# EFFECTIVENESS OF 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE ON RADIOLOGICAL PRIMARY ENDPOINT PNEUMONIA AMONG CASES OF SEVERE COMMUNITY ACQUIRED PNEUMONIA IN CHILDREN IN NORTHERN INDIA: A MULTI-SITE HOSPITAL-BASED STUDY

Short Title: **EFFECTIVENESS OF PCV13 OF SEVERE COMMUNITY ACQUIRED PNEUMONIA IN CHILDREN IN INDIA**

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# EFFECTIVENESS OF 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE ON RADIOLOGICAL PRIMARY ENDPOINT PNEUMONIA AMONG CASES OF SEVERE COMMUNITY ACQUIRED PNEUMONIA IN CHILDREN IN NORTHERN INDIA: A MULTI-SITE HOSPITAL-BASED STUDY


## ABSTRACT

**Background:** *Streptococcus pneumoniae* is the leading bacterial cause of community acquired pneumonia (CAP) in children and produces primary end point pneumonia with or without infiltrates (PEP±I) in chest x-rays (CXRs). Pneumococcal Conjugate Vaccination 13 (PCV13) has been introduced in the national immunization program in India since 2017. Our aim was to compare the PEP±I on CXR in children hospitalized with WHO-defined severe CAP among those who had received ≥ 2 doses of PCV13 (exposed) versus unexposed.

**Methods:** Prospective hospital-based pneumonia surveillance data analysis of three districts of Northern India which had introduced PCV in 2017/2018. Included were children aged 2-23 months, hospitalized with severe CAP, with interpretable CXR, after parental consent. Clinical data was abstracted from hospital records and exposure to PCV from immunization card. CXR were interpreted by a panel of three independent blinded radiologists.

**Findings:** From May2017-March2020, 2658 subjects were included, of which 586 (22·0%) exposed to PCV13. PEP±I was found 555 (20·9%), of which 94 (16·9%) exposed. Crude vaccine effectiveness was 33·0% (95% CI, 15·0 to 48·0). In conditional logistic regression, adjusted odds ratio (OR) for PEP±I with exposure was 0·74 (95% CI, 0·58 to 0·95). Crude OR of hospital mortality in those with PEP±I was 3·86 (95% CI, 1·83 to 8·15, p<0·001).

**Interpretation:** In severe CAP, vaccination with ≥2 doses of PCV13 had statistically significantly reduced odds of having PEP±I. Since the latter had increased odds of hospital mortality due to CAP, country wide coverage with PCV13 is essential on priority.



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**Keywords**: Community Acquired Pneumonia, Radiological Findings, Primary Endpoint Pneumonia, PCV13, children, India

**Research in context**

**Evidence before this study:**

- Community Acquired Pneumonia is the leading cause of mortality in children less than 5 years of age in India.
- Bacterial pneumonia is largely due to *Streptococcus pneumoniae,* globally as well as in India.
- Pneumonia caused by *Streptococcus pneumoniae,* results in primary endpoint pneumonia with or without infiltrates on chest x-ray.
- Pneumococcal conjugate vaccine (PCV) has good effectiveness against clinical and radiological pneumonia in clinical trials, none of which were done in India.

**Added value of this study:**

- PCV13 was introduced National Immunization Program in year 2017 in India. Analysis of data during introduction of PCV13 gave a unique natural opportunity to assess outcome (radiological primary end point pneumonia with or without infiltrates) as well as expose to ≥ 2 doses of PCV13 in subjects from the same setting and with clinical presentation of WHO defined severe community acquired pneumonia, possibly for the first time.
- Adjusted Vaccine Effectiveness of PCV13 against primary end point pneumonia with or without infiltrates possibly due to *Streptococcus pneumoniae,* is 26·0% (95% CI, 5·0 to 42·0).
- Primary endpoint pneumonia with or without infiltrates increased hospital mortality (Adjusted OR 3·86 (95% CI, 1·83 to 8·15)).

**Implication of all the available evidence:**

- PCV13 in India has shown vaccine efficacy against primary endpoint pneumonia with or without infiltrates at par with other countries. Since cases of severe pneumonia with primary endpoint pneumonia with or without infiltrates on chest x-ray have increased odds of hospital mortality, there is an urgent need to introduced PCV13 in entire country.

## INTRODUCTION

Community acquired pneumonia (CAP) is a leading cause of potentially vaccine-preventable illness and death among under-five children in India. Globally, the number of deaths due to pneumonia among under-five (U5) children was 0·9 million (95% UI 0·8–1·1) in 2015, with more than 80% of deaths occurring in those aged 1–59 months (0·8 million [0·7–0·9])[1]. In 2015, the WHO African Region had the highest burden of pneumonia deaths (0·5 million [95% UI 0·4–0·6]) among U5 children, followed by the South-East Asia Region (0·2 million [0·2–0·3]). Both these regions account for more than three-quarters of global pneumonia deaths among U5 children[1]. Within these regions, five countries-India, Nigeria, Indonesia, Pakistan, and China-contribute to more than 54% of global cases of CAP[1] with 32% burden from India alone[1].

Pneumococcal conjugate vaccine (PCV) has been recommended by the World Health Organization (WHO) to prevent CAP[4]. WHO recommends its inclusion in the national immunization programme (NIP) of countries with high CAP related morbidity and mortality[5]. In compliance with the WHO recommendations, the Government of India, introduced PCV13 (Prevnar ® by Pfizer) in the NIP in 2017 in a phased manner from select districts[6]. The dose-schedule of PCV13 in NIP in India is 6 weeks, 14 weeks and 9 months (booster dose)[6,7].

Various types of PCV vaccines are available like PCV7, PCV10, PCV13 and Pneumococcal Polysaccharide Vaccine 23. There is scientific evidence to suggest that PCV13 is protective against bacteraemic pneumonia with serotype coverage of 64%, whereas in non-bacteraemic pneumonia, the serotype coverage is only 34%[8]. A reduction of CAP due to increased coverage of PCV among children has been reported in different settings as well[9,10].

We analyzed data of an ongoing multi-site study to compare the chest-radiograph findings of primary endpoint pneumonia with or without infiltrates (PEP±I) in children aged 2-23 months hospitalized with WHO-defined severe CAP among those who had received two or more doses of PCV13 (exposed) versus who had not, in three districts of Northern India. We also compared hospital mortality among those with and without PEP±I on chest x ray (CXR) as a secondary objective. This work was done as part of hospital-based surveillance on CAP among children (2-59 months) ongoing in these districts in India since 2015[11].

## METHODS

The study analyzed data from three districts of Uttar Pradesh and Bihar, Northern India where PCV13 had been introduced in 2017/2018. Uttar Pradesh is the fourth largest state by area (93,023 $mi^2$) and is the most populous in India[12]. Bihar has an area of 36,357 $mi^2$ and is the third most populous state[13]. The study reports data of Lucknow district of Uttar Pradesh and Patna and Darbhanga districts of Bihar.

An active, hospital-based surveillance system was established for this study[11]. Hospitals included in the analysis were private and public hospitals that admitted pediatric patients. A total of 92 public and private hospitals participated from three districts whose data was analyzed. Recruitment was done by trained surveillance officers[11,14,15]. At each participating hospital, surveillance officers identified children by reviewing admission logbooks. Children of eligible age, admitted with history of fast breathing with/without chest in-drawing were then identified from hospital records. Included were children hospitalized with symptoms of WHO-defined severe CAP who were permanent resident of the project district, with illness of <14 days and who were neither hospitalized nor recruited previously in the study. Excluded were those with cough for >14 days or prior hospitalization. Excluded from the analysis were those ≥ 24 months of age as they were not eligible for PCV13. `*Pneumonia*` was defined as fast breathing above age-specific cut-off (≥50 breaths/min between 2–11 months and ≥40 breaths/min between 12-59 months) with/without cough/fever[16]. Child was classified as `*severe pneumonia*` in the presence of at least one of the following: (a) oxygen saturation <90% or central cyanosis or (b) severe respiratory distress (eg, grunting, very severe chest in-drawing) or (c) signs of pneumonia with a general danger sign (inability to breast feed or drink, lethargy or reduced level of consciousness, convulsions) or, (d) severe malnutrition[16].

After obtaining written, informed consent from the parents/legal guardians, trained surveillance officers abstracted demographic and clinical data from the hospital records. Standardized questionnaire has been published elsewhere[11]. Socio-demographic information was obtained by interviewing parents/guardians. Anthropometry (weight and height) were noted from hospital records. Clinical data was recorded by pre-existing trained hospital staff at the time of hospitalization. Clinical outcome (discharge or death) was noted from the hospital logbook on follow-up. Detailed methodology of data collection has been published elsewhere[11,14,15].

PCV vaccination status was noted from the vaccination card issued by the hospital giving the vaccine. If the vaccination card was un-available, information about the child`s PCV status was sought from the parents/caregivers. They were asked if their child received Pneumococcal Conjugate Vaccine (PCV) at 6 weeks/14 weeks/9 months of age. If the reply was affirmative, the parent/caregivers were further asked if the

vaccine had been administered by intramuscular injection in the right mid-thigh of infant at those times along with another vaccine. If the response to both the questions was affirmative, then the child was considered vaccinated with PCV. Those who had received two or more doses of PCV13 were exposed and the rest were unexposed.

A copy of Chest X-Ray (CXR) was collected from the hospital, if done on advice of the treating physician. Collected CXRs were either analogue or digital. All CXRs were digitalized and stored online at www.capxrs.org. A panel of trained radiologists, using WHO methodology, interpreted CXRs by first categorizing the quality of film as '*interpretable*' or '*un-interpretable*'. Interpretable CXRs were classified as either `*optimal/adequate*` or `*suboptimal*``. Thereafter, CXRs were interpreted for radiological abnormality, and categorized as abnormal or normal. An abnormal CXR was categorized as 'PEP only' or 'other infiltrates only' or 'both PEP and other infiltrates`[16]. Outcome of interest was presence of PEP±I on CXR and these were "cases". The rest were categorized as controls. Standardized WHO case definition of PEP and other infiltrates has been used[16] and has been reported elsewhere[15].

**Statistical Analysis**

In this analysis, we included children aged 2-23 months hospitalized with severe CAP in three districts which has introduced PCV13. Cases were those who had PEP±I and controls were those who had either normal CXRs or only other infiltrates. Descriptive statistics of independent variables, such as anthropometric and clinical, were calculated. The mean and standard deviation for continuous data and percentage for categorical data was calculated using software Statistical package of social science (SPSS version 26)[17]. We compared independent variables among cases and control and also among those who had been exposed to PCV vaccination.

Weight-for-age (WAZ) z-score of each child was calculated using WHO Anthro Survey Analyzer[18]. Malnutrition status were categorized as WAZ > -2SD (normal), WAZ ≤ -2SD (malnourished) and WAZ ≤ -3SD (Severe malnutrition)[16]. We used chi-square test for comparison of categorical data and student's t-test for continuous data. A p value of < 0·05 was taken as statistically significant using a two-tailed distribution.

Independent variable that had univariate association with two tailed p value ≤ 0·1 with outcome were used in conditional logistic regression model. Conditional logistic regression model was done where dependent variable was chest x ray abnormality (PEP±I versus & others). Adjusted odds ratio (OR) with 95% confidence interval (CI) are being reported. Also vaccine effectiveness (VE) were calculated by using the formula, VE is equal to 100% (1-OR) with 95% confidence interval.

**Ethics**

The study was approved by the Ethical Review Committee of each site. Parents/legal guardians of children provided written, informed consent for participation. Standardized procedures were followed for case enrolment and data-collection. The study protocol and data collection forms are publicly available[11,14,15].

**RESULTS**

This study was conducted from May 2017-March 2020. In this study, 3132 hospitalized children with severe CAP met the eligibility criteria for analysis. Details of recruitment are given in Figure 1. Caregivers of 0·9% (28/3132) refused consent and 12·3%(386/3132) had no CXRs, hence were excluded. Among the 2718 with CXRs, we removed 3·0%(60/2718) as films were uninterpretable. There after 2658 children were included for the analysis. Among the 2658 included children, only 22·0% (586/2658) received ≥ 2 doses of PCV13. Of these 16·0% (94/586) had PEP±I, and 83·9% (492/586) had normal or other infiltrates. Among 78·0% (2072/2658) children with (0-1) doses of PCV13, 22·2% (461/2072) had PEP±I, 77·8% (1611/2072) had normal or other infiltrates (Figure 1).

Table 1 shows the overall descriptive statistics. Mean age of children was 7·8 months, mean height was 64·8 cm and mean weight was 6·6 kg. Average fever duration of children was four days.

From Darbhanga 48·6% (285/586), from Lucknow 43·9% (257/586) and from Patna 7·5% (44/586) of included children received ≥ 2 doses of PCV13. Table 2 compares the socio-demographic and clinical variables and CXR findings among the children exposed or unexposed to PCV vaccine. Variables were statistically significantly different among the children with and without exposure to PCV vaccine were gender, place of residence, mother's education, immunization status (excluding PCV), biomass fuel, wheezing on auscultation, vomiting everything, respiratory rate, chest x-ray abnormalities and malnutrition status.

Table 3 shows the univariate association of independent variables such as socio-demographic, clinical variables among cases-control. Gender, family type, father smoking status, wheezing, vomiting everything, PCV vaccine exposure and malnutrition were associated with PEP±I. Overall hospital mortality due to severe CAP was 1·1%

(28/2658). Crude OR of hospital mortality with PEP with or without infiltrates was 3·86 (95% CI, 1·83 to 8·15, p<0·001).

Table 4 shows the results of conditional logistics regression model, where the dependent variables was PEP±I versus others CXRs. We found that receiving ≥ 2 doses of PCV13 reduced the odds of having PEP±I (adjusted OR 0·74, 95% CI, 0·58 to 0·95). Crude VE was 33·0% (95% CI, 15·0 to 48·0) which translate adjusted VE was 26·0% which is from range (95% CI, 5·0 to 42·0).

**DISCUSSION**

This multi-site study was analyzed to compare the chest-radiograph findings of PEP±I among those who had received ≥ 2 doses of PCV13 (exposed) versus those who had not (unexposed), in children aged 2-23 months, hospitalized with severe WHO-defined severe CAP, in three districts of Northern India. We found that those who had received ≥2 doses of PCV13 were at statistically reduced odds of having PEP±I in CXR. Crude vaccine effectiveness (VE) was found to be 33·0% (95% CI, 15·0 to 48·0). Adjusted VE was found to be 26·0% (95% CI, 5·0 to 42·0%). Standard WHO definition of CAP was used in this study. CXRs were evaluated by a panel of trained external radiologists using standard WHO-methodology of CXR interpretation[15]. The study therefore had internal as well and external validity and can be compared to similar studies that used the same methodology[19,20].

In our study, among the 2658 included children, less than one-fourth (22·0%, 586/2658) had received ≥ 2 doses of PCV13. This happened because the Government of India introduced PCV13 in a phased manner across the country and even within allotted districts the vaccine coverage was taking time to optimize[6].

WHO has established that PEP±I in CXR is commonly caused by *Streptococcus pneumoniae*[21]. Hence those with these findings on CXR were case and the rest controls. For exposure to PCV13, we categorized them as exposed into those who received: (i) 0-1 doses and (ii) ≥ 2 doses of PCV13. This was done as ours was a pragmatic study and children of different ages were enrolled as they were hospitalized. Earlier PCV vaccine trials have shown that odds reduction for radiological pneumonia occurs after ≥2 PCV doses[22,23], hence our approach is evidence-based.

Efficacy of PCV vaccination to reduce radiological pneumonia among young children has been widely reported in scientific literature[9,22,23]. A randomized, placebo-controlled, double-blind trial conducted on Gambian children found that PCV9 was 37% efficacious against the first episode of radiological pneumonia[23]. Likewise, a South African trial reported that PCV9 reduced the incidence of first episodes of radiologically confirmed alveolar consolidation by 20-25% in children without human immunodeficiency virus (HIV) infection[22]. These are similar to 26% odds reduction in PEP±I in our study. Since our study area has a low prevalence of HIV[24], subjects were not tested for it. Our findings differ from an effectiveness study of PCV10 on WHO-defined radiological pneumonia among children in Bangladesh[25], where unlike our study, the crude and adjusted VE for ≥2 doses of PCV10 were statistically insignificant[25]. Our study could not estimate the efficacy of PCV on clinical pneumonia, but the Gambian study did report that vaccination with PCV9 reduced the first episodes of clinical pneumonia by 7%[23].

In a trial of PCV9 in South Africa, there was an insignificant reduction in all-cause as well as pneumonia specific mortality among the HIV infected as well as uninfected children[22]. However, in another trial in Gambia, PCV9 vaccination statistically significantly reduced all-cause of mortality in infants by 14-16%[23]. In our analysis, we found that the PEP±I was associated with three times odds of hospital mortality in severe CAP.

**Strengths and Limitations**

The study has several strengths. This was a multi-site hospital-based surveillance for radiological pneumonia in which standardized definition of CAP was used for recruitment[16]. Uniform methodology of data by trained surveillance officers ensured quality. We also used WHO-recommended methodology for interpreting CXRs by a panel of trained radiologists[15], who had been a part of the study since its inception in 2015. This ensured internal and external validity. Use of data of three representative sites and standardized methods will help in extrapolating our results to other similar sites in Northern India. We noted information about PCV vaccination from the vaccination card of the child. However, when the vaccination card was unavailable, information was sought by interviewing caregivers/parents. Hence, there could be recall bias.

**CONCLUSION**

We found that exposure to ≥ 2 doses of PCV13, statistically significantly reduced the odds of PEP±I in children hospitalized for severe CAP as well as hospital mortality. Further studies are needed to see the effect of PCV13 on reduction of incidence of clinical pneumonia and cause-specific mortality in community settings.

**Author Contributions:** SA conceived and designed the study. SA, MA, CR, KNM, NV, CBK, PKJ, RY, TR supervised data acquisition. Data management was done by PD. Interpretation of chest x-rays was done by AC, NM, RCS and NK. CMP and AKP conducted the statistical analysis of the data. The paper was written by SA, TR and CMP. All authors were involved in drafting and revising the work and approved final submission.

**Data availability:** The full dataset will be made available on request and agreement by the study team.

**Ethical approval:** The protocol was approved by the Ethics Review Committee of King George's Medical University (Lucknow), Patna Medical College and Hospital (Patna) and Darbhanga Medical College and Hospital (Darbhanga). The caregivers/ guardians of children signed the written, informed consent for participation in the study.

**Declaration of Competing Interest:** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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**Figure Legend**

**Figure 1:** Flow diagram of hospitalized children (2-23 months) with community acquired pneumonia recruited from Lucknow, Patna (May2018 to March2020) and Darbhanga (May 2017-March 2020).

**Table Legends**

**Table 1:** Anthropometric measurement with clinical variable of hospitalized children aged 2-23 months.

**Table 2:** Comparison of socio-demographic and clinical variables and CXRs findings among the children exposed or unexposed to PCV vaccine.

**Table 3:** Univariate association of socio-demographic and clinical variables among cases and control.

**Table 4:** Association of CXR abnormalities with ≥ 2 doses of PCV13, controlling for independent variable in conditional logistic regression.

**Table 1: Anthropometric measurement with clinical variable of hospitalized children aged 2-23 months.**

| Anthropometric measurement | N=2658 | Mean±SD |
|---|---|---|
| Age (months) | 2658 | 7·8±5·9 |
| Height (cm) | 2658 | 64·8±8·3 |
| Weight (Kg) | 2658 | 6·6±2·1 |
| Fever duration (days) | 2658 | 4±2 |

**Abbreviations: SD:** Standard deviation

**Table 2: Comparison of socio-demographic and clinical variables and CXRs findings among the children exposed or unexposed to PCV vaccine.**

| Variables Column n (%) | Pneumococcal Conjugate Vaccine Dose | | |
|---|---|---|---|
| | With ≥ 2 dose N=586 | With (0-1) dose N=2072 | p value |
| **Age (months) ( Mean±SD)** | 8·37±4·00 | 7·57±6·23 | 0·004 |
| **Gender** | | | |
| Male | 438 (74·7) | 1455 (70·2) | 0·03 |
| Female | 148 (25·3) | 617 (29·8) | |
| **Family Type** | | | |
| Joint | 408 (69·6) | 1464 (70·7) | 0·63 |
| Nuclear | 178 (30·4) | 608 (29·3) | |
| **Place of residence** | | | |
| Rural | 322 (54·9) | 1243 (60·0) | 0·03 |
| Urban | 264 (45·1) | 829 (40·0) | |
| **Mother's education** | | | |
| No formal education | 241 (41·1) | 1146 (55·3) | <0·001 |
| Formal education | 345 (58·9) | 926 (44·7) | |
| **Smoking status-father** | | | |
| Yes | 84 (14·3) | 354 (17·1) | 0·11 |
| No | 502 (85·7) | 1718 (82·9) | |
| **Immunization status (excluding PCV)** | | | |
| Complete for age | 558 (95·2) | 1524 (73·6) | <0·001 |
| Incomplete for age | 28 (4·8) | 548 (26·4) | |
| **Biomass fuel** | | | |
| Yes | 219 (37·4) | 1035 (50·0) | <0·001 |
| No | 367 (62·6) | 1037 (50·0) | |
| **Fever** | | | |
| Yes | 510 (87·0) | 1799 (86·8) | 0·90 |
| No | 76 (13·0) | 273 (13·2) | |
| **Pallor** | | | |
| Yes | 318 (54·3) | 1106 (53·4) | 0·70 |
| No | 268 (45·7) | 966 (46·6) | |
| **Wheezing on auscultation** | | | |
| Yes | 495 (84·5) | 1635 (78·9) | 0·003 |
| No | 91 (15·5) | 437 (21·1) | |
| **Vomiting everything** | | | |
| Yes | 251 (42·8) | 747 (36·1) | 0·003 |
| No | 335 (57·2) | 1325 (63·9) | |
| **Respiratory rate** | | | |
| Less than or equal 60 | 373 (63·7) | 1206 (58·2) | 0·02 |
| Greater than 60 | 213 (36·3) | 866 (41·8) | |

| | | | |
|---|---|---|---|
| **Chest X-ray** | | | |
| PEP with or without infiltrates | 94 (16·0) | 461 (22·2) | <0·001 |
| Normal | 319 (54·4) | 1172 (56·6) | |
| Other infiltrates | 173 (29·5) | 439 (21·2) | |
| **Malnutrition status** | | | |
| Normal | 420 (71·7) | 1176 (56·8) | <0·001 |
| Malnutrition | 101 (17·2) | 495 (23·9) | |
| Severe malnutrition | 65 (11·1) | 401 (19·4) | |

**Abbreviations: PCV:** Pneumococcal Conjugate Vaccine, **PEP:** Primary end point pneumonia, **SD:** Standard deviation

**Table 3: Univariate association of socio-demographic and clinical variables among cases and control.**

| **Variables**<br>**Column n (%)** | **Radiological Chest X-rays** | | |
|---|---|---|---|
| | **PEP with or without infiltrates**<br>**N=555** | **Normal & Other infiltrates**<br>**N=2103** | **p value** |
| **Age (months) ( Mean±SD)** | 7·41±6·11 | 7·84±5·78 | 0·12 |
| **Gender** | | | |
| Male | 363(65·4) | 1530(72·8) | 0·001 |
| Female | 192(34·6) | 573(27·2) | |
| **Family Type** | | | |
| Joint | 412(74·2) | 1460(69·4) | 0·03 |
| Nuclear | 143(25·8) | 643(30·6) | |
| **Place of residence** | | | |
| Rural | 323(58·2) | 1242(59·1) | 0·71 |
| Urban | 232(41·8) | 861(40·9) | |
| **Mother's education** | | | |
| No formal education | 293(52·8) | 1094(52·0) | 0·75 |
| Formal education | 262(47·2) | 1009(48·0) | |
| **Smoking status-father** | | | |
| Yes | 105(18·9) | 333(15·8) | 0·08 |
| No | 450(81·1) | 1770(84·2) | |
| **Immunization status (excluding PCV)** | | | |
| Complete for age | 422(76·0) | 1660(78·9) | 0·14 |
| Incomplete for age | 133(24·0) | 443(21·1) | |
| **Biomass fuel** | | | |
| Yes | 251(45·2) | 1003(47·7) | 0·30 |
| No | 304(54·8) | 1100(52·3) | |
| **Clinical features** | | | |
| **Fever** | | | |
| Yes | 490(88·3) | 1819(86·5) | 0·27 |
| No | 65(11·7) | 284(13·5) | |
| **Pallor** | | | |
| Yes | 308(55·5) | 1116(53·1) | 0·31 |
| No | 247(44·5) | 987(46·9) | |
| **Wheezing on auscultation** | | | |
| Yes | 418(75·3) | 1712(81·4) | 0·001 |
| No | 137(24·7) | 391(18·6) | |
| **Vomiting everything** | | | |
| Yes | 176(31·7) | 822(39·1) | 0·001 |
| No | 379(68·3) | 1281(60·9) | |
| **Respiratory rate** | | | |
| Less than or equal 60 | 325(58·6) | 1254(59·6) | 0·65 |

| Variables<br>Column n (%) | Radiological Chest X-rays | | |
|---|---|---|---|
| | PEP with or without infiltrates<br>N=555 | Normal & Other infiltrates<br>N=2103 | p value |
| Greater than 60 | 230(41·4) | 849(40·4) | |
| **PCV dose** | | | |
| PCV (0-1) dose | 461(83·1) | 1611(76·6) | 0·001 |
| PCV (≥ 2) dose | 94(16·9) | 492(23·4) | |
| **Malnutrition status** | | | |
| Normal | 299(53·9) | 1297(61·7) | <0·001 |
| Malnutrition | 114(20·5) | 482(22·9) | |
| Severe malnutrition | 142(25·6) | 324(15·4) | |

**Abbreviations: PCV:** Pneumococcal Conjugate Vaccine, **PEP:** Primary end point pneumonia, **SD:** Standard deviation

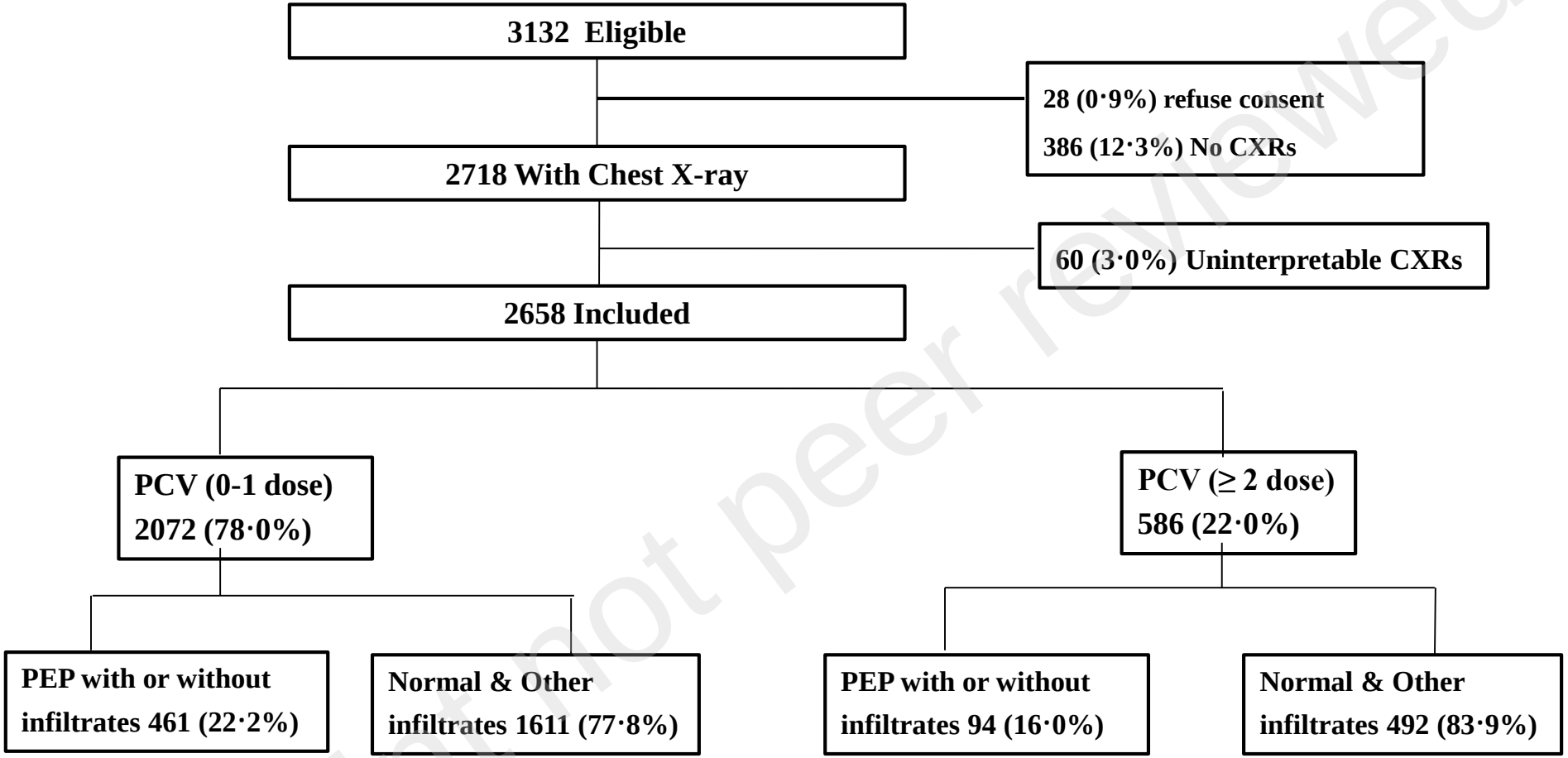
**Table 4: Association of CXR abnormalities with ≥ 2 doses of PCV13, controlling for independent variable in conditional logistic regression.**

| Variables | Model I<br>PEP with or without infiltrates/Normal & Other infiltrates[ref] | | |
|---|---|---|---|
| | N= 2658 | Adjusted OR<br>(95% CI) | p Value |
| **PCV Doses** | **n** | | |
| No or one Dose[ref] | 2072 | -- | -- |
| Two or more Dose | 586 | 0·74<br>(0·58 to 0·95) | 0·02 |
| **Gender** | | | |
| Male[ref] | 1893 | | |
| Female | 765 | 1·43<br>(1·17 to 1·75) | 0·001 |
| **Family Type** | | | |
| Nuclear[ref] | 786 | -- | -- |
| Joint | 1872 | 1·22<br>(0·98 to 1·51) | 0·07 |
| **Wheezing** | 2130 | 0·74<br>(0·59 to 0·92) | 0·008 |
| **Vomiting everything** | 998 | 0·73<br>(0·60 to 0·90) | 0·002 |
| **Malnutrition status** | | | |
| Normal[ref] | 1596 | -- | -- |
| Malnutrition | 596 | 1·06<br>(0·83 to 1·35) | 0·64 |
| Severe Malnutrition | 466 | 1·86<br>(1·47 to 2·36) | <0·001 |

**Abbreviations: PCV:** Pneumococcal Conjugate Vaccine, **PEP:** Primary end point pneumonia. **Ref:** Reference category, **Adjusted OR:** Adjusted Odd Ratio

Figure 1

**Figure 1: Flow diagram of hospitalized children (2-23 months) with community acquired pneumonia recruited from Lucknow, Patna (May2018 to March2020), and Darbhanga (May 2017-March 2020).**




**Abbreviations:**

CXR: Chest X ray, PCV: Pneumococcal Conjugate Vaccination, PEP: Primary Endpoint Pneumonia