

Association between Immunization Status and Encephalitis in Pediatric Measles Cases

Aneeza Nawaz, Rashid Nawaz

ABSTRACT:

Objective: To examine the association between measles immunization status and encephalitis among hospitalized children aged 1–5 years with measles.

Study Design and Setting: Analytical cross-sectional study conducted in the Department of Pediatric Medicine, Allied Hospital, Faisalabad.

Methodology: Total 133 children aged 1–5 years with clinically compatible measles were enrolled. Children with chronic systemic disease, immunocompromised status, or hereditary syndromes were excluded. Immunization status was verified from the EPI vaccination card. Measles case classification followed WHO surveillance criteria; measles-specific IgM and/or RT-PCR was used for laboratory confirmation. Encephalitis was defined by sustained altered mental status with supportive neurological features. Pearson chi-square testing was used for the primary 2×2 comparison because expected cell counts were adequate; two-sided Fisher exact testing was reported as a sensitivity analysis. Statistical significance was defined as $p < 0.05$.

Results: Mean age was 3.12 ± 1.18 years. Of 133 children, 46 (34.6%) were fully immunized and 87 (65.4%) were un-immunized/incompletely immunized. Encephalitis occurred in 21/133 children (15.8%; 95% CI 10.6%–22.9%): 3/46 fully immunized children (6.5%) and 18/87 un-immunized/incompletely immunized children (20.7%). The crude sample OR was 3.74 with a conditional exact 95% CI of 0.996–20.81; the crude PR/RR was 3.17 (95% CI 0.95–8.32) and the RD was 14.2 percentage points (95% CI 1.0–24.7). Pearson chi-square $p = 0.033$; two-sided Fisher exact $p = 0.044$. Delayed presentation (> 7 days) was also associated with encephalitis in unadjusted analysis.

Conclusion: Among hospitalized pediatric measles cases, un-immunized/incompletely immunized status was associated with a higher observed frequency of encephalitis than full immunization.

Keywords: Measles; Encephalitis; Immunization; Vaccination; Child.

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INTRODUCTION:

Measles is a highly contagious vaccine-preventable viral disease caused by measles virus, an enveloped single-stranded RNA virus of the genus Morbillivirus. Despite availability of an effective vaccine, measles outbreaks continue to occur because of suboptimal vaccine coverage, delayed or missed immunization, population movement, vaccine hesitancy, and disruption of routine health services. Transmission occurs mainly through respiratory droplets and airborne particles, including during the period before the characteristic rash appears.¹

The typical clinical course begins with fever, cough, coryza, conjunctivitis, and Koplik spots, followed by a generalized maculopapular rash. Measles is a systemic infection and may be complicated by pneumonia, diarrhea, otitis media, keratitis, malnutrition, febrile seizures, encephalitis, and death.² Reviews also emphasize acute complications, post-measles immune suppression, and delayed neurological consequences.^{3,4} Neurological involvement is among the most serious complications of measles. Acute measles encephalitis may present with altered consciousness, lethargy, seizures, ataxia, focal neurological deficits, and cerebrospinal-fluid pleocytosis. Although less common than respiratory and gastrointestinal complications, encephalitis may be associated with prolonged hospitalization, epilepsy, neurodevelopmental disability, and mortality.^{5,6} Immunization is an important determinant of susceptibility to measles and may also be associated with disease severity. Breakthrough measles can occur in vaccinated individuals, but severe complications are more frequently reported in unvaccinated or under-vaccinated populations.⁷ Measles-containing vaccines are highly effective in preventing infection and transmission when administered according to the

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recommended schedule.^{8,9} In Pakistan and other low- and middle-income settings, gaps in routine immunization, missed opportunities, difficulties with vaccine access, inadequate documentation, poverty, and other health-system barriers can contribute to measles outbreaks. Hospital-based local data are therefore useful for describing the burden of severe complications among children who require medical care. Beyond immunization status, factors such as nutritional status, delayed presentation, household crowding, parental education, and access to primary care may influence measles outcomes. These factors are particularly relevant in young children, who depend on caregivers for timely vaccination and treatment. The present study aimed to examine the association between immunization status and encephalitis among hospitalized pediatric measles cases aged 1–5 years. The analysis was intended to describe an association and not to establish that immunization status independently caused or prevented encephalitis.

METHODOLOGY:

This analytical cross-sectional study was conducted in the Department of Pediatric Medicine, Allied Hospital, Faisalabad, from 16 October 2025 to 15 April 2026 after approval from the institutional ethical review committee (Ref No. 48.ERC/FMU/2023-24/517; approval date: 16 October 2024). Written informed consent was obtained from parents or guardians before enrollment, and participant confidentiality was maintained throughout data collection and analysis. A total of 133 children were included. The original sample size was calculated using the WHO single-proportion approach with a 95% confidence level, 6% absolute precision, and an expected encephalitis frequency of 14.5% among children with measles. No separate *a priori* sample-size calculation was performed for the primary two-group comparison of encephalitis by immunization status; therefore, the study may have had limited power and precision for that association. Non-probability consecutive sampling was used. Children aged 1–5 years of either sex who met the clinical definition of measles were eligible. Immunization status was verified from the EPI card or other available vaccination record. Measles was classified using WHO surveillance criteria. A clinically compatible measles case was defined as fever with a generalized maculopapular non-vesicular rash and at least one of cough, coryza, or conjunctivitis, or a case clinically suspected as measles by the treating physician. Laboratory confirmation, when available, was based on measles-specific IgM and/or detection of measles virus RNA by RT-PCR. The analytic dataset did not contain a separate variable identifying which enrolled children had laboratory-confirmed measles; therefore, the proportion laboratory-confirmed could not be quantified. Immunization status was classified as fully immunized when age-appropriate measles-containing vaccine doses were documented, and as un-immunized/incompletely immunized when no dose or an incomplete age-appropriate schedule

was documented. Encephalitis was identified using an accepted clinical framework requiring sustained altered mental status with supportive neurological features; CSF pleocytosis was supportive when lumbar puncture was clinically indicated and not contraindicated.

Children with major chronic systemic disease such as congenital heart disease or chronic renal disease, documented immunocompromised status, or hereditary syndromes that could materially influence infection severity or neurological outcome were excluded before enrollment. The analytic dataset contained enrolled participants only and did not include a screening log; consequently, the number of children screened or excluded by individual criterion could not be reported. Demographic and clinical information was recorded on a predesigned proforma using the same operational definitions for all enrolled children, including age, sex, weight, duration of measles illness before presentation, residence, immunization status, monthly family income, maternal education, and encephalitis status. Delayed presentation was defined *a priori* for analysis as presentation more than 7 days after onset of measles illness. Each child underwent general and neurological examination by the pediatric team. Level of consciousness, seizures, lethargy, ataxia, and other neurological manifestations were documented in children with suspected encephalitis. CSF examination and laboratory measles confirmation were used when clinically indicated or available. Data were analyzed using SPSS version 25.0. Quantitative variables were summarized using mean $\pm$ SD; distributional form was additionally assessed with the Shapiro–Wilk test, and median (IQR) was reported for variables showing evidence of non-normality. Categorical variables were summarized as frequency and percentage. For the primary 2 $\times$ 2 comparison of immunization status with encephalitis, Pearson chi-square testing was used because expected cell counts were adequate ($\chi^2=4.543$; $p=0.033$), and the two-sided Fisher exact test ($p=0.044$) was reported as a small-sample sensitivity analysis. The crude sample odds ratio (OR) was accompanied by a conditional exact 95% CI; the prevalence/risk ratio (PR/RR) and absolute risk difference (RD) with 95% CIs were also reported. The RR CI used a log-adjusted method and the RD CI used the Newcombe method. Exploratory stratum-specific immunization effects were summarized with exact OR CIs, and heterogeneity across strata was assessed using the Tarone-adjusted Breslow–Day test rather than comparing subgroup-specific *p*-values. Because only 21 encephalitis events occurred, subgroup and interaction analyses were considered exploratory and a stable multivariable model was not supported by the available data. Statistical significance was defined as $p<0.05$.

RESULTS:

A total of 133 children with measles were included. Mean age was 3.12 ± 1.18 years (range 1–5 years), with median 3.08 years (IQR 2.07–4.15); age showed evidence of non-

normality on Shapiro–Wilk testing. Forty-nine children (36.8%) were aged 1–2 years and 84 (63.2%) were aged 3–5 years. There were 76 males (57.1%) and 57 females (42.9%). Mean weight was 12.66 ± 2.83 kg, with median 12.4 kg (IQR 10.6–14.9), and did not show evidence of departure from normality. Mean duration of measles illness before presentation was 6.83 ± 2.17 days, with median 6.6 days (IQR 5.1–8.4); duration showed evidence of non-normality. Regarding residence, 82 children (61.7%) were from rural areas and 51 (38.3%) from urban areas. Seventy-one families (53.4%) had a monthly income <25,000 PKR, 43 (32.3%) had an income of 25,000–50,000 PKR, and 19 (14.3%) had an income >50,000 PKR. Maternal education was recorded as uneducated in 58 (43.6%), primary in 37 (27.8%), middle in 22 (16.5%), and matric or above in 16 (12.0%). Forty-six of 133 children (34.6%) were fully immunized according to available EPI vaccination documentation, whereas 87 (65.4%) were un-immunized / incompletely immunized. Encephalitis occurred in 3/46 fully immunized children (6.5%) and 18/87 un-immunized / incompletely immunized children (20.7%). The crude sample OR was 3.74; its conditional exact 95% CI was 0.996–20.81. The corresponding crude PR/RR was 3.17 (95% CI 0.95–8.32), and the absolute RD was 14.2 percentage points (95% CI 1.0–24.7 percentage points). These estimates are unadjusted and imprecise because of the small number of events in the fully immunized group.

Overall, 21/133 children (15.8%; Wilson 95% CI 10.6%–22.9%) were classified as having encephalitis and 112/133 (84.2%) were not. Altered level of consciousness was the most frequently recorded neurological manifestation, followed by seizures, lethargy, and ataxia. CSF pleocytosis was recorded in 8/21 children classified as having encephalitis (38.1%). Because the analytic dataset did not distinguish a negative CSF result from lumbar puncture not performed, this figure represents the proportion with recorded supportive CSF pleocytosis rather than the proportion undergoing CSF examination. The primary comparison showed a higher observed encephalitis frequency in the un-immunized/incompletely immunized group (20.7%) than in the fully immunized group (6.5%). Pearson chi-square $p=0.033$ and two-sided Fisher exact $p=0.044$. The crude sample OR was 3.74, but the conditional exact 95% CI was wide (0.996–20.81); the crude PR/RR was 3.17 (95% CI 0.95–8.32) and the RD was 14.2 percentage points (95% CI 1.0–24.7). The magnitude of the point estimates should therefore be interpreted cautiously; these results describe an unadjusted association and do not establish an independent causal or protective effect. Exploratory subgroup analyses examined whether the crude immunization–encephalitis association was consistent across age, sex, residence, presentation timing, and income strata. Stratum-specific estimates were imprecise, and two strata contained zero encephalitis events among fully immunized children. Tarone-

adjusted Breslow–Day tests did not provide clear evidence of heterogeneity of the immunization OR by age (interaction $p=0.178$), sex ($p=0.327$), residence ($p=0.717$), delayed presentation ($p=0.509$), or income group ($p=0.846$). These analyses were exploratory because of the small number of outcome events.

Duration of illness before presentation was associated with encephalitis in unadjusted analysis. Among children presenting within 7 days, 9/89 (10.1%) had encephalitis, compared with 12/44 (27.3%) presenting after 7 days. The crude OR for delayed presentation was 3.30 (exact 95% CI 1.15–9.82), the crude RR was 2.70 (95% CI 1.23–5.68), and the RD was 17.2 percentage points (95% CI 3.6–32.5). Pearson chi-square $p=0.011$; two-sided Fisher exact $p=0.021$. Delayed presentation is therefore an important potential confounder of the crude immunization–encephalitis association. Encephalitis occurred in 15/71 children (21.1%) from families with monthly income <25,000 PKR and 6/62 (9.7%) from families with income =25,000 PKR. This unadjusted comparison was not statistically significant (Pearson $p=0.071$): crude OR 2.48 (exact 95% CI 0.84–8.40), RR 2.18 (95% CI 0.89–4.88), and RD 11.4 percentage points (95% CI -1.2 to 23.5). Exploratory ordinal trend analyses did not show a statistically significant trend for income category ($p=0.123$) or maternal education category ($p=0.225$). These analyses were not prespecified and should be interpreted cautiously. All subgroup analyses were exploratory and unadjusted. The observed immunization–encephalitis relationship should therefore not be interpreted as an independent effect within subgroups. Delayed presentation, socioeconomic circumstances, nutritional status, and access to care may contribute to the observed association.

DISCUSSION

This analytical cross-sectional study examined the association between immunization status and encephalitis among hospitalized children with measles. Encephalitis was identified in 21/133 children (15.8%), and its observed frequency was higher among un-immunized/incompletely immunized children than among fully immunized children. Encephalitis occurred in 20.7% of un-immunized / incompletely immunized children compared with 6.5% of fully immunized children, corresponding to a crude OR of 3.74 (95% CI 1.04–13.45). Because the study was cross-sectional and the estimate was unadjusted, this finding should be interpreted as an association rather than evidence that immunization status independently caused or prevented encephalitis. Pakistani hospital-based literature provides relevant local context. Ullah et al. reported that many hospitalized children with measles in Dera Ismail Khan were not immunized and documented neurological complications including encephalitis.⁹ Similarly, Kulsoom et al. described encephalitis among hospitalized children with measles at a tertiary-care pediatric center in Karachi.¹⁰ These reports demonstrate the continuing local burden of

Table 1. Baseline demographic, socioeconomic, immunization, and maternal-education characteristics of pediatric measles cases (n=133)

Variable	Frequency	Percentage
Age 1–2 years	49	36.8%
Age 3–5 years	84	63.2%
Male	76	57.1%
Female	57	42.9%
Rural residence	82	61.7%
Urban residence	51	38.3%
Fully immunized	46	34.6%
Un-immunized/incompletely immunized	87	65.4%
Monthly income <25,000 PKR	71	53.4%
Monthly income 25,000–50,000 PKR	43	32.3%
Monthly income >50,000 PKR	19	14.3%
Mother uneducated	58	43.6%
Primary education	37	27.8%
Middle education	22	16.5%
Matric and above	16	12.0%

Table 2. Frequency of encephalitis among pediatric measles cases with 95% confidence interval

Encephalitis status	Frequency	Percentage	95% CI for proportion
Present	21	15.8%	10.6%–22.9%
Absent	112	84.2%	77.1%–89.4%
Total	133	100.0%	—

Table 3. Crude association between immunization status and encephalitis with small-sample confidence intervals

Immunization status	Encephalitis n/N (%)	Crude OR (exact 95% CI)	Crude PR/RR (95% CI)	RD, percentage points (95% CI)	p-value
Fully immunized	3/46 (6.5%)	Reference	Reference	Reference	—
Un-/incompletely immunized	18/87 (20.7%)	3.74 (0.996–20.81)	3.17 (0.95–8.32)	14.2 (1.0–24.7)	Pearson 0.033; Fisher 0.044
Total	21/133 (15.8%)	—	—	—	—

Table 4. Exploratory stratum-specific immunization–encephalitis associations and interaction tests

Subgroup	Stratum	Fully immunized: encephalitis n/N (%)	Un-/incompletely immunized: encephalitis n/N (%)	Crude OR (exact 95% CI)	Interaction p*
Age	1–2 years	0/22 (0.0%)	6/27 (22.2%)	8 (1.06–8)	0.178
	3–5 years	3/24 (12.5%)	12/60 (20.0%)	1.74 (0.41–10.59)	
Sex	Male	3/28 (10.7%)	10/48 (20.8%)	2.17 (0.49–13.49)	0.327
	Female	0/18 (0.0%)	8/39 (20.5%)	8 (0.86–8)	
Residence	Rural	2/27 (7.4%)	14/55 (25.5%)	4.21 (0.85–41.22)	0.717
	Urban	1/19 (5.3%)	4/32 (12.5%)	2.53 (0.23–133.56)	
Presentation	≤7 days	2/34 (5.9%)	7/55 (12.7%)	2.31 (0.41–24.21)	0.509
	>7 days	1/12 (8.3%)	11/32 (34.4%)	5.58 (0.65–270.17)	
Income	<25,000 PKR	2/20 (10.0%)	13/51 (25.5%)	3.04 (0.59–30.57)	0.846
	≥25,000 PKR	1/26 (3.8%)	5/36 (13.9%)	3.96 (0.40–198.20)	

*Interaction p-values are Tarone-adjusted Breslow–Day tests for homogeneity of odds ratios. Exact conditional OR confidence intervals are shown; infinity reflects zero encephalitis events in the fully immunized stratum. Analyses are exploratory

severe measles complications, although differences in population, case definitions, and referral patterns limit direct numerical comparison. International hospital-based studies have likewise reported more severe measles outcomes among unvaccinated or incompletely vaccinated children. Mawlood et al. described differences in clinical characteristics and outcomes according to vaccination status in children with measles in Iraq.¹¹ These observations are directionally

consistent with the present unadjusted association, but they do not establish that immunization status alone explains encephalitis risk. Alsulaiman et al. described hospitalized pediatric measles cases during the 2023 outbreak in Northern Jordan and reported a high proportion of children without complete vaccination.¹² In the present cohort, 65.4% of hospitalized measles cases were un-immunized/incompletely immunized, underscoring the importance of gaps in routine

immunization among children presenting with measles.

Bursal et al. reported clustering of severe measles outcomes among unvaccinated children in Türkiye.¹³ Although intensive-care admission and mortality were not primary outcomes in the present study, the findings provide broader context for the relationship between vaccination status and measles severity. The present study specifically evaluated encephalitis and should not be extrapolated to other severe outcomes. Mathis et al. reported that many measles cases in the 2025 United States outbreak occurred among unvaccinated individuals or those with unknown vaccination status.¹⁴ Differences in health systems and outbreak settings limit direct comparison, but the findings illustrate how immunity gaps can sustain measles transmission. The lower observed frequency of encephalitis among fully immunized children should be interpreted cautiously. Evidence from systematic reviews supports the effectiveness of measles-containing vaccines in preventing measles infection,¹⁵ but the present study enrolled only children who already had measles and was not designed to estimate vaccine effectiveness against infection or to prove protection against encephalitis. Socioeconomic and access-related factors may also influence vaccination and clinical outcomes. Comfort et al. described associations between subnational vaccine coverage, migration, and measles occurrence in Iraq.¹⁶ In the present study, rural residence was more common overall, but its unadjusted association with encephalitis was not statistically significant. No causal inference regarding access to vaccination or referral can be drawn from these data.

Low family income was common in this cohort. Encephalitis occurred in 21.1% of children from families with monthly income <25,000 PKR and 9.7% of those with higher income, but this difference was not statistically significant ($p=0.071$). Income should therefore be viewed as a potential contextual factor rather than an established determinant of encephalitis in this study. Most children were aged 3–5 years. This age group should ordinarily have received age-appropriate measles-containing vaccine doses under routine immunization schedules. The age distribution therefore highlights the importance of timely vaccination and catch-up strategies, although the present hospital-based sample cannot estimate population-level vaccine coverage. Three fully immunized children developed encephalitis. Breakthrough measles and complications can occur despite documented vaccination, and possible explanations include primary vaccine failure, recording error, variation in immune response, or intense exposure. These possibilities were not measured in the present study and should not be treated as demonstrated mechanisms. Evidence on long-term measles immunity also emphasizes the importance of vaccination timing and schedule completion.¹⁷ However, antibody titers and timing of individual vaccine doses were not assessed in this study, so no conclusions can be drawn regarding waning immunity or immunogenicity in the enrolled children.

Mohamud et al. reported more complications among unvaccinated than vaccinated hospitalized children with measles in Somalia.¹⁸ This is broadly consistent with the present finding of a higher observed encephalitis frequency among children without complete immunization, while the current analysis remains crude and subject to confounding. Orhan et al. described measles in a migration-affected population in south-eastern Türkiye and highlighted the importance of under-immunized communities.¹⁹ Migration was not measured in the present study. Rural residence, income, and incomplete immunization should therefore be interpreted as separate recorded characteristics rather than as evidence of a specific migration-related mechanism.

Measles-associated central nervous system disease can be severe. Reports of encephalitis in immunocompromised children illustrate this potential complication,²⁰ although immunocompromised children were excluded from the present study. Consequently, those case reports provide clinical context but are not directly comparable with this cohort. Rettenbacher-Riefler et al. described measles seroprevalence in young children and emphasized vulnerability during early childhood.²¹ In the present study, 36.8% of participants were aged 1–2 years. This supports attention to timely age-appropriate immunization but does not allow inference regarding individual antibody protection.

Ghosh et al. reviewed biological, programmatic, and population-level factors influencing measles vaccine efficacy, effectiveness, and immunogenicity.²² Such factors provide useful context for interpreting immunization data, but they were not directly measured in this study. The present results therefore support only an observed association between recorded immunization status and encephalitis. Delayed presentation was also associated with encephalitis: 27.3% of children presenting after >7 days had encephalitis compared with 10.1% presenting within 7 days. The crude OR was 3.30 (exact 95% CI 1.15–9.82), the crude RR was 2.70 (95% CI 1.23–5.68), and the absolute RD was 17.2 percentage points (95% CI 3.6–32.5). Because delayed presentation may be related both to access to care and to illness severity, it is an important potential confounder. The lack of multivariable adjustment means that the independent contribution of immunization status cannot be separated from delayed presentation and other factors.

Limitations: This was a single-center, hospital-based analytical cross-sectional study, which may over-represent more severe measles cases and cannot establish temporality or causality. The sample size was based on estimation of a single proportion rather than an a priori two-group comparison, so the primary association and interaction analyses may be underpowered and their confidence intervals are wide. Immunization status depended on available vaccination documentation, so misclassification is possible. The analytic dataset did not identify which measles cases were laboratory-confirmed and did not distinguish a negative

CSF result from lumbar puncture not performed; therefore, verification and outcome-classification bias cannot be excluded. The screening log and number excluded by each criterion were not available in the analytic dataset. Only 21 encephalitis events occurred, including three among fully immunized children, limiting multivariable adjustment and making subgroup estimates unstable. Delayed presentation was associated with encephalitis and may confound the observed relationship, while nutritional status, access to care, and other clinical determinants may contribute residual confounding. These limitations preclude interpretation of immunization status as an independent causal or protective factor.

CONCLUSION

Among hospitalized children aged 1–5 years with measles, un-immunized/incompletely immunized status was associated with a higher observed frequency of encephalitis than full immunization. Delayed presentation beyond 7 days was also associated with encephalitis in unadjusted analysis. Because of the cross-sectional design and absence of multivariable adjustment, these findings do not establish an independent causal or protective effect. The results support continued emphasis on timely measles immunization, early recognition of neurological symptoms, and prompt pediatric evaluation.

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Authors Contribution:

Aneeza Nawaz: Conception and Design, acquisition of data analysis

Rashid Nawaz: Interpretation of data, drafting and critical revision, final approval of the version to be published

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