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Original Research Article

Association between childhood vaccination status and hospitalization due to vaccine-preventable diseases in children

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Abstract: ***Background:*** Vaccine-preventable diseases remain a significant cause of morbidity and hospitalization for children in LMICs, such as Pakistan. Low immunisation status and nutritional vulnerability can predispose to increased risk of serious illness leading to admission to hospital. In this study, the relationship between childhood immunization status and hospitalization for vaccine-preventable diseases was assessed. ***Methods***: In this prospective study 300 children admitted to a tertiary care hospital in Pakistan were included. Demographic, socioeconomic, nutritional, diagnostic and clinical outcome data was recorded. Vaccination status was grouped as full, partial, or none (for age). Vaccine-preventable disease-related hospitalization was the primary outcome. The data was analyzed by using IBM SPSS Statistics version 27. Univariable and multivariable binary logistic regression analysis were conducted. ***Results***: 112 (37.3%) admissions were due to vaccine preventable diseases. The percentage of children who were fully vaccinated for children hospitalized for VPD was 25.0%, compared to 69.1% of children admitted for reasons other than VPD. However, total adjustment, partial vaccination had 4-fold higher odds (aOR 4.12, 95% CI 2.18–7.79) of VPD hospitalization, and children who were not vaccinated had more than 8-fold higher odds (aOR 8.34, 95% CI 3.78–18.41). Undernutrition also was independently related to VPD hospitalization. Admission to VPD was linked to increased length of hospital stay, complications, increased use of the intensive care unit and mortality. ***Conclusion***: Incomplete vaccination was strongly associated with VPD-related hospitalization and adverse clinical outcomes. Strengthening routine immunization and nutritional support may substantially reduce preventable pediatric hospital burden in Pakistan.

Keywords: Childhood vaccination; Vaccine-preventable diseases; Hospitalization; Immunization status; Undernutrition; Pakistan

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INTRODUCTION

Vaccination is among the most successful public health interventions for lowering the morbidity, disability, hospitalisation and mortality rates of children due to infectious diseases. At a global level, vaccines have saved millions of lives and vaccination programmes of the last 50 years have been estimated to have saved over 150 million lives, most of which are attributed to the benefits for infants. However, vaccine-preventable diseases (VPDs), such as measles, pertussis, diphtheria, pneumococcal disease, rotavirus infection, poliomyelitis and tuberculosis, still result in significant morbidity for children, especially in low and middle income countries, where vaccine coverage is sub-optimal [1].

Children who are not fully immunized or have missed

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certain vaccine doses are at risk not just of infection but of serious disease leading to hospitalization [2]. Vaccine preventable infections can lead to pneumonia, encephalitis (brain inflammation), dehydration, respiratory problems, neurological issues (inflammation of the brain), long-term disability and death. Measles is an important example, as complications and deaths are more likely among children who are not or under-vaccinated, and especially those in countries or communities with less robust health systems. Therefore, hospitalizations for a VPD can serve as a valuable indicator of the provision of routine immunization services and missed opportunities for disease prevention [3].

Pakistan still has huge challenges to ensure the uniform immunization for the children [4]. While the national Expanded Programme on Immunization (EPI) has significantly increased access to routine vaccines, socioeconomic disadvantages, parental education, limited access to health services, geographic barriers, vaccine hesitation, population movement and interruptions to immunization services cause disparities. Pakistan has been identified as one of the countries with a high burden of un- or under-vaccinated children, and susceptible populations where outbreaks of VPD and severe childhood infections can occur [5]. These challenges are of special significance as South Asia continues to contribute a significant proportion of child deaths, many of which are preventable or treatable [6].

Evaluation of immunisation status in hospital is helpful in quantifying the clinical consequences of incomplete immunisation. The immunisation status of children admitted with vaccine preventable diseases can vary significantly from other children admitted for other reasons and knowing this relationship could help target high risk groups and enhance prevention action [7,8]. In Pakistan, however, local evidence to directly test for an association between regular childhood vaccination coverage and hospitalization due to VPDs is limited. This connection is important for reinforcement of immunization counseling and attainment of age-appropriate vaccination coverage as well as opportunities for vaccination in community and health care settings [9].

To this end, the present study was conducted to establish any association between vaccination status and vaccination preventable diseases (VPD) related hospitalizations among children in Pakistan and to compare the incidence of VPD related hospitalizations amongst full vaccination, partial vaccination and under immunized children for age, accordingly.

MATERIALS AND METHODS

Study design and setting

The study was prospective, observational and was carried out in the paediatric department of a tertiary care teaching hospital in Pakistan during a predetermined study period. The study compared the rates of hospitalization for vaccine-preventable diseases (VPDs) in children according to their vaccination status. Children presenting to the ED or to Peds Inpatient Services, and needing hospital admission, were screened for eligibility.

Study population

Children from 1 month to 15 years old admitted to the hospital during the study period were included. Vaccination status was determined based on the child's age and the vaccine coverage as per the Expanded Programme on Immunization (EPI) of Pakistan. Those children with incomplete clinical records, uncertain vaccination status (either due to history or vaccination documents unavailable) or those admitted only for elective procedures were excluded. The principal diagnosis for admission of the children in the hospital was used to classify the children as having a vaccine-preventable or a non-vaccine-preventable condition for the main analysis. The type of sampling and the number of samples. A non-probability consecutive sampling technique was used. The children that were admitted into the hospital during the study period were consecutively ordered until the set sample size was reached. All children eligible to admission during the study period were consecutively admitted until the required sample size was reached. The sample size was determined based on a hypothesized difference in proportion of children hospitalized for VPD among fully vaccinated children and those not fully vaccinated with a 95% confidence level, 80% statistical power, and 5% level of significance. Another proportion was given for information not complete or not verifiable.

Data collection

A structured proforma was used to collect the data. Data gathered were age, sex, residence, education level of parents, socioeconomic status of the family, sibling count, nutritional status, breastfeeding history, previous hospitalizations, and pertinent chronic diseases. The presenting symptoms, duration of illness, diagnosis on admission, complications, level of care, length of hospital stay and in-hospital outcome were also recorded. Laboratory, microbiological and radiological results were documented if applicable as evidence for the final diagnosis.

Assessment of vaccination status

Vaccination status was determined from the EPI vaccination card whenever available. When the card was unavailable, detailed caregiver history was obtained and cross-checked with available health records where possible. Children were classified into three groups:

a) Fully vaccinated for age: all EPI vaccines and doses appropriate for the child's age had been received.
b) Partially vaccinated: at least one recommended vaccine dose had been received, but one or more age-appropriate doses were missing.

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c) Unvaccinated: no routine childhood vaccine had been received.

Vaccination status was assessed relative to the child's age rather than simply by the absolute number of doses received.

Definition of vaccine-preventable disease

Routine childhood immunization schedule vaccine-preventable diseases included diseases for which an effective vaccine was available, and diseases that were otherwise recommended for childhood vaccination in Pakistan. These included where clinically appropriate, tuberculosis, poliomyelitis, diphtheria, pertussis, tetanus, hepatitis B, Haemophilus influenzae type b disease, pneumococcal disease, rotavirus gastroenteritis, measles and typhoid fever. The diagnosis was based on the conventional clinical criteria, and where appropriate and possible, laboratory and/or radiological confirmation. In diseases that have typical clinical syndromes, final diagnosis made by the treating pediatrician was used after reviewing the full clinical record. The main outcome was hospitalization for any vaccine preventable disease. Childhood immunization status (fully vaccinated, partially vaccinated, or unvaccinated for age) was the main exposure. ICU admission and development of complications, hospital stay, requirement of respiratory or circulatory support, and in-hospital death (if applicable) were other secondary outcomes.

Nutritional assessment

Standard pediatric methods were used for the measurement of weight and/or length/height. Nutritional status was determined using age-appropriate anthropometric indices using the WHO growth standards. Children were classified as being in the normal nutritional range, moderate or severe undernutrition based on the weight-for-age, height-for-age or weight-for-height/length applicable for the case.

Statistical analysis

The IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA) software was used for data entry and analysis. All the continuous variables were evaluated for normality and are presented as mean ± SD when they were normally distributed, and median (IQR) when they were skewed. Frequencies and percentages were used to present the data on categorical variables. The Pearson chi-square test or Fisher's exact test was used to compare the proportion of children who were vaccinated to those who were not for both admissions with VPDs and non-VPDs. The independent-samples t-test or Mann–Whitney U test was used for the analysis of continuous variables, depending on the distribution of data. A binary logistic regression analysis was used to assess the relationship between vaccination status and hospitalization for VPD. Univariable analysis crude odds ratios with 95% confidence intervals were calculated. Those variables which were clinically relevant or with p-value <0.20 on univariable analysis were included in a multivariable logistic regression model. All odds ratios and 95% confidence intervals were adjusted for age, sex, socioeconomic status, parental education, nutritional status, and comorbidities. Collinearity and model fit were evaluated and prior to the final model interpretation. A two-tailed p value <0.05 was defined as a significant statistical difference.

RESULTS

Children admitted to hospital for vaccine preventable diseases were more likely to be from a socio-economically deprived household and rural areas (Table 1). The VPD group were more likely to have maternal education at or below primary level (66.1% vs 44.7%, p<0.001), and undernutrition (43.8% vs 23.9%, p<0.001). Additionally, affected children were more likely to have low socioeconomic status and larger household size, although this could be related to the potential of social vulnerability and nutritional disadvantage clustering with incomplete preventive care. Age, sex, chronic comorbidity and previous hospitalisation, however, were broadly similar across groups.

Table 1. Sociodemographic and clinical characteristics according to hospitalization due to vaccine-preventable disease

Variable	Overall (N=300)	Non-VPD hospitalization (n=188)	VPD hospitalization (n=112)	Test statistic	p-value
Age, years, mean ± SD	4.3 ± 3.4	4.5 ± 3.5	3.9 ± 3.1	t = 1.50	0.135
Male sex, n (%)	168 S(56.0)	103 (54.8)	65 (58.0)	$\chi^2 = 0.30$	0.584
Rural residence, n (%)	161 (53.7)	89 (47.3)	72 (64.3)	$\chi^2 = 8.11$	0.004
Maternal education ≤primary, n (%)	158 (52.7)	84 (44.7)	74 (66.1)	$\chi^2 = 12.88$	<0.001
Paternal education ≤primary, n (%)	136 (45.3)	75 (39.9)	61 (54.5)	$\chi^2 = 6.08$	0.014
Low socioeconomic status, n (%)	154 (51.3)	85 (45.2)	69 (61.6)	$\chi^2 = 7.55$	0.006
≥4 children in household, n (%)	137 (45.7)	76 (40.4)	61 (54.5)	$\chi^2 = 5.61$	0.018
Undernutrition, n (%)	94 (31.3)	45 (23.9)	49 (43.8)	$\chi^2 = 12.81$	<0.001
Exclusive breastfeeding for 6	173 (57.7)	116 (61.7)	57 (50.9)	$\chi^2 = 3.38$	0.066

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months, n (%)					
Chronic comorbidity, n (%)	47 (15.7)	31 (16.5)	16 (14.3)	$\chi^2 = 0.26$	0.612
Previous hospitalization, n (%)	56 (18.7)	31 (16.5)	25 (22.3)	$\chi^2 = 1.59$	0.207

Legend: VPD = vaccine-preventable disease; SD = standard deviation. The independent-samples t-test was used for continuous variables and Pearson's chi-square test for categorical variables.

The vaccination status was significantly and proportionately associated with VPD-related hospitalization, as shown in Table 2. Vaccination rates were significantly lower among VPD children (25.0%) than among non-VPD children (69.1%) with partial vaccination and complete non-vaccination rates higher among VPD admissions ($p<0.001$). As immunization completeness declined, the pattern grew even stronger and clear, suggesting a definite dose-response relationship between the reduction in immunization and increase in hospitalization for diseases. This result highlights the possible clinical significance of partially immunising children instead of finishing their age appropriate vaccination programs.

Table 2. Association between age-appropriate vaccination status and VPD-related hospitalization

Vaccination status	Overall (N=300)	Non-VPD hospitalization (n=188)	VPD hospitalization (n=112)	Test statistic	p-value
Fully vaccinated for age	158 (52.7)	130 (69.1)	28 (25.0)		
Partially vaccinated	94 (31.3)	44 (23.4)	50 (44.6)		
Unvaccinated	48 (16.0)	14 (7.4)	34 (30.4)		
Overall comparison				$\chi^2 = 59.10$	<0.001

Legend: Vaccination status was determined according to age-appropriate doses in the Pakistan routine immunization schedule. Pearson's chi-square test demonstrated a significant association between vaccination status and VPD-related hospitalization.

The most common vaccine preventable diagnoses were measles (30.4%) and pertussis and pneumococcal disease (both 24.0%). Measles was seen to be more concentrated among partially vaccinated and unvaccinated children, whereas pneumococcal and rotavirus disease were more evenly spread out among the various vaccination groups. There was significant variation in overall disease distribution with vaccination status ($p=0.027$), which may indicate that incomplete vaccination could not only affect the risk of hospitalization, but also the type of VPDs seen. The high levels of measles also underscore the ongoing importance of achieving and preserving high rates of routine immunization.

Table 3. Distribution of vaccine-preventable diseases among hospitalized children according to vaccination status

VPD diagnosis	Total (n=112)	Fully vaccinated (n=28)	Partially vaccinated (n=50)	Unvaccinated (n=34)
Measles	34 (30.4)	4 (14.3)	16 (32.0)	14 (41.2)
Pertussis	18 (16.1)	3 (10.7)	9 (18.0)	6 (17.6)
Pneumococcal disease	17 (15.2)	7 (25.0)	7 (14.0)	3 (8.8)
Rotavirus gastroenteritis	15 (13.4)	5 (17.9)	7 (14.0)	3 (8.8)
Tuberculosis	10 (8.9)	4 (14.3)	3 (6.0)	3 (8.8)
Typhoid fever	8 (7.1)	3 (10.7)	4 (8.0)	1 (2.9)
Diphtheria	5 (4.5)	1 (3.6)	2 (4.0)	2 (5.9)
Tetanus/other EPI-preventable disease	5 (4.5)	1 (3.6)	2 (4.0)	2 (5.9)

Children who were admitted with vaccine preventable diseases had a significantly more complex hospital course (see Table 4). They had a longer mean hospital stay (5.8 vs 3.9 days, $p<0.001$), higher complication rates (31.3% vs 13.3%, $p<0.001$), and more frequent ICU admission (18.8% vs 7.4%, $p=0.003$). The incidence of respiratory support and vasopressor use was also higher, further suggesting increased acute clinical severity in VPD admissions. This group also had higher in-hospital mortality (8.0% vs 2.1%, $p=0.020$), indicating that these infections were not only related to being hospitalized but also were linked to more severe outcomes.

Table 4. Clinical outcomes according to VPD-related hospitalization

Outcome	Non-VPD hospitalization (n=188)	VPD hospitalization (n=112)	p-value
Hospital stay, days, mean ± SD	3.9 ± 1.8	5.8 ± 2.7	<0.001
Any complication, n (%)	25 (13.3)	35 (31.3)	<0.001
ICU admission, n (%)	14 (7.4)	21 (18.8)	0.003
Respiratory support required, n (%)	18 (9.6)	26 (23.2)	0.001

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Inotropic/vasopressor support, n (%)	6 (3.2)	10 (8.9)	0.034
In-hospital mortality, n (%)	4 (2.1)	9 (8.0)	0.020
Discharged improved, n (%)	181 (96.3)	100 (89.3)	0.021

Legend: ICU = intensive care unit; SD = standard deviation. Independent-samples t-test was used for length of stay, Pearson's chi-square test for categorical variables with adequate expected counts, and Fisher's exact test when expected cell frequencies were small.

Vaccination status was the most significant factor that continued to be associated with hospitalization for VPD after adjustment for potential confounders (Table 5). Both partially vaccinated children and unvaccinated children had significantly increased odds of VPD admission compared to fully vaccinated children (aOR 4.12, 95% CI 2.18–7.79 and aOR 8.34, 95% CI 3.78–18.41, respectively; both p<0.001). Nutritional vulnerability also independently associated with hospitalization (aOR 1.91, p=0.025), suggesting that nutritional vulnerability might increase the risk of infection. Rural residence, parental education, socioeconomic status, and household size, in contrast, were no longer statistically significant post-adjustment, suggesting much of this effect may have been mediated by vaccination status and nutritional condition.

Table 5. Logistic regression analysis of factors associated with hospitalization due to a vaccine-preventable disease

Predictor	Crude OR (95% CI)	Wald χ^2	p-value	Adjusted OR (95% CI)	Wald χ^2	p-value
Fully vaccinated for age	Reference	—	—	Reference	—	—
Partially vaccinated	5.28 (2.95–9.45)	30.7	<0.001	4.12 (2.18–7.79)	18.9	<0.001
Unvaccinated	11.28 (5.48–23.21)	43.1	<0.001	8.34 (3.78–18.41)	27.6	<0.001
Rural residence	2.02 (1.25–3.27)	8.10	0.004	1.55 (0.90–2.66)	2.48	0.115
Maternal education ≤primary	2.41 (1.48–3.92)	12.7	<0.001	1.68 (0.96–2.95)	3.29	0.070
Low socioeconomic status	1.94 (1.21–3.12)	7.49	0.006	1.43 (0.82–2.50)	1.59	0.207
≥4 children in household	1.77 (1.10–2.84)	5.53	0.019	1.31 (0.77–2.22)	0.99	0.320
Undernutrition	2.48 (1.50–4.10)	12.7	<0.001	1.91 (1.08–3.37)	5.01	0.025
Exclusive breastfeeding for 6 months	0.64 (0.40–1.03)	3.37	0.066	0.76 (0.44–1.31)	0.98	0.322

Legend: A two-sided p <0.05 was considered statistically significant.

DISCUSSION

In the current study, a statistically significant relationship was found between the incomplete immunization status in childhood and hospitalization for vaccine preventable diseases (VPDs). Children who were admitted with VPDs were more likely to come from households that were rural and poor, and had less maternal education and undernutrition compared to those that were not admitted with VPDs. The results of the study agree with country immunization trends in Pakistan, which have shown an increase in the coverage of immunisation over time, but are not uniform among geographic and socioeconomic groups. According to the Pakistan Demographic and Health Survey 2017–18, 4% of children (aged 12–23 months) had not been immunized with any of the basic vaccines; there was significant regional variation and the coverage varied by the characteristics of the household [10].

The most significant result of the present study was the dose-response association between vaccination status and VPD-related hospitalization. Completed vaccinations for age was much more common in children who were admitted with VPDs than partial and complete non-vaccination. Completed vaccinations for age was significantly less common in children admitted with VPDs, compared with partial and complete non-vaccination. This is supported by recent evidence from Pakistan. In a case-control study conducted by Fazal et al., [11] in Rawalpindi and Islamabad, there were significantly greater odds of children suffering from measles who had never been vaccinated (odds ratio 8.2) [11]. This is very similar to the present adjusted analysis, which found that fully unvaccinated children had over eight times the risk of VPD-related hospitalization of fully vaccinated children.

In the current study, the highest number of VPD admissions were for measles, and this case cluster was especially strong in the partially vaccinated and unvaccinated children. This is also in line with recently published data from Sialkot on 323 confirmed cases of measles, wherein 60.4% of children were not vaccinated and 39.6% were vaccinated [12]. This research has also shown that unvaccinated children had a significantly higher prevalence of moderate and severe acute malnutrition. In both studies, a large proportion of the children were incompletely vaccinated, emphasizing the susceptibility that results from failure or delay in immunisation dosages, especially in areas where measles transmission is ongoing.

Another significant finding was the link between nutritional status and hospitalization in the VPD. The prevalence of undernutrition was significantly higher and persisted as an independent risk factor for the condition in children admitted to hospital with VPDs. Aurangzeb et al. conducted a study at Pakistan Institute of Medical Sciences and reported that there was a significant association of under nutrition and lack of measles

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vaccination with mortality as 47.8% of children eligible for measles vaccines were not vaccinated and 17% died while admitted to the hospital with measles complications [13]. These results support the notion that low nutritional status and suboptimal immunisation status may synergistically affect vulnerability to severe infection.

Children who were admitted with VPDs in the present study also had a more severe hospital course, with longer length of stay, increased hospital complications, increased use of the intensive care unit, increased use of respiratory support, and increased in-hospital mortality. Similar results were noted by Riaz ul Haq et al. in a tertiary care Measles cohort in Pakistan with 40.4% of children needing admission to the Intensive Care Unit, and a mortality rate of 14.4% of those admitted to the ICU. Significant association with pneumonia, diarrhea and overall outcome was observed with immunization status [14]. Although the authors did not look at measles specifically in their study, that one is in line with the general trend seen here: Inadequate immunization relates to both the presence of the disease, and worse clinical outcomes when seeking hospitalization.

Complications of measles have also been well documented from earlier observations in Pakistan where children were hospitalized for various complications. It was found that in a Rawalpindi cohort, pneumonia was the most common complication of measles and lack of awareness was an important barrier to child immunization [15,16,18]. The results are applicable to the current study since they indicate that the lack of vaccination may be a symptom of a general lack of awareness and access to preventive health care, not just the absence of a vaccine dose. This could also account for the fact that residence in rural areas and low levels of parental education were found to be significantly associated with the outcome of this study in the unadjusted model but were not significant when vaccination and nutritional level were adjusted for.

Zero-dose and under-vaccinated children continue to be public-health issues in Pakistan. Even with the improvement in routine immunization services in the country, WHO/UNICEF estimates for 2023 still show a large proportion of children as zero-dosed. In other countries, the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) have noted that there is an uneven distribution of children who are not receiving routine immunizations, with children clustered in “poor, rural, remote and fragile” areas [17,19]. This overall trend is in line with the social pattern of the present study, where children from rural and lower socio-economic statuses were more likely to be admitted to the VPD.

These relationships were further elaborated by the results of the multivariable analyses. After accounting for demographic and socioeconomic factors, partial vaccination was linked to about four times greater odds of VPD hospitalization compared to complete vaccination, and more than eight times greater odds of hospitalization compared to complete vaccination. By contrast, parental education, household size and socioeconomic status were no longer independently significant. This indicates that the impact of multiple social disadvantages might partly be mediated by lower rates of vaccination and poorer nutritional status. The pattern of dose-response from progressively incomplete vaccination coverage to hospitalization supports an epidemiological plausibility of this association, but the study design does not prove the individual-level vaccine effectiveness.

The results of the two studies together confirm the need for full and age-appropriate immunisation and nutrition support to control severe childhood infectious disease in Pakistan. The admission to the hospital should also be a time to review the immunization history, catch-up vaccines, discuss immunizations, and connect with ongoing EPI services upon discharge. These interventions might be significant for children born into socioeconomically and rurally disadvantaged families where missed vaccinations and delayed care use occur.

Limitations

There were some limitations of this study. The results may not be relevant to the entire pediatric population of Pakistan because of its single-center hospital-based study design, which may exclude children not requiring hospitalisation. Vaccination status was determined using vaccination cards where available and by caregiver recall where vaccination cards were not available, which may lead to recall and/or misclassification bias. Clinical diagnosis was used as the main method to identify some vaccine-preventable diseases where confirmatory microbiological testing was not consistently available. Furthermore, the observational study design may only show an association, but not prove the cause or estimate the vaccine effectiveness.

CONCLUSION

Incomplete childhood immunization was strongly associated with hospitalization due to vaccine-preventable diseases. Partially vaccinated and unvaccinated children had substantially higher odds of VPD-related admission compared with those fully vaccinated for age, while undernutrition remained an additional independent risk factor. Children hospitalized with VPDs also experienced greater clinical severity, longer hospital stays, more complications, increased ICU requirements, and higher mortality.

These findings emphasize the importance of completing age-appropriate vaccination schedules and addressing nutritional vulnerability to reduce preventable childhood morbidity and hospitalization in Pakistan. Future multicenter prospective studies should validate these findings across different regions of Pakistan and assess

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whether hospital-based vaccination screening, catch-up immunization, and nutritional interventions can reduce subsequent VPD-related admissions.

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