192 (3)	1,931 (3)
NCR	7,809 (31)	1,145 (19)	8,569 (24)	17,523 (26)
Total	25,166 (100)	6,034 (100)	35,829 (100)	67,029 (100)

Table 2. Comparison of age, sex and area of residence of confirmed measles cases with or without pneumonia, January 2013 to 20 December 2014, Philippines

	Cases with pneumonia Frequency (%)	Cases without pneumonia Frequency (%)	No data on pneumonia Frequency (%)	Total (%)	p-value[1]
Age					
<5 years	3,052 (74)	8,306 (51)	2,328 (48)	13,686 (54)	<0.0001
5 - 14 years	435 (10)	2,325 (14)	696 (14)	3,456 (14)	
15 - 24 years	389 (9)	3,377 (21)	997 (21)	4,763 (19)	
25 years & above	257 (7)	2,070 (13)	754 (16)	3,081 (12)	
Missing	13 (0)	126 (1)	41 (1)	180 (1)	
Total	4,146 (100)	16,204 (100)	4,816 (100)	25,166 (100)	
Sex					
Male	2,228 (54)	8,579 (53)	2,533 (53)	13,340 (47)	0.96
Female	1,918 (46)	7,625 (47)	2,283 (47)	11,826 (53)	
Total	4,146 (100)	16,204 (100)	4,816 (100)	25,166 (100)	
Area of residence					
Luzon	1,783 (43)	8,195 (51)	1,171 (24)	11,149 (44)	<0.0001
Visayas	328 (8)	1,012 (6)	867 (18)	2,207 (9)	
Mindanao	714 (17)	1,385 (9)	1,902 (39)	4,001 (16)	
Metro Manila	1,321 (32)	5,612 (35)	876 (18)	7809 (31)	
Total	4,146 (100)	16,204 (100)	4,816 (100)	25166 (100)	

[1] *Chi-square test*

The highest proportion of pneumonia cases were observed among <5 years old (74%). There was little difference in sex but most of pneumonia cases were from Luzon (43%). The baseline characteristics of measles cases with pneumonia are described in Table 2. Clinical manifestations, vaccination status, hospital admission, history of travel, place of probable exposure, and exposure to probable measles case are presented in Table 3.

Nearly all pneumonia cases had fever, rash and cough. Seventy-three percent of pneumonia cases had conjunctivitis, 84% had colds and 92% were admitted in a hospital. Only 20% of measles related pneumonia cases received measles-containing vaccine. Most pneumonia cases (60%) had no history of travel to an area with known measles transmission but 48% were exposed to other measles cases and exposure probably occurred from the community (45%).

Sex (p=0.96), fever (p=0.30), rash (p=0.53), colds/runny nose (p=0.22), history of travel to an area with known measles transmission (p=0.15), and place of probable exposure (p=0.19) were not associated with having pneumonia. These variables were excluded from multivariate analysis. Variables with evidence of an association with pneumonia included age, area of residence, receipt of any MCV, presence of cough and red eye, hospital admission, and exposure to other confirmed measles case (Table 4).

DISCUSSION

National measles surveillance data from 2013 to 2014 was analyzed to identify potential risk factors for developing pneumonia among measles cases. In this study, 16% of confirmed measles cases had pneumonia. Potential risk factors identified were younger age, residence in Mindanao, presence of cough, conjunctivitis, and hospital admission. Receipt of a measles-containing vaccine was found to be protective against developing pneumonia among measles cases.

Age was an important risk factor in the development of pneumonia among measles confirmed cases. Majority of measles cases with pneumonia (74%) were less than 5 years old. Children in this age group were more likely to develop pneumonia than older children. Malnutrition may play a role in the development of pneumonia by further decreasing the immune response brought by having measles infection. A hospital-based study in Makati, Philippines showed that measles patients with pneumonia were more likely to be marginally underweight compared to those who did not have pneumonia.[16] However, the study did not mention which particular age group had the most number of marginally underweight children or if nutritional status was measured before or after the diagnosis of pneumonia.

Measles cases living in Mindanao had twice the risk of developing pneumonia compared to those living in Luzon, Visayas and Metro Manila. This can be attributed to the low socio-economic status of the people living in this island. Seven out of the 10 poorest provinces in the Philippines can be found in Mindanao.[17] Low socio-economic status leads to poor access to health care, lack of maternal education, poor hygiene, and malnutrition.

Among the clinical manifestations of measles, cough and conjunctivitis were found to be associated with developing pneumonia. Measles infection can be acquired through the respiratory tract and occasionally through the conjunctiva. When the virus infects the reticuloendothelial system, secondary viremia occurs where the skin and respiratory tract become infected manifesting the disease.[2] The presence of cough and conjunctivitis with pneumonia may be due

Table 3. Clinical characteristics, measles vaccination status and other exposure variables of confirmed measles cases with or without pneumonia, January 2013 to 20 December 2014, Philippines

	Cases with pneumonia	Cases without pneumonia	Missing	Total	p-value[1]
Receipt of any MCV					
No	2,930 (71)	7,246 (45)	2,025 (42)	12,201 (48)	<0.0001
Yes	849 (20)	4,030 (25)	865 (18)	5,744 (23)	
Missing	367 (9)	4,928 (30)	1,926 (40)	7,221 (29)	
Total	4,146 (100)	16,204 (100)	4,816 (100)	25,166 (100)	
Presence of fever					
No	2 (0)	4 (0)	0 (0)	6	0.30
Yes	4,128 (100)	13,756 (85)	3,379 (70)	2,1263	
Missing	16 (0)	2,444 (15)	1,437 (30)	3,897	
Total	4,146 (100)	16,204 (100)	4,816 (100)	25,166 (100)	
Presence of cough					
No	39 (1)	490 (3)	124 (3)	653 (3)	<0.0001
Yes	3,982 (96)	12,638 (78)	3,203 (67)	19,823 (79)	
Missing	125 (3)	3,076 (19)	1,489 (31)	4,690 (18)	
Total	4,146 (100)	16,204 (100)	4,816 (100)	25,166 (100)	
Presence of rash					
No	0 (0)	7 (0)	2 (0)	9 (0)	0.53
Yes	4,141 (100)	15,857 (98)	4,755 (99)	24,753 (98)	
Missing	5 (0)	340 (2)	59 (1)	404 (2)	
Total	4,146 (100)	16,204 (100)	4,816 (100)	25,166 (100)	
Presence of runny nose / colds					
No	483 (12)	2,269 (14)	591 (12)	3,343 (13)	0.22
Yes	3,494 (84)	10,596 (65)	2,651 (55)	16,741 (67)	
Missing	169 (4)	3,339 (21)	1,574 (33)	5,082 (20)	
Total	4,146 (100)	16,204 (100)	4,816 (100)	25,166 (100)	
Presence of red eye / conjunctivitis					
No	923 (22)	3,670 (23)	874 (18)	5,467 (22)	0.003
Yes	3,021 (73)	9,053 (56)	2,314 (48)	14,388 (57)	
Missing	202 (5)	3,481 (21)	1,628 (34)	5,311 (21)	
Total	4,146 (100)	16,204 (100)	4,816 (100)	25,166 (100)	
Hospital admission					
No	337 (8)	5,330 (33)	854 (18)	6,521 (26)	<0.0001
Yes	3,808 (92)	8,955 (55)	2,564 (53)	15,327 (61)	
Missing	1 (0)	1,919 (12)	1,398 (29)	3,318 (13)	
Total	4,146 (100)	16,204 (100)	4,816 (100)	25,166 (100)	
History of travel					
No	2,496 (60)	6,622 (41)	2,136 (44)	11,254 (45)	0.15
Yes	685 (17)	1,926 (12)	433 (9)	3,044 (12)	
Missing	965 (23)	7,656 (47)	2,247 (47)	10,868 (43)	
Total	4,146 (100)	16,204 (100)	4,816 (100)	25,166 (100)	
Place of probable exposure					
Daycare/school	71 (2)	423 (3)	94 (2)	588 (2)	0.19
Health center facility	139 (3)	351 (2)	85 (2)	575 (2)	
Home/dormitory	857 (21)	2,581 (16)	727 (15)	4,165 (17)	
Community	1,860 (45)	4,816 (30)	1,300 (27)	7,976 (32)	
Missing	1,219 (29)	8,033 (50)	2,610 (54)	11,862 (47)	
Total	4,146 (100)	16,204 (100)	4,816 (100)	25,166 (100)	
Exposure to other measles case					
No	1,031 (25)	3,617 (22)	1,004 (21)	5,652 (22)	0.034
Yes	1,983 (48)	4,931 (30)	1,219 (25)	8,133 (32)	
Missing	1,132 (27)	7,656 (47)	2,593 (54)	11,381 (45)	
Total	4,146 (100)	16,204 (100)	4,816 (100)	25,166 (100)	

[1] Chi-square test

to immune suppression caused by measles infection and/ or malnutrition with probable secondary viral or bacterial co-infection.[1] Hospital admission was also identified as associated with pneumonia among confirmed measles cases. This association may be because sicker children were more likely to be hospitalized i.e.: due to reverse causation.

Table 4. Crude and adjusted odds ratio of identified risk factors for developing pneumonia among confirmed measles cases

	Crude OR[1] (95% CI[2])	p-value[3]	Adjusted OR[1] (95% CI[2])	p-value[3]	p-value[4]
Age					
<5yrs	2.38 (1.84-3.07)	<0.0001	2.49 (1.81-3.42)	<0.0001	<0.0001
5-14 yrs	1.97 (1.47-2.65)	<0.0001	2.34 (1.64-3.33)	<0.0001	
15-24 yrs	0.80 (0.58-1.11)	0.19	0.97 (0.66-1.42)	0.865	
25 & above	1		1		
Area of residence					
Metro Manila	1		1		<0.0001
Luzon	1.63 (1.40-1.90)	<0.0001	1.47 (1.23-1.75)	0.0001	
Visayas	1.56 (1.17-2.07)	0.002	1.3 (0.96-1.77)	0.092	
Mindanao	3.09 (2.52-3.79)	<0.0001	2.18 (1.74-2.74)	0.0001	
Receipt of any MCV					
No	1		1		
Yes	0.64 (0.55-0.75)	<0.0001	0.74 (0.63-0.87)	<0.0001	<0.0001
Cough					
No	1		1		
Yes	5.87 (2.62-13.17)	<0.0001	5.51 (2.04-14.86)	0.001	<0.0001
Red eye / Conjunctivitis					
No	1		1		
Yes	1.26 (1.08-1.47)	0.003	1.31 (1.11-1.55)	0.02	<0.0001
Hospital admission					
No	1		1		
Yes	3.47 (2.88-4.18)	<0.0001	3.16 (2.57-3.90)	<0.0001	<0.0001
Exposure to other measles case					
No	1				
Yes	1.17 (1.01-1.36)	0.035			

[1] Odds ratio. [2] Confidence interval. [3] Wald's test. [4] Likelihood ratio test

Measles cases who received measles-containing vaccine were less likely to have pneumonia (OR: 0.74, 95% CI: 0.63-0.87). It has been shown that vaccinated children who develop measles have a much lower rate of complications than unvaccinated children.[2] A study in Brazil on risk factors for childhood pneumonia showed that measles vaccine was associated with a 21% reduction in the risk of developing pneumonia even among non-measles cases.[18]

Pneumonia is the most common complication of measles and causes most measles-related deaths. Identification of risk factors for developing pneumonia among measles cases is important for prompt identification and management. Vaccination with a measles containing vaccine helps prevent measles and its complications.

CONCLUSIONS

Measles associated pneumonia has been a complication and a major cause of death during the 2013 outbreak in the Philippines and was noted among very young children and in regions where poverty was more prevalent like in Mindanao. Other risk factors identified for the development of pneumonia among measles cases were presence of cough, red eye, and hospital admission. Measles cases who received MCV were less likely to develop pneumonia. These risk factors can help identify cases requiring prompt management to reduce morbidity and mortality in any future outbreaks.

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