Original Article :

Adverse Events After 13-Valent Pneumococcal Vaccination in Infants and Children: Insights from a Tertiary Care Hospital in Eastern India

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Abstract

Background and Aims:
The 13-valent pneumococcal conjugate vaccine (PCV13) is widely used to prevent invasive pneumococcal diseases in children. However, real-world safety data through active surveillance remain limited in many settings, including Eastern India. The aim of this study was to estimate the incidence, types, and risk factors of adverse events following immunization (AEFIs) with PCV13 among infants and young children in a tertiary care setting.

Methods:
A descriptive observational study was conducted at the Immunization Clinic of Calcutta National Medical College, Kolkata, from April to September 2024. Infants receiving any PCV13 dose were monitored for AEFIs using structured telephone follow-up at 24 hours, 48 hours, and 5–7 days post-vaccination. A standardized, pre-validated questionnaire was used for uniform data collection. Descriptive statistics, chi-square test, and reporting odds ratios were applied.

Results:
Out of 1,176 PCV13 doses given to 791 children, 569 AEFIs were reported in 435 children (48.38 per 100 doses). Fever (86.1%) was the most common reaction, followed by tenderness (16.87%), swelling (11.78%), and erythema (5.62%). Only one serious AEFI (0.09 per 100 doses) occurred. Younger age, preterm birth, and low birth weight were significant risk factors. AEFI incidence was highest after the first dose.

Conclusions:
PCV13 was generally safe and well tolerated. Most AEFIs were mild and self-limiting. The findings highlight the value of active surveillance and targeted caregiver education, especially for high-risk infants receiving their first dose.

Keywords:
Adverse Events, 13-Valent Pneumococcal Vaccination, India

Introduction:

Streptococcus pneumoniae is a leading cause of morbidity and mortality in children worldwide, responsible for invasive diseases such as pneumonia, meningitis, septicaemia, and otitis media, particularly in children under five years of age and the elderly[1,2]. Despite the availability of over 90 pneumococcal serotypes, a limited subset accounts for the majority of invasive pneumococcal disease (IPD)[3]. The development and implementation of pneumococcal conjugate vaccines (PCVs) have significantly reduced IPD by enhancing immunogenicity through T-cell-dependent immune responses and providing herd protection[4,5].

In response to the global pneumococcal disease burden, the World Health Organization (WHO) recommends the inclusion of PCVs in national immunization schedules [6]. India introduced the 13-valent pneumococcal conjugate vaccine (PCV13) into its Universal Immunization Programme (UIP) in 2017, beginning with high-burden states such as Himachal Pradesh, Uttar Pradesh, Madhya Pradesh, Bihar, and Haryana [7]. PCV13 offers protection against 13 clinically relevant serotypes and is administered in a 2+1 schedule at 6 and 14 weeks, with a booster dose at 9 months. Countries such as China have also adopted PCV13, with varying immunization strategies [8].

While pre-licensure trials and post-marketing data have affirmed the vaccine's safety and efficacy [9,10], ongoing pharmacovigilance is critical. Adverse Events Following Immunization (AEFIs), although rare, can undermine public trust if not adequately monitored and addressed [11]. Passive surveillance systems are valuable but often suffer from underreporting, especially for mild or self-limiting events [12]. Therefore, integrating active surveillance methods, including structured follow-up, enhances data reliability and early detection of rare or severe AEFIs.

Given the limited data from real-world settings in India, particularly in Eastern regions, this study aims to estimate the incidence and characterize the nature and risk factors of AEFIs following PCV13 administration among infants and children in a tertiary care hospital setting. These findings are intended to support evidence-based immunization policies and strengthen public health vaccine safety frameworks.

Materials and Methods:

This observational descriptive study was conducted at the Immunization Clinic of Calcutta National Medical College, Kolkata, from April to September 2024. The objective was to assess the incidence, pattern, and associated risk factors of adverse events following immunization (AEFIs)

with the 13-valent pneumococcal conjugate vaccine (PCV13) in infants and young children.

As per the Indian Universal Immunization Programme (UIP), PCV13 was administered in a three-dose schedule: two primary doses at 6 and 14 weeks of age, followed by a booster dose at 9 months. Each 0.5 mL dose was given intramuscularly into the anterolateral aspect of the right mid-thigh. At 6 and 14 weeks, PCV13 was co-administered with the pentavalent vaccine, following standard immunization protocols.

All infants attending the immunization clinic during the study period and receiving any dose of PCV13 were considered for inclusion. Each PCV13 dose constituted a study unit.

Inclusion criteria:

- Infants receiving at least one dose of PCV13 during the study period.
- Informed consent obtained from parents or legal guardians.

Exclusion criteria:

- Infants with high-grade fever or acute illness at the time of vaccination.
- History of seizures, hypersensitivity, or prior adverse reaction to vaccines.
- Known immunodeficiencies, malignancies, or tumour conditions.
- Refusal to provide consent.

Following vaccination, parents/guardians were counselled regarding potential adverse events. Immediate post-vaccination observation was done for 30 minutes. Contact information was collected for active follow-up, and a dedicated phone number was provided for event reporting.

AEFIs were monitored using both passive surveillance (self-reported by parents) and active follow-up via standardized telephone interviews. A structured and pre-validated questionnaire was used to collect data uniformly across all follow-ups. This questionnaire was designed in accordance with WHO and Ministry of Health AEFI reporting guidelines and included closed-ended questions on local and systemic symptoms, onset time, duration, and severity.

Follow-up calls were conducted at three-time intervals:

- Within 24 hours of vaccination (preferably within 8 hours),
- At 48 hours post-vaccination,
- Between 5 to 7 days after vaccination.

All telephone interviews were conducted by trained researchers using a structured, pre-validated questionnaire based on WHO AEFI guidelines. This ensured consistency in data collection across all follow-up intervals. The questionnaire included closed-ended items regarding local and systemic symptoms, onset time, duration, severity, and care-seeking behaviour.

To minimize recall bias, follow-up calls were made within a 7-day window of vaccination, with the first call ideally within 8 hours. Parents were encouraged to keep a symptom diary, and any significant events could be immediately reported through a dedicated helpline number. Interviewers followed a standardized script and received uniform training to reduce inter-observer variability. In addition, caregivers were informed during the initial counselling about possible AEFIs to improve reporting accuracy.

AEFIs were classified according to WHO causality criteria:

- Vaccine product-related reaction
- Vaccine quality defect-related reaction
- Immunization error-related reaction
- Immunization anxiety-related reaction
- Coincidental event

Severity was categorized as:

- Non-serious AEFIs: Reactions requiring minimal or no medical intervention.
- Serious AEFIs: Events resulting in hospitalization, life-threatening conditions, disability, or death.

Severe AEFIs refer to the adverse events that are more intense than mild reactions (e.g., prolonged fever, persistent irritability, marked discomfort), but do not meet the World Health Organization criteria for "serious" events (such as hospitalization, life-threatening conditions, or permanent disability). While they may require outpatient medical attention, they do not result in significant long-term consequences.

In cases of multiple vaccine co-administration, local site-specific reactions were attributed to the injection site, while systemic reactions were considered as potential outcomes of all administered vaccines.

Data on AEFIs were recorded from immunization clinic registers and follow-up responses. Descriptive statistics were used to analyse the distribution of AEFIs across age, gender, gestational age, birth weight, and dose number.

The Chi-square test (with significance set at $p < 0.05$) was used to evaluate associations between variables. Reporting Odds Ratios (RORs) with 95% confidence intervals were calculated for disproportionality analysis, with a positive safety signal defined as lower limit of 95% CI >1.

Data were entered and managed in Microsoft Excel and analysed using IBM SPSS Statistics for Windows, Version 25.0.

Results:

The study analysed the incidence of Adverse Events Following Immunization (AEFI) among children receiving the Pneumococcal Conjugate Vaccine (PCV).

A total of 1,176 doses were administered to 791 children, with 569 AEFI cases reported, affecting 435 children (Table 1).

Table 1: Summary of PCV Vaccination and AEFI Cases.

Parameter	Value
Total number of PCV doses given	1176
Total number of children received PCV	791
Total number of AEFIs reported	569
Total number of children developed AEFI	435

Table 2 presents the demographic and birth characteristics of the study participants and their association with AEFI occurrence. Infants aged 0-2 months had the highest risk (OR: 2.21, 95% CI: 1.55-3.14), followed by those aged 2-6 months (OR: 1.52, 95% CI: 1.08-2.14), with the lowest AEFI incidence in infants >6 months. Preterm infants (OR: 2.68, 95% CI: 1.89-3.80) and those with low birth weight (OR: 2.54, 95% CI: 1.85-3.49) were significantly more likely to develop AEFI. Family type and birth order showed moderate associations with AEFI, while gender did not significantly influence AEFI occurrence.

Table 2: Distribution of Study Participants According to Their Demographic and Birth Characteristics and AEFI Occurrence (n=791).

Variable	Category	Total (n=791) (%)	Any AEFI	No AEFI	Odds Ratio (95% CI)
Age	0-2 months	230 (29.08%)	163 (70.87%)	67 (29.13%)	2.21 (1.55-3.14)
	2-6 months	318 (40.20%)	184 (57.86%)	134 (42.14%)	1.52 (1.08-2.14)
	>6 months	243 (30.72%)	88 (36.21%)	155 (63.79%)	1 (Reference)
Gender	Male	434 (54.86%)	241 (55.53%)	193 (44.47%)	1.05 (0.79-1.40)
	Female	357 (45.14%)	194 (54.34%)	163 (45.66%)	1 (Reference)
Family Type	Nuclear	540 (68.30%)	315 (58.33%)	225 (41.67%)	1.38 (1.03-1.85)
	Joint	251 (31.70%)	120 (47.81%)	131 (52.19%)	1 (Reference)
Birth Order	1st Child	459 (58.02%)	275 (59.91%)	184 (40.09%)	1.26 (0.95-1.67)
	2nd Child and above	332 (41.98%)	160 (48.19%)	172 (51.81%)	1 (Reference)
Gestational Age	Preterm	221 (28.00%)	160 (72.40%)	61 (27.60%)	2.68 (1.89-3.80)
	Full-term	570 (72.00%)	275 (48.25%)	295 (51.75%)	1 (Reference)
Birth Weight	Low birth weight	288 (36.42%)	205 (71.18%)	83 (28.82%)	2.54 (1.85-3.49)
	Normal birth weight	503 (63.58%)	230 (45.72%)	273 (54.28%)	1 (Reference)

Table 3 details the nature of AEFIs. The most common reaction was fever (86.12%), with an incidence of 41.67 per 100 doses, followed by tenderness (16.87%), swelling (11.78%), and erythema (5.62%). A single case (0.18%) of convulsion requiring hospitalization was reported, with an incidence of 0.09 per 100 doses.

Table 3: Distribution of AEFI Following PCV Vaccine (Multiple Response, n=569).

Nature of AEFI	Total Number of Reported Cases (%)	Incidence per 100 Vaccine Doses (n=1176)
Fever	490 (86.12%)	41.67
Tenderness	96 (16.87%)	8.16
Swelling	67 (11.78%)	5.70
Erythema	32 (5.62%)	2.72
Convulsion requiring hospitalization	1 (0.18%)	0.09

Table 4 outlines the incidence of AEFI by PCV dose. The 1st and 2nd doses had the highest AEFI incidence (63.22 and 62.44 per 100 doses, respectively), whereas the booster dose had a significantly lower AEFI rate (10.22 per 100 doses). The association between dose number and AEFI occurrence was statistically significant ($\chi^2 = 219.09$, $p < 0.001$).

Table 4: Incidence of AEFIs After PCV13 Administration.

Dose	No. of Doses (%)	No. of AEFIs Reported (%)	Incidence per 100 Doses	p-value
1st Dose	435 (36.98%)	275 (48.41%)	63.22	
2nd Dose	418 (35.57%)	261 (45.82%)	62.44	< 0.001
Booster Dose	323 (27.45%)	33 (5.77%)	10.22	
Total	**1176 (100%)**	**569 (100%)**	**48.38**	

Discussion:

This study provides valuable real-world evidence on the safety profile of the 13-valent pneumococcal conjugate vaccine (PCV13) in infants and young children in Eastern India. The overall incidence of adverse events following immunization (AEFIs) was 48.38 per 100 doses, with most events being mild and self-limiting. Fever was the most commonly reported AEFI, aligning with the known reactogenic profile of PCV13 and consistent with global post-marketing surveillance data [10].

A significantly higher incidence of AEFIs was observed following the first (63.22 per 100 doses) and second doses (62.44 per 100 doses), while the booster dose had a substantially lower incidence (10.22 per 100 doses). This decline in reactogenicity across successive doses may

reflect a phenomenon of immune adaptation. Primary exposure to the vaccine antigen likely elicits a robust innate immune response due to antigen novelty, resulting in increased reactogenic symptoms such as fever. Subsequent exposures engage adaptive immune memory, which produces a more regulated and efficient response, reducing the likelihood and intensity of adverse events [13].

This trend has been corroborated by other international studies. Zhang et al. (2021), in a multicentric safety surveillance study in China, reported a higher incidence of fever and local reactions after the primary PCV13 doses, with a notable reduction following the booster dose [9]. Similarly, Littlejohn et al. observed a decline in both local and systemic AEFIs among Australian infants following booster immunization, attributing the changes to improved caregiver preparedness and immunological tolerance [13]. These findings reinforce our results and support the hypothesis of immunological desensitization after repeated antigen exposure.

Demographic and birth-related characteristics significantly influenced AEFI risk. Infants aged 0–2 months, those born preterm, and those with low birth weight showed notably higher odds of experiencing AEFIs. These associations are likely due to the immaturity of the neonatal immune system and metabolic pathways in preterm and underweight infants. The altered cytokine responses and reduced regulatory T-cell activity in such infants increase their susceptibility to heightened inflammatory responses after vaccination. Angelidou and Levy demonstrated that preterm neonates mount disproportionate proinflammatory responses, which may account for increased reactogenicity [14]. These insights underscore the need for tailored surveillance strategies for high-risk neonatal populations.

In contrast, gender and birth order did not significantly impact AEFI incidence in our cohort. While previous studies, such as Kuter et al., have noted a slight male predominance in post-vaccination fever [16], our findings suggest that such differences may not be universal and could vary based on regional or genetic factors, or potentially be influenced by sample size and other confounders.

Encouragingly, only one serious AEFI was reported (a single convulsion requiring hospitalization), resulting in a low incidence of 0.09 per 100 doses. This finding aligns with the global safety profile of PCV13, which indicates that serious adverse events are exceedingly rare. A systematic review by Chilson et al. concluded that PCV13-related serious AEFIs occur at a very low rate and are outweighed by

the vaccine's substantial benefits in preventing invasive pneumococcal disease [10].

A major strength of this study lies in its mixed surveillance approach, combining passive and active follow-ups using a structured and standardized questionnaire. This method enhances data completeness, mitigates underreporting of mild events, and allows timely detection of both common and rare AEFIs. To further standardize follow-ups, interviewers were trained uniformly, and calls were scheduled within tight time frames to reduce recall bias. Caregiver education and use of a dedicated helpline may also have contributed to improved reporting accuracy.

Nonetheless, some limitations should be acknowledged. First, the single-centre study design may limit generalizability. Second, despite efforts to reduce recall bias through early follow-ups, some mild or transient AEFIs may still have gone unreported. Lastly, the lack of laboratory-confirmed outcomes (e.g., for fever or convulsions) may constrain mechanistic interpretations.

Conclusion:

This study confirms that PCV13 has a favourable safety profile, with the majority of AEFIs being mild, transient, and occurring primarily after the first two doses. The significant decline in AEFIs following the booster dose supports the hypothesis of immune adaptation. High-risk groups, including preterm and low-birth-weight infants, exhibited higher AEFI rates, necessitating closer follow-up.

The study recommendations the following:

- Enhanced Surveillance Systems: Incorporate routine active follow-up for all infants receiving PCV13, especially for the first dose and among preterm/ low birth weight infants. Mobile-based reporting apps may further improve timely AEFI capture.
- Caregiver Sensitization: Distribute printed leaflets and conduct brief counselling sessions to inform caregivers about expected AEFIs and warning signs, improving both reporting and vaccine confidence.
- Training of Frontline Workers: Regular AEFI training programs should be conducted for ANMs, ASHAs, and healthcare providers, with a focus on early identification, classification, and timely referral.
- Policy Integration: National AEFI surveillance guidelines should promote integration of active methods in tertiary centres. Evidence from this study may support consideration of extended observation or follow-up protocols for high-risk neonates.
- Research Continuity: Multicentric studies with longer follow-up periods

should be initiated to evaluate rare and delayed AEFIs and to explore the immunological mechanisms underpinning reactogenicity.

Clinical importance:

This study highlights the clinical significance of monitoring AEFIs following PCV13 administration to ensure vaccine safety and public confidence. The findings emphasize the need for proactive management of common AEFIs, such as fever and tenderness, particularly after the first dose. Improved caregiver education and healthcare provider training can enhance vaccine acceptance and adherence, ultimately reducing morbidity from pneumococcal diseases.

Conflicts of interest: None.

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