AUDIT ARTICLE

Risk factors for mortality among admitted children with complications of measles in Pakistan: An observational study

Brekhna Aurangzeb[1], Areesh Fatmee[2], Rehmana Waris[3], Nighat Haider[4], Asma Berjees[5], Syed Hashim Raza[6]

Abstract

Objective: To identify the vaccination status and risk factors for mortality in children admitted with complications of measles.

Methods: The retrospective study was conducted at Children Hospital, Pakistan Institute of Medical Sciences, Islamabad, Pakistan, and comprised data of children admitted with complications of measles between 2013 and 2017. Information on vaccination history, complications of measles, anthropometry, hospital stay and outcome within 15 days of admission was retrieved from hospital records. Data was analysed using Stata 14.

Results: Of the 307 children admitted, 79(26%) were aged <9 months and were excluded. Of the remaining 228 subjects, 109(47.8) were unvaccinated. Risk factors significantly associated with mortality were an unvaccinated state of measles vaccine, being stunted, and encephalitis in comparison with pneumonia ($p<0.05$). A total of 39(17%) children died within 15 days of admission.

Conclusion: Encephalitis, non-vaccination and under-nutrition were significantly associated with mortality in children with complications of measles.

Keywords: Child, Measles, Risk factors, Mortality, Vaccination. (JPMA 71: 497; 2021)

DOI: https://doi.org/10.47391/JPMA.977

Introduction

Measles is a highly infectious disease that causes significant morbidity and mortality despite several years of effective vaccine and implementation policies by governments and the World Health Organisation (WHO). Globally, in 2017, there were 6.7 million measles cases and 110,000 measles-related deaths.[1] Measles cases have tripled to 364,808 during the first seven months of 2019 compared to the same period in the previous year despite all the efforts in the domain of vaccination.[1] In Pakistan, the incidence of confirmed measles cases was 24.6 per million cases between 2000 and 2009, and has increased to 80.4 per million between 2010 and 2018.[2] About 30-40% of patients with measles develop one or more complications.[3] Measles damages almost all organs of the body as a result of damage to mucous membranes and transient and profound immunosupression.[3,4] This may last for months after measles, and leads to complications and death. One in 12 children with measles develop diarrhoea.[3] Measles-associated diarrhoea can result from the measles virus itself or secondary bacterial and viral infection may add to the severity and duration of illness.[3,4] One out of 20 children develops pneumonia which causes 56-86% of measles-related deaths.[3] Primary measles encephalitis occurs in 1-3 per 1000 measles-infected patients and may be caused by primary viral invasion of the brain followed by chemokines and lymphocytic infiltration.[3,4] Mortality with measles encephalitis is 10-15% and a further 25% have permanent severe neurological damage.[3] Post-infectious encephalomyelitis (PIE) occurs in 1 in 1000 measles-infected persons due to immune reaction to the myelin basic protein and can also result in permanent damage to the nervous system.[3,4] Measles can cause or worsen malnutrition due to mouth ulcers, anorexia, diarrhoea, which further worsens complications, risk of secondary infections and mortality.[3,4] Complications are high in children aged <5 years.[3,4] Thus, measles is a devastating disease with severe complications and fatality.[3,4]

There are several known risk factors for complicated measles and death. These are non-vaccination, malnutrition, young age at infection, immune deficiency, overcrowding, lack of healthcare facilities, vitamin A deficiency and severe complications of measles, such as pneumonia and encephalitis.[3-6] Although measles is endemic in Pakistan, during the last five years the country has faced two epidemics; in 2013 and 2017, and many children with complicated measles were hospitalised with high mortality rates.[2,6-8] Hence, identification of risk factors for mortality with complications of measles is important for clinicians and policy-makers for better management of measles in children. The current study was planned to identify the vaccination status and risk factors for mortality in children admitted with complications of measles.

Subjects and Methods

The study was conducted on Children admitted with complication of measles at the Infectious Disease Ward of Children Hospital, Pakistan Institute of Medical Sciences (PIMS), Islamabad, Pakistan. The data was collected

[1,3-6]Children Hospital, Pakistan Institute of Medical Sciences, Islamabad, Pakistan; [2]PMAS, Arid Agriculture University, Rawalpindi, Pakistan.

Correspondence: Brekhna Aurangzeb. e-mail: brekhna.aurangzeb@gmail.com

retrospectively for the period 1st January 2013 to 31st December 2017, in March 2018. The hospital is a tertiary care, public-sector hospital catering to patients from a vast range of rural and urban populations in and around the federal capital. The approval for the study was obtained from the ethics review board of Shaheed Zulfiqar Ali Bhutto Medical University, PIMS, Islamabad, which waived off the requirement of informed consent as it was a retrospective review.

Data was retrieved from the Medical Records Department of the hospital. Information regarding name, gender, age at diagnosis, measles vaccination history, month and year of presentation, presenting complaints, presence of complications, such as pneumonia, encephalitis, gastroenteritis, dehydration, weight, height, duration of hospital stay and outcome were extracted. Weight for age and height for age were calculated using Epi-Info 7 according to WHO charts as z scores and standard deviations.[9] Malnutrition was defined, according to the WHO Global database on Child Growth and Nutrition, as underweight meaning weight for age <-2SD and stunting as height for age <-2SD.[9] Measles and complications of measles were diagnosed according to WHO definitions by the clinicians on service and the hospital utilised it as the diagnostic standard. Measles was diagnosed on WHO clinical criteria Measles Surveillance Guidelines with the following symptoms; high-grade fever preceding the appearance of rash by 2-4 days, generalised erythematous maculopapular, non-vesicular rash and one or more of the following: cough, conjunctivitis or coryza, or as suspected measles by healthcare professional.[10] Pneumonia was classified according to the WHO criteria of respiratory rate and chest in-drawing.[10] Central nervous system (CNS) involvement was considered if there was lethargy, irritability, headache, fits, disorientation or neurological deficits.[10] Measles-related death was defined as death within 15 days of onset of the rash, unless death was because of some other disease or unrelated cause. Children were managed in the ward according to the standard WHO protocol with broad-spectrum intravenous (IV) antibiotics, chloramphenicol eye drops and vitamin A capsules.[10]

Data was analysed using Stata 14. Frequencies and percentages were calculated for categorical variables. Measles mortality rate was calculated for each category, followed by logistic regression analysis to identify potential risk factors for mortality due to complications of measles without adjusting for other covariates. All variables with $p \leq 0.2$ were then included in a multivariate logistic regression model, which was constructed using a step-wise backward elimination procedure. Odds ratios (OR) and their 95% confidence interval (CI) were calculated. Unadjusted OR and adjusted OR (AOR) with 95%CI were calculated. P<0.05 was considered statistically significant.

Results

Of the 307 children admitted with complications of measles, 79(26%) were aged <9 months and were excluded as they were not old enough to receive measles vaccine. Of the remaining 228(74%) subjects, 138(60.5%) were males and 90(39.5) were females. Overall, 109(47.8) subjects were non-vaccinated and 39(17%) children died within 15 days of admission. The data was compared along different

Table-1: Baseline characteristics and Comparison of background characteristics among admitted children with measles complication by their outcome (n=228).

Background characteristics	n(%)	Alive	Death n (%)	Odds ratio n (%)	95% CI	*p*-value
Year of enrolment						
2013	89 (39.0)	77 (86.5)	12 (13.5)	1	(reference)	
2014	54 (23.7)	46 (85.2)	8 (14.8)	1.12	(0.42, 2.93)	0.824
2015	24 (10.5)	17 (70.8)	7 (29.2)	2.64	(0.91, 7.70)	0.075
2016	23 (10.1)	20 (87.0)	3 (13.0)	0.96	(0.23, 3.74)	0.956
2017	38 (16.8)	29 (76.3)	9 (23.7)	1.99	(0.76, 5.22)	0.161
Age categories						
9-12 months	51 (22.4)	44 (86.3)	7 (13.7)	1	(reference)	
1-5 years	128 (56.1)	106 (82.8)	22 (17.2)	1.3	(0.52, 3.27)	0.571
More than 5 years	49 (21.5)	39 (79.6)	10 (20.4)	1.61	(0.56, 4.64)	0.376
Sex of child						
Male	138 (60.5)	117 (84.8)	21 (15.2)	1	(reference)	
Female	90 (39.5)	72 (80.0)	18 (20.0)	1.39	(0.70, 2.79)	0.35
Measles vaccination status						
Two doses	70 (30.7)	67(95.47)	3(4.3)	1	(reference)	
One dose	49 (21.5)	39(79.6)	10(20.4)	5.73	(1.49, 22.07)	0.001
Un vaccination	109 (47.8)	83(76.2)	26(23.8)	7	(2.03, 24.01)	0.011
Nutritional status						
Underweight						
No	70 (30.7)	139 (88.0)	19 (12.0)	1	(reference)	
Yes	158 (69.3)	50 (71.4)	20 (28.6)	2.93	(1.44, 5.93)	0.003
Stunted						
No	60 (26.3)	153 (91.1)	15 (8.9)	1	(reference)	
Yes	168 (73.7)	36 (60.0)	24 (40.0)	6.8	(3.24, 14.26)	<0.0001
Complications of measles						
Pneumonia	144 (63.2)	125 (86.8)	19 (13.2)	1	(reference)	
Encephalitis	20 (8.8)	7 (35.0)	13 (65.0)	12.22	(4.33, 34.49)	<0.0001
Multiple	27 (11.8)	23 (85.2)	4 (14.8)	1.14	(0.36, 3.67)	0.821
Others*	37 (16.2)	34 (91.9)	3 (8.1)	0.58	(0.16, 2.08)	0.403

*Others include diarrhoea, otitis media, oral lesions, thrombocytopenia, hepatitis etc; CI: Confidence interval

Table-2: Risk factors for mortality in admitted children with measles complications: results of multivariate logistic regression analysis.

Risk factors	Adjusted odds ratio	95% CI	*p*-value
Measles vaccination status			
Unvaccinated	2.69	(1.16, 6.22)	0.021
Nutritional status			
Stunted	5.23	(2.33, 11.73)	<0.0001
Complications			
Encephalitis	8.21	(2.67, 25.22)	<0.0001

CI: Confidence interval

variables (Table 1). Adjusted odds of mortality were significantly higher in children who were non-vaccinated, stunted and had encephalitis compared to their counterparts after adjusting for other confounding factors (Table 2).

Discussion

The study identified some key risk factors for mortality in admitted children with complications of measles. Encephalitis conferred a statistically significant elevated risk of mortality compared to children with pneumonia. Non-vaccination and under-nutrition at the time of admission were also significant risk factors for mortality in children with complicated measles. These findings are useful for paediatricians, clinicians, managers and policymakers working in child health and nutrition programmes to strengthen vaccination coverage and to improve nutritional interventions and to subsequently reduce the morbidity and mortality associated with measles. the results are comparable with other studies carried out in similar clinical settings.[6-8,11-16]

Case fatality in the current study was quite high. Previous studies from various countries including different cities of Pakistan showed case fatality rate ranging from <1% to 18% in children with complications of measles (Table 3). This variation in case fatality depends on the study population (rural or urban), average age of infection, the nutritional, vaccination, immunological and socioeconomic status of the population, accessibility to the healthcare and the availability of facilities at the healthcare centre.[3-5,17] Measles outbreaks even in developed countries are associated with the same complications, but low mortality, high morbidity and hospitalisation costs.[18]

Children with encephalitis as a complication of measles had higher odds of death compared to children who had measles with pneumonia in the current study. Similarly, neurological complications are reported as a risk factor for mortality by other studies.[6] This can occur because of encephalitis itself or post-infectious encephalomyelitis (PIE) which is due to abnormal immune responses to the myelin basic protein within days of onset of measles rash.[4] Death can also occur because of measles inclusion body encephalitis (MIBE) which is progressive viral infection of the brain in immune-compromised individuals that results in neurological damage and death within months of acute measles infection.[4] Another significant feature of the current, study similar to comparative studies from other parts of the country, was the higher number of measles cases in the younger age group which increased the risk of death due to neurological complications of measles such as sub-acute sclerosing pan encephalitis.[6-8,11-13,16]

Pneumonia was the commonest complication of measles for hospitalisation in the current study similar to other studies.[4,7,8,13,14,19-20] Pneumonia has been reported to be 2-27% in population with measles reported from community based studies from developing countries and in 16-77% of children hospitalised with measles.[18,19,22,23] It has been reported to be from 21% to 93% in children presenting with measles in different hospitals of Pakistan (Table 3). Pneumonia causes measles-related deaths and in the current study it caused 13% deaths.[3] Pneumonia may be caused by secondary bacterial or viral infections.[4] The reason for mortality with measles pneumonia depends on severity of diseases, multisystem involvement of the disease and that measles cause immunosuppression and bacterial super infection can occur.[3,4]

The current study found under-nutrition was a risk factor for mortality with higher odds of death in stunted children than

Table-3: Percentage of age <9 months, unvaccinated, complications and case fatality rate in various studies.

Author, year	Age	Vaccination status	Complications		Case fatality
	<9 months	Unvaccinated	Pneumonia	Encephalitis	rate
Pakistani studies					
Current study	26%	48%	63%	9%	17%
Khan et al[16]	30%	65%	54.4%	6%	0.5%
Hussain et al 2016[11]	50%	89%	42%	4%	2%
Habibullah et al 2016[15]	NA	35%	60%	NA	7%
Haq et al 2015[7]	14%	71%	45%	4%	NA
Javed et al 2014[6]	34%*	66%	80%	8%	9%
Mushtaq et al 2012[8]	41%*	60%	93%	NA	16%
Siddiq et al 2006[12]	12%	57%	21%	NA	2%
Rehman et al 2008[14]	NA	43%	40%	NA	5%
Aurangzeb et al 2005[13]	21%*	43%	40%	9%	3%
International studies					
Donas et al 2014[18]	NA	NA	34%	5%	0%
Onoja et al 2013[19]	25%	NA	60%	5%	18%
Arenz et al 2009[22]	42%**	NA	54%	7%	2%
Ariyasriwatana 2003[20]	23.9%	56%	62.2%	NA	0.6%

*<1 year; **<2 years. NA= Data not available.

normal children. The finding is in agreement with other studies.[3,6] In a study in South Africa, low weight for age z score was associated with increased mortality with a 35% increase in OR for every standard deviation below expected weight for age.[24] In addition, with low weight for age z score there was double the risk of readmission to hospital.[24] Malnourished children have severe complications in measles due to multiple impairments in their immune system and prolonged excretion of measles virus.[4] Furthermore, measles contributes to malnutrition and ill health due to protein losing enteropathy, increased metabolic demand, decreased food intake and the hospitalised children may further show reduction in weight and delayed recovery.[4]

In the current study population, non-vaccinated children had a significantly higher odds of death compared to children who had received at least one dose of measles vaccine which is similar to other studies in hospitalised children and extensive review of epidemiological studies from the community.[8,25] This is because vaccinated children do not have severe measles.[25] Furthermore, measles vaccination has added beneficial effect on reducing child mortality not only from measles but also from other causes.[26]

In the current study significant proportion of children were non-vaccinated which is similar to studies from other cities of Pakistan.[7,8,12,15,17] Also, substantial numbers of children with measles (26%) were age <9 months . These infants represent secondary cases rather than index cases and are at risk of complications of measles because of higher exposure to infection at home and are also at risk of long-term devastating neurological consequences of measles.[2] Pakistan immunization coverage for first dose of measles vaccine has been increased from 57% in 2000 to 76% in 2017, whereas the coverage for the second dose has improved from 30% in 2009 to 45% in 2017.[2] Many supplementary immunisation activities have also been done, but the vaccination is still far from optimal and needs to be improved to ≥90% nationally and ≥80% in every district of Pakistan to increase the herd immunity to eradicate measles which will also help in preventing measles in infants.[2] Lower age of infection in children occurs in low population immunity areas, higher birth rate and low socioeconomic conditions.[4] Another significant feature was that measles occurred in 21% of those vaccinated with one dose and 30% of those vaccinated with two doses which is similar to reports from other parts of the country.[21,27] Though the vaccine has a high sensitivity and specificity in preventing measles, but measles can occur in vaccinated children because of primary or secondary vaccine failure.[4,21,27,28] Primary vaccine failure means failure to seroconvert after vaccination either because of problem with the maintenance of the cold chain of vaccine, administration problems or the host, and secondary vaccine failure means waning immunity after seroconversion.[28] Hence, there is a dire need to improve vaccination coverage along with the pathway from the vaccine procurement till administration to improve vaccination and its efficacy to eliminate measles.[2,28] As preventing measles through vaccination result in 58 times more economic benefit,[5] the commitment of politicians, government, health professional and public has to be enhanced.[2,28] Further, the current government policy on measles vaccination and strategies to implement measles vaccination in remote areas need to be reviewed and additional supplementary immunisation similar to polio vaccination campaign may be arranged to increase herd immunity.[4,28]

The current study reduced the effects of confounders by conducting multivariate analyses which is its strength.

The current study has some limitations also. It collected information for admitted children from a single centre and the data may not be representative of the whole country. The data was collected by review of the medical records of admitted children with complications of measles over 5 years and were based on documentation by the treating physicians. There was no control group of non-complicated measles cases for comparison. Serological data to confirm measles diagnosis and duration of complication from measles vaccination was not available.

Conclusion

The case fatality rate of complications of measles was 17%. Half of the children were vaccinated and had complications of measles, whereas the other half were non-vaccinated. Encephalitis, non-vaccination and under-nutrition were significantly associated with mortality in children with complications of measles.

Disclaimer: None.

Conflict of interest: None.

Source of Funding: None.

References

1. WHO. New measles surveillance data from WHO. [Online] 2014 [Cited 2019 Jan 01]. Available from: URL: https://www.who.int/immunization/newsroom/new-measles-data-august-2019/en/.
2. Mere M, Goodson J, Chandio A, Rana M, Hasan Q, Teleb N, et al. Progress Toward Measles Elimination — Pakistan, 2000–2018. Morb Mortal Wkly Rep 2019; 68: 505-10.
3. Bester JC. Measles and measles vaccination: a review. JAMA pediatr 2016; 170: 1209-15.
4. Moss WJ. Measles. The Lancet 2017; 390: 2490-502.

5. Portnoy A, Jit M, Ferrari M, Hanson M, Brenzel L, Verguet S. Estimates of case-fatality ratios of measles in low-income and middle-income countries: a systematic review and modelling analysis. Lancet Global Health 2019; 7: e472-e81.
6. Javed T, Bibi A, Chishti AL, Siddique K. Morbidity and Mortality Pattern of Hospitalized Children with Measles at Mayo Hospital, Lahore (Epidemic 2013). Ann King Edward Med Uni 2014; 20: 55-60.
7. Haq M, Masood N, Sharif M, Asghar R. Review of cases admitted in Paediatric department, Benazir Bhutto Hospital,Rawalpindi during epidemic 2013. Professional Med J 2015; 22: 1116-21.
8. Mushtaq A, Naz S, Bari A, Masood T. Measles in children: still a problem today. Pak J Med Health Sci 2012; 6: 755-8.
9. WHO. Epi Info software. [Online] 2014 [Cited 2019 Jan 01]. Available from: URL: https://www.who.int/ncds/surveillance/steps/resources/EpiInfo/en/.
10. WHO. Integrated Management of Childhood Illness; Chart Booklet. [Online] 2014 [Cited 2019 Jan 01]. Available from: URL: https://apps.who.int/iris/bitstream/handle/10665/104772/9789241506823_Chartbook_eng.pdf?sequence=16.
11. Hussain S, Yasir M, Tarar SH. Measles; Demographic profile and associated morbidities of measles cases admitted in a teaching Hospital. Pak Armed Forces Med J 2016; 66: 92-7.
12. Siddiq M, Saeed M. Study of measles cases reported to District Headquarter hospital, Bahawalnagar. Pak Pediatr J 2006; 30: 16-22.
13. Aurangzeb B, Nisar YB, Hazir T, Burki F, Hassan M. Clinical outcome in children hospitalized with complicated measles. J Coll Physicians Surg Pak 2005; 15: 547-51.
14. Rehman A, Siddiqui T, Idris M. Clinical outcome in measles patients hospitalized with complications. J Ayub Med Coll Abbottabad 2008; 20: 14-6.
15. Habibullah S, Ashraf J, Shakeel AAM. Case-control study for measles outbreak in a tertiary care hospital. Pak J Med Res 2016; 55: 7-10.
16. Khan F, Gandapur AJ, Ali I, Zeb R, Ahmad W. Demographic and Clinical profile of children hospitalised with measles infection in Peshawar. Khyber Med Uni J 2019; 11: 79-84.
17. Oyefolu AOB, Oyero OG, Anjorin AA, Salu OB, Kabir'O A, Omilabu SA. Measles morbidity and mortality trend in Nigeria: A 10-year hospital-based retrospective study in Lagos State, Nigeria. J Microbiol Infect Dis 2016; 6: 12-8.
18. Donas A, Marty-Nussbaumer A, Roost HP, Neuhaus TJ. Measles epidemic in a highly developed country: low mortality, high morbidity and extensive costs. Klinische Padiatrie 2014; 226: 13-8.
19. Onoja A, Adeniji A, Faneye A. Measles complications in a Nigerian hospital setting. Clin Rev Opin 2013; 5: 18-23.
20. Ariyasriwatana C, Kalayanarooj S. Severity of measles: a study at the Queen Sirikit National Institute of Child Health. J Med Assoc Thailand 2004; 87: 581-8.
21. Ameer M, Aziz S, Ehsan S, Kulsoom U. Frequency of Immunisation Status, Complications and Outcome in Children Admitted with Measles in Public and Private Sector Hospitals of Karachi. Ann Abbasi Shaheed Hospital Karachi Med Dent Coll 2018; 23: 21-8.
22. Arenz S, Fischer R, Wildner M. Measles outbreak in Germany: clinical presentation and outcome of children hospitalized for measles in 2006. Pediatr Infect Dis J 2009; 28: 1030-2.
23. Ariyasriwatana C. Trend of measles morbidity in Thailand. J Med Assoc Thailand 2003; 86: S707-18.
24. le Roux M, Nuttall J, Eley S. South African measles outbreak 2009-2010 as experienced by a paediatric hospital. South Afr Med J 2012; 102: 760-4.
25. Wolfson LJ, Grais RF, Luquero FJ, Birmingham ME, Strebel PM. Estimates of measles case fatality ratios: a comprehensive review of community-based studies. Int J Epidemiol 2009; 38: 192-205.
26. Fisker AB, Rodrigues A, Martins C, Ravn H, Byberg S, Thysen S, et al. Reduced all-cause child mortality after general measles vaccination campaign in rural Guinea-Bissau. Pediatr Infect Dis J 2015; 34: 1369-76.
27. Khan N, Faquih E, Hasan S. Increased incidence of measles in vaccinated population of Pakistan. J Pak Med Assoc 2015; 65: 1244-7.
28. Islam A, Younas Z, Qadri KFI, Alelwani W, Rauf M, Qadri I. The Battle against Measles in Pakistan-the Current Scenario. Gastro Med Res 2019 ;3: 1-3.