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Chest Radiograph Findings in children aged 2-59 months hospitalized with Community-Acquired Pneumonia, prior to the introduction of Pneumococcal Conjugate Vaccine in India

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Title: *Chest Radiograph Findings in children aged 2-59 months hospitalized with Community-Acquired Pneumonia, prior to the introduction of Pneumococcal Conjugate Vaccine in India*

Short Title: *Radiological Findings in Children hospitalized with Community-Acquired Pneumonia in India Pre-Pneumococcal Conjugate Vaccine introduction*

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ABSTRACT

Objectives: To assess radiological abnormalities in chest X-rays and to identify the demographic and clinical correlates in children aged 2-59 months, hospitalized with World Health Organization defined community-acquired pneumonia, who reside in pre-specified districts of India

Design: Prospective, hospital-based surveillance

Setting: Multi-site study conducted in a network of 117 secondary/tertiary care hospitals in four districts of Uttar Pradesh and Bihar, India.

Participants: Included were children aged 2-59 months hospitalized with community-acquired pneumonia, residing in project district, with duration of illness of <14 days and who were not hospitalized elsewhere for this episode or nor had been recruited previously.

Main outcome measure: Radiological abnormalities in the chest X-rays, where there was concordance between two or more of the panel of three trained radiologists.

Results: From January 2015 to April 2017, 3214 cases were recruited and in 99.40 % (3195/3214) chest X-rays were available. Among 88.54 % (2829/3195) interpretable X-rays, 34.53 % (977/ 2829, 95% C.I. 32.78 - 36.28) had some radiological abnormalities, while the rest were normal. Primary end point pneumonia alone or with other infiltrates was found in 22.44 % (635/2829, C.I. 20.90 %-23.98 %), other infiltrates only in 12.09% (342/ 2829; C.I. 10.88 %-13.29 %). There was a statistically significant inter-district variation in radiological abnormality. Statistically significantly higher proportion of abnormal chest X-ray was found among girls, those with weight for age z score ≤ -3 SD, longer duration of fever, pallor and with exposure to biomass fuel.

Conclusions: Among hospitalized cases of community-acquired pneumonia, almost one-third children had abnormal chest radiographs of which about two-thirds had abnormalities related with possible bacterial etiology (*Streptococcus pneumoniae*). Hence introduction of pneumococcal vaccination is likely to reduce burden of childhood pneumonia in India.

Key words: Chest radiographs, Hospitalized community-acquired pneumonia, under-five, *Streptococcus pneumoniae*, India

Strengths and Limitations of the Study

- Prospective, multisite recruitments from a large hospital surveillance network established for the project in four districts in two states of India that have high under-five mortality rates
- Standardized World Health Organization definition was used for identifying hospitalized cases of clinical pneumonia
- Radiological abnormalities interpreted by a panel of three trained radiologists at locations out of the surveillance network, blinded to each other as well as clinical features of the case
- Since pre-existing X-rays machines were used, there was variation in the quality of images obtained, which were minimized by digitizing them centrally
- Laboratory investigations were according to the routine hospital practice and were not uniform across hospitals, since the study objective was to assess radiological abnormalities in chest X-rays of recruited cases .

INTRODUCTION

Community-acquired pneumonia (CAP) is the single largest infectious cause of death in young children worldwide. Globally, pneumonia accounts for 16% of deaths in children under-five years of age and results in almost one million deaths (0.9 million children in 2016) every year^{1 2}. Most deaths due to pneumonia occur in low and middle income countries particularly in sub-Saharan Africa and South Asia^{2 3}. In India, there were approximately 0.44 million under-five deaths due to CAP in the year 2015⁴.

CAP could have viral or bacterial etiology⁵⁻⁷. Etiology varies from country to country and also across different time periods. Pediatric bacterial pneumonia is predominantly caused by *Streptococcus pneumoniae* (SP) and *Hemophilus influenzae Type B* (HiB) while Respiratory syncytial virus and Influenza A or B virus are important contributors of pediatric viral pneumonia^{5 6}. The World Health Organization (WHO) recommends the introduction of Pneumococcal Conjugate Vaccine (PCV) in the national immunization programme (NIP) of countries with high child mortality rates, which includes India⁸. Consequently, PCV-13 was launched in May 2017 under the NIP of five Indian states (Uttar Pradesh, Bihar, Rajasthan, Madhya Pradesh and Himachal Pradesh) in a phased manner⁹. It is expected to be rolled out in other parts of the country in the coming days. Vaccination against HiB is already under the NIP since 2011.

Differentiating bacterial from viral etiology of CAP on clinical features or by investigations remains difficult^{7 10 11}. Several PCV probe trials have used radiographically confirmed alveolar

1 pneumonia, also called end-point pneumonia, to be an outcome for vaccine efficacy and this has
2
3 been endorsed by WHO ¹²⁻¹⁴.
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10 The current study was a hospital-based surveillance to assess the radiological abnormalities in
11 chest X-rays (CXRs) and to identify the demographic clinical correlates of specific radiological
12 abnormalities in children aged 2-59 months, hospitalized with WHO defined CAP, residing in
13 pre-specified districts of Uttar Pradesh and Bihar, India.
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22 **METHODS**

23 **Setting**

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25 This multi-site site prospective study was conducted in Lucknow and Etawah districts of Uttar
26 Pradesh and Patna & Darbhanga districts of Bihar, India. Uttar Pradesh is the most populated
27 state of India and Bihar third populated ^{15 16}. Lucknow district has urban population of 66.2% ¹⁵
28 and Patna district 43.07% ¹⁶. In contrast, only 22.3%¹⁵ population of Etawah district and 9.74%¹⁶
29 population of Darbhanga district reside in rural areas. All four project districts have poor socio-
30 demographic and child health indicators ^{15 16 17}.
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41 **Study Population**

42 A hospital-based surveillance system was established for this study. Recruitment was done from
43 a network of public and private hospitals, which provided either secondary or tertiary level care,
44 which admitted children. Children aged 2-59 months hospitalized in network hospitals with
45 history of fast breathing with/without chest in-drawing were screened ¹⁷.
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Children with cough and respiratory symptoms for ≥ 14 days were excluded¹⁷. Children with history of hospitalization within 14 days of recruitment were excluded to remove the potential risk of acquiring hospital-acquired pneumonia¹⁷. Included were children hospitalized with symptoms of WHO defined CAP and residing in the project district. WHO has developed guidelines for the identification of CAP by the community health workers¹⁸. According to these guidelines, CAP is defined as the presence of fast breathing above age-specific cutoff. The cutoff for infants less than 2 months is 60 more breaths per minute (bpm), for 2-11 months of age 50 or more bpm and 12-59 months of age is 40 or more bpm¹⁸. In addition, WHO has defined severe pneumonia as CAP with presence of certain danger signs such as not able to drink, persistent vomiting, convulsions, lethargy or unconsciousness, stridor in a calm child or severe malnutrition¹⁸. Children with fast breathing with or without chest in-drawing are classified as “pneumonia” and children with pneumonia and with any danger signs are classified as “severe pneumonia”¹⁸.

Data collection

Information on socio-demographic and clinical variables was obtained by trained surveillance officers. Socio-demographic information was collected through face-to-face interviews from the parent/caregiver of the recruited child. Clinical data and anthropometric information (height, weight, mid-arm circumference and head circumference) was abstracted from clinical records of admitting hospital. Clinical Outcome (survival or mortality) was noted^{17 19}.

Chest x-ray (CXR) image acquisition and archiving

CXR (poster-anterior view) was done on the advice of treating physician as part of routine clinical care. Surveillance staff obtained CXR at the time of recruitment. CXRs were either analogous or digital. In case of digital CXRs, second copy was obtained where possible. If only

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3 single analog image was available, then the CXR hardcopy was obtained from the
4 parent/guardian after the child was discharged. If this could not be done, image of the hardcopy
5 was captured. CXR machines were not provided through the project.
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12 CXRs of recruited cases were subsequently scanned and converted into digital format using a
13 diagnostic-quality film image digitalizer (Microteck International Limited, model Medi 6000
14 plus)²⁰. CXRs obtained/converted into digital image were stored as per the standard operating
15 procedure and were subsequently archived for web-based radiological interpretation. Digital
16 images were stored in JPEG format at 300 dpi resolution. Each CXR file was anonymized and
17 given a unique identification number. Digital CXRs were uploaded on online data management
18 software (www.capxrs.org), developed especially for the project. De-identified CXRs were
19 uploaded every month in batches by the data manager.
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30 31 **Interpretation of radiological images**

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33 A panel of radiologists was constituted for standardized interpretations of pediatric CXRs. Four
34 radiologists were part of this panel, one of whom was Project Co-Investigator-Radiology.
35 Radiologists were trained as per the methodology developed by Department of Immunization,
36 Vaccines, and Biologicals of the World Health Organization (WHO)¹¹.
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45 After training, radiologists were required to independently review CXRs and register their
46 findings in an online standardized chest radiograph interpretation form [S1 Appendix]. For
47 optimal viewing of CXRs, all readers used similar workstations. Specifications were provided for
48 the computer monitor and hardware to be used. It was ensured that monitors had the correct
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3 brightness and contrast adjustment for optimal viewing. The sequence of presentation of CXR to
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5 the readers was randomized.
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10 Radiographic interpretation was done on film quality, findings of CXRs and conclusion.
11 Radiologists interpreted film quality as follows: (a) *'Adequate/optimal'* for features allow
12 confident interpretation of consolidation and pleural effusion as well as other infiltrates; (b)
13 *'Suboptimal'* for features allow interpretation of consolidation and pleural effusion, but not of
14 other infiltrates or findings and (c) *'Un-interpretable'* pertaining to features of the image that are
15 not interpretable with respect to presence or absence of consolidation or pleural effusion without
16 additional images ¹².
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28 After interpreting film quality, readers interpreted the pathological findings. For each
29 radiographic finding, there were two options to be chosen: 'yes' for the presence of findings and
30 'no' for its absence. Pathological findings were classified into (a) *'significant pathology'* such as
31 presence of consolidation, infiltrates or effusion; (b) *'end-point consolidation'* for CXRs with a
32 dense or confluent opacity that occupies a portion or whole of a lobe or the entire lung, that may
33 or may not contain air bronchograms ; (c) *'other (non end-point) infiltrate'* for CXRs with linear
34 and patchy opacities (interstitial infiltrate) in a lacy pattern, featuring peri-bronchial thickening
35 and multiple areas of atelectasis; also including minor patchy infiltrates that are not of sufficient
36 magnitude to constitute endpoint consolidation, and small areas of atelectasis that in children
37 may be difficult to distinguish from consolidation and (d) *'pleural effusion'* on presence of fluid
38 in the lateral pleural space between the lung and chest wall that is spatially associated with a
39 pulmonary parenchymal infiltrate (including 'other infiltrate') or has obliterated enough of the
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3 hemithorax to obscure any infiltrate; in most cases, this will be seen at the costo-phrenic angle or
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5 as a layer of fluid adjacent to the lateral chest-wall; this does not include fluid seen in the
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7 horizontal or oblique fissures ¹².
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12 Radiologists concluded their interpretations of CXRs as per WHO guidelines ¹². Conclusions
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14 were categorised into: (a) '*Primary End Point Pneumonia only*' (PEP) on the presence of
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16 consolidation or pleural effusion; (b) '*Other (non end-point) infiltrate only*' on the presence of
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18 other (non-consolidation) infiltrates as defined above in the absence of a pleural effusion (c)
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20 '*Both PEP and other infiltrate*' and (d) '*Normal*' when there were no findings consistent with
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22 '*endpoint consolidation*' or '*other infiltrate*' or '*pleural effusion*' ¹².
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29 After radiological interpretation, online data was archived, stored and checked for
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31 inconsistencies and completeness by the data manager. CXRs with concordant and discordant
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33 interpretations were identified. Interpretations were considered concordant when two or more
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35 radiologists agreed on the same. If all the three radiologists disagreed on set of findings, then
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37 such CXRs with discordant interpretations were forwarded to the study arbitrator (Project Co-
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39 Investigator-Radiology) using customized software (www.capxrs.org). Arbitrator read discordant
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41 CXRs and submitted the interpretation to the data manager. Readings of arbitrator were taken as
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43 final in case of discordant interpretations.
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47 **Data management and statistical analysis**

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50 Clinical data of hospital surveillance network was entered online in customized software.
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52 Primary entry was by the four participating sites. Secondary data entry was done by the
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54 coordinating site in different customized software. Anonymized CXRs were uploaded on
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3 customized software. Each of the three panelists had independent access to them. They assessed
4 the CXRs online, blind to peer assessments as well as clinical features of the case, and uploaded
5 their findings online. CXR assessment data was downloaded from the online software in MS
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10 Access database.

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15 Exploratory data analysis was performed for outlier detection and missing observations for all
16 the variables. Descriptive statistics was calculated for measurable variables in Mean \pm Standard
17 Deviation (M \pm SD) and categorical variables in percent (%). Un-interpretable CXRs were
18 removed from analysis. Among interpretable CXRs, radiological abnormalities, which were
19 reported by two members of the panel, were taken as final. Weight-for-age z-score each child
20 was calculated using Epi-Info software ²¹. Weight-for-age z score (WAZ) of ≤ -3 was taken as
21 `underweight` ²². Kappa statistics was performed for agreement analysis among radiologists for
22 CXRs findings. Statistical analysis was performed using SPSS version 22.0 (Chicago, IL) ²³. A p
23 value of <0.05 was taken as statistically significant using a two-tailed distribution.

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38 Univariate analysis was performed to evaluate heterogeneity stratified by four participating sites
39 for socio-demographic variables such as age, gender, place of residence, type of house, type of
40 family, maternal & paternal education and their occupation, use of biomass fuel for cooking and
41 parental smoking status. Likewise, univariate analysis was done for clinical variables such as
42 height, weight, duration of illness and percent oxygen saturation, in cases where pulse oximetry
43 was done.
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We report proportions of radiological abnormalities among hospitalized children for CAP for four districts. Univariate analysis was performed to find out associated socio-demographic variables and clinical signs of CAP with radiological abnormalities. Chi-square test was used to find out association for categorical variables and student's t-test for continuous variables. Multivariate binary logistic regression was performed find association of presence of various radiological abnormalities among cases hospitalized for CAP, controlling for district of residence and other variables that had univariate association with radiological abnormalities (p value ≤ 0.2) and/or were clinically meaningful.

Thereafter, we developed and report four models for estimation of adjusted odds ratios of socio-demographic and clinical variables with specific radiological abnormalities (dependent variable).

In these four models, dependent (outcome) were as follows:

Model I: Abnormal vs. Normal

Model II: Primary End Point Pneumonia alone or with infiltrates vs. Normal

Model III: Primary End Point Pneumonia alone vs. Normal

Model IV: Other infiltrates only vs. Normal

Independent variables that were kept across all the four models were : participating districts, age, gender, use of biomass fuel, symptoms of CAP such as duration of illness, presence of rhonchi, pallor and vomiting and malnutrition status of the case [WAZ ≤ -2 (malnourished) and WAZ ≤ -3 (severely malnourished)].

Patient and public involvement in research

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3 Health Ministry Steering Committee of Indian Council of Medical Research, New Delhi, India
4 approved the study. State governments of Uttar Pradesh and Bihar gave consent for initiating the
5 study. Written, informed consent was obtained from parents/guardians of eligible children who
6 were willing to participate in the study. Written informed consent was also taken from the
7 administration of hospital for participation.
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18 RESULTS

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21 A total of 3290 hospitalized cases were screened in hospital surveillance network of Lucknow
22 and Etawah districts of Uttar Pradesh and Patna & Darbhanga districts of Bihar from January
23 2015 to April 2017. Out of these, 3214 cases fulfilling the WHO diagnosis of CAP were included
24 [Figure 1]. Among them, 3195 (99.40%) cases were enrolled with CXRs and in 19 (1.0%) cases
25 CXRs were not done. Concordance among ≥ 2 radiologists for CXRs findings was 86.0%. Kappa
26 statistics was calculated for agreement of CXRs findings between Reader 1 vs. Reader 2
27 ($K_1=0.31$), Reader 2 vs. Reader 3 ($K_2=0.46$) and Reader 3 vs. Reader 1 ($K_3=0.42$). Thereafter, out
28 of these 88.54% (2829/3195) CXRs were found interpretable and remaining 11.45% (366/3195)
29 were found un-interpretable by radiologists. Among interpretable CXRs, we found 22.44%
30 (635/2829) children had primary end point pneumonia (PEP) alone or with infiltrates, other
31 infiltrates only 12.09% (342/2829) and 65.46% (1852/2829) had normal CXRs findings [Figure
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51 **Table 1** shows univariate distribution of socio-demographic and clinical variables among
52 hospitalized cases across four participating districts. A statistically significant variation was
53 observed in all socio-demographic variables such as place of residence, type of house, type of
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family, maternal and paternal education and occupation, use of biomass fuel and parental smoking status across the four districts. We also found and report clinical variables of recruited cases across the four districts in **table 1**. While oxygen saturation by pulse-oxymetry was statistically significantly different across the sites, the proportion of cases with oxygen saturation $\leq 92\%$ was found not significant in the children across four districts ($p=0.13$).

Table 1: Distribution of socio-demographic and clinical variables among hospitalized children for participating districts (Jan 2015-April 2017)

Characteristics	Lucknow	Etawah	Patna	Darbhanga	Total	p value
Socio-demographic Characteristics	n=1025 (%)	n=389 (%)	n=744 (%)	n=671 (%)	N=2829 (%)	
Gender						
Male	659(64.29)	287(73.78)	557(74.87)	502(74.81)	2005(70.87)	<0.0001
Place of residence						
Rural	195(19.02)	279(71.72)	304(40.86)	614(91.51)	1392(49.20)	<0.0001
Urban	830(80.98)	110(28.28)	440(59.14)	57(8.49)	1437(50.80)	
Family Type						
Joint	688(67.12)	360(92.54)	707(95.03)	383(57.08)	2138(75.57)	<0.0001
Nuclear	337(32.88)	29(7.46)	37(4.97)	287(42.77)	690(24.39)	
House type						
Mud	64(6.24)	54(13.88)	123(16.53)	374(55.74)	615(21.74)	
Bricks	854(83.32)	256(65.81)	453(60.89)	85(12.67)	1648(58.25)	<0.0001
Combined	107(10.4)	79(20.31)	168(22.58)	212(31.59)	566(20.01)	
Mother's Education						
No formal education	203(19.80)	56(14.40)	328(44.09)	496(73.92)	1083(38.28)	
Class I-V	108(10.54)	28(7.20)	82(11.02)	38(5.66)	256(9.05)	<0.0001
Class VI-XII	379(36.98)	176(45.24)	243(33.66)	112(16.69)	910(32.17)	
Graduate/ Post graduation	335(32.68)	129(33.16)	91(12.23)	25(3.73)	580(20.50)	
Father's Education						
No formal education	167(16.29)	29(7.46)	153(20.56)	345(51.42)	694(24.53)	
Class I-V	85(8.29)	19(4.88)	91(12.23)	82(12.22)	277(9.79)	
Class VI-XII	437(42.63)	206(52.96)	328(44.09)	205(30.55)	1176(41.57)	<0.0001
Graduate/ Post graduation	336(32.78)	135(34.70)	172(23.12)	39(5.81)	682(24.11)	
Birth Order						
0	435(42.44)	187(48.07)	315(42.34)	192(28.61)	1129(39.91)	
1 st	343(33.46)	120(30.85)	235(31.59)	258(38.45)	956(33.79)	<0.0001
2 nd	153(14.93)	47(12.08)	129(17.34)	137(20.42)	466(16.47)	
More than 2 nd	93(9.07)	35(9.00)	62(8.33)	83(12.37)	273(9.65)	
Immunization Status						
Complete for age	792(77.27)	300(77.12)	711(95.56)	544(81.07)	2347(82.96)	
Incomplete for age	220(21.46)	84(21.59)	25(3.36)	126(18.78)	455(16.08)	<0.0001

Unimmunized	13(1.27)	5(1.29)	8(1.08)	1(0.15)	27(0.95)	
Currently Breast Feeding						
Yes	653(63.71)	256(65.81)	589(79.17)	537(80.03)	2035(71.93)	<0.0001
No	372(36.29)	133(34.19)	155(20.83)	134(19.97)	794(28.07)	
Father's Occupation						
Unemployed	13(1.27)	20(5.14)	27(3.63)	63(9.39)	123(4.35)	
Daily wages	329(32.10)	81(20.82)	165(22.18)	474(70.64)	1049(37.08)	
Salaried/ Professional	397(38.73)	104(26.74)	245(32.93)	55(8.20)	801(28.31)	<0.0001
Self-Employment	286(27.90)	184(47.30)	307(41.26)	79(11.77)	856(30.26)	
Mother's Occupation						
Home maker	961(93.76)	376(96.66)	701(94.22)	484(72.13)	2522(89.15)	
Daily wages	17(1.66)	3(0.77)	17(2.28)	171(25.48)	208(7.35)	
Salaried/Professionals	47(4.59)	9(2.31)	18(2.42)	7(1.04)	81(2.86)	<0.0001
Self-Employment	0(0.0)	1(0.26)	8(1.08)	9(1.34)	18(0.64)	
Biomass fuel						
Yes	211(20.59)	245(62.98)	263(35.35)	609(90.76)	1328(46.94)	<0.0001
No	814(79.41)	144(37.02)	481(64.65)	62(9.24)	1501(53.06)	
Smoking Status-Father						
Yes	152(14.83)	45(11.57)	56(7.53)	59(8.79)	312(11.03)	<0.0001
No	873(85.17)	344(88.43)	688(92.47)	612(91.21)	2517(88.97)	
Indoor smoking-Father						
Yes	83(8.10)	21(5.40)	16(2.15)	43(6.41)	163(5.76)	<0.0001
No	942(91.90)	368(91.60)	728(97.85)	628(93.59)	2666(94.24)	
Smoking Status-Family member						
Yes	129(12.59)	55(14.14)	45(6.05)	102(15.20)	331(11.70)	<0.0001
No	896(87.41)	334(85.86)	699(93.95)	569(84.80)	2498(83.30)	
Indoor smoking – Family member						
Yes	84(8.20)	27(6.94)	27(3.63)	94(14.01)	232(8.20)	<0.0001
No	941(91.80)	362(93.06)	717(96.37)	577(85.99)	2597(91.80)	
Clinical Variables at the time of admission at hospital	n, Mean± SD	n, Mean± SD	n, Mean± SD	n, Mean± SD	n, Mean± SD	p value
Age (months)	1025, 14.53±13.88	389, 10.69±10.95	744, 10.26±11.35	671, 12.30±13.29	2829, 12.35±12.85	<0.0001
Height (cm)	303, 68.61±13.78	324, 70.66±13.75	34, 64.38±10.25	266, 70.46±12.14	927, 69.70±13.26	<0.018
Weight (Kg)	900, 7.89±3.02	387, 7.35±2.74	682, 7.07±2.79	643, 7.70±2.88	2612, 7.55±2.90	<0.0001
Fever Duration (days)	929, 4.46±2.71	321, 3.59±2.37	689, 4.25±2.52	569, 3.54±2.47	2508, 4.08±2.59	<0.0001
Oxygen saturation (%)	528, 93.68±5.56	343, 92.56±6.20	236, 92.23±5.28	319, 94.19±4.63	1426, 93.28±5.53	<0.0001
≤92 Oxygen Saturation Value	179, 88.26±6.37	132, 87.12±6.94	122, 88.57±4.69	70, 87.1±4.17	503, 87.87±5.98	0.13

Table 2 shows proportions of radiological pneumonia among cases hospitalized for CAP in four participating districts. We found higher proportion of radiological abnormalities in Patna district [38.58 (95% CI: 35.07-42.07)] and Lucknow district [37.95 (95%CI: 34.98-40.92)] which have a large and urban population. Lower proportion of radiological abnormalities were noted in Etawah district [29.31 (95%CI: 24.78-33.82)] and Darbhanga district [27.87 (95% CI: 24.47-31.26)] which in contrast had larger rural population. We also observed correspondingly higher proportion of PEP alone or with other infiltrates in districts of Lucknow [72.49 (95% CI: 68.05-76.93)]; and Patna [64.11 (95% CI: 58.56-69.66)] and lower in districts of Etawah [64.04 (95% CI: 55.22 -72.84)]; and Darbhanga [51.34 (95% CI: 44.17-58.50)].

Table 2 also describes univariate distribution of socio-demographic and clinical factors of CAP among hospitalized children aged 2-59 months. We observed statistically significant district-wise heterogeneity in radiological abnormalities. Statistically significantly higher proportion of females hospitalized for CAP had radiologically abnormal CXR. Likewise, statistically significantly higher proportion of abnormal vs. normal CXRs findings were reported in hospitalized cases who had symptoms of fever, pallor rhonchi and vomiting or were malnourished.

Table 2: Distribution of socio-demographic and clinical factors by chest radiograph findings among hospitalized children from January 2015-April 2017

Socio-demographic & clinical factors	Interpretable chest X rays				Abnormal chest X rays		
	N=2829	Normal 1852 n (%)	Abnormal 977 n (%)	p value	PEP* alone or with other infiltrate 635 n (%)	Other infiltrates 342 n (%)	p value
Participating site							
Lucknow	1025	636 (62.05)	389 (37.95)		282 (72.49)	107 (27.51)	

Etawah	389	275 (70.69)	114 (29.31)	<0.0001	73 (64.04)	41 (35.96)	<0.0001
Patna	744	457 (61.42)	287 (38.58)		184 (64.11)	103 (35.89)	
Darbhanga	671	484 (72.13)	187 (27.87)		96 (51.34)	91 (48.66)	
Age-group (months)							
2-11	1865	1223 (65.58)	642 (34.42)	0.86	409 (63.71)	233 (36.29)	0.26
12-59	964	629 (65.25)	335 (34.75)		226 (67.46)	109 (32.54)	
Gender							
Male	2005	1354 (67.53)	651 (32.46)	<0.0001	426 (65.44)	225 (34.56)	0.72
Female	824	498 (60.43)	326 (39.56)		209 (64.44)	117 (35.89)	
Place of residence							
Rural	1392	921 (66.16)	471 (33.83)	0.44	299 (63.48)	172 (36.52)	0.34
Urban	1437	931 (64.78)	506 (35.21)		336 (66.40)	170 (33.60)	
Biomass fuel							
Yes	1501	867 (65.29)	461 (34.71)	0.44	294(63.77)	167 (36.23)	0.24
No	1328	985 (65.62)	516 (34.38)		341 (66.09)	175 (33.91)	
Immunization status							
Complete for age	2347	1546 (68.87)	801 (34.12)	0.32	516 (64.42)	285 (35.58)	0.54
Incomplete	482	306 (63.48)	176 (36.51)		119 (67.61)	57 (32.39)	
Symptoms of pneumonia							
Fever	2499	1616 (64.66)	883 (35.33)	0.014	575 (65.12)	308 (34.88)	0.82
Cyanosis	62	39 (62.90)	23 (37.09)	0.34	16 (69.57)	7 (30.43)	0.64
Pallor	764	465 (60.86)	299 (39.13)	0.002	200 (66.89)	99 (33.11)	0.41
Rhonchi	2054	1377 (67.03)	677 (32.96)	0.005	415 (61.30)	262 (38.70)	0.0003
Duration of illness fever in	2508	3.91±2.51	4.40±2.70	<0.0001	4.57±2.82	4.08±2.44	0.011

days (Mean ± SD)							
Danger Signs of pneumonia							
Vomiting	899	605 (67.30)	294 (32.70)	0.17	174 (59.18)	120 (40.82)	0.01
Lethargy	1101	732 (66.49)	369 (33.51)	0.39	247 (66.94)	122 (33.06)	0.33
Difficulty in breathing	2705	1766 (65.29)	939 (34.71)	0.39	609 (64.86)	330 (35.14)	0.73
Inability to drink	937	612 (65.31)	325 (34.69)	0.46	211 (64.92)	114 (35.08)	0.97
Convulsion	148	98 (66.22)	50 (33.78)	0.93	33 (66.0)	17 (34.0)	0.87
Blue Lips	42	27 (64.29)	15 (35.71)	0.87	12 (80.0)	3 (20.0)	0.28
Malnutrition Status							
Normal *	1912	1312 (68.62)	600 (31.38)	< 0.0001	374 (62.33)	226 (37.67)	0.06
Malnutrition*	485	314 (64.74)	171 (35.26)		115 (67.25)	56 (32.75)	
Severe malnutrition*	432	226 (52.31)	206 (47.69)		146 (70.87)	60 (29.13)	

*Normal-weight of age z score > -2SD; Malnutrition-weight of age z ≤ -2SD and Severe malnutrition-weight of age z ≤ -3SD

Table 3 describes four multivariate logistic regression models to find associates of abnormal CXR findings. After controlling for age, gender, symptoms of pneumonia, duration of illness, biomass fuel and malnutrition status of cases, statistically significant district-wise heterogeneity remained in the first three models. Models I, II and III had similar associates for radiological abnormalities whereas Model IV was different. Across all the four models, female cases of CAP and those who had severe malnutrition had statistically significantly higher risk for having abnormal CXRs. A higher risk of radiological abnormalities was also observed in those children who had longer duration of illness.

Table 3: Independent Associations between Chest Radiograph Findings and demographic and clinical factors, among hospitalized children January 2015-April 2017

Variables	Model – I Abnormal/Normal ^{Ref}		Model – II PEP alone or with other infiltrate /Normal ^{Ref}		Model – III PEP alone Vs. Normal ^{Ref}		Model – IV Other infiltrate / Normal ^{Ref}	
	Adjusted Odd Ratio (95%CI)	p value	Adjusted Odd Ratio (95%CI)	p value	Adjusted Odd Ratio (95%CI)	p value	Adjusted Odd Ratio (95%CI)	P value
Districts								
Lucknow Vs. Others	1.58 (1.20-2.10)	<0.0001	2.07 (1.48-2.89)	<0.0001	2.20 (1.52-3.19)	<0.0001	0.98 (0.65-1.47)	0.93
Etawah Vs. Others	1.22 (0.88-1.70)	0.23	1.30 (0.87-1.95)	0.19	1.49 (0.95-2.30)	0.07	1.17 (0.74-1.87)	0.50
Patna Vs. Others	1.67 (1.27-2.20)	<0.0001	1.89 (1.36-2.64)	<0.0001	2.25 (1.56-3.24)	<0.0001	1.39 (0.95-2.07)	0.09
Age – Group (months)								
2-11 ^{Ref}								
12-59	0.92 (0.77-1.10)	0.34	0.95 (0.77-1.17)	0.62	1.03 (0.82-1.29)	0.79	0.86 (0.66-1.13)	0.27
Gender								
Male ^{Ref}								
Female	1.39 (1.16-1.66)	<0.0001	1.34 (1.08-1.65)	0.008	1.28 (1.01-1.61)	0.03	1.48 (1.14-1.92)	0.004
Symptoms of pneumonia[¶]								
Rhonchi	0.83 (0.68-1.01)	0.06	0.72 (0.57-0.90)	0.005	0.75 (0.59-0.96)	0.02	1.14 (0.83-1.55)	0.42
Pallor	1.30 (1.08-1.58)	0.006	1.28 (1.03-1.60)	0.02	1.22 (0.95-1.55)	0.12	1.34 (1.01-1.77)	0.04
Vomiting	0.90 (0.75-1.09)	0.28	0.80 (0.64-0.99)	0.04	0.78 (0.62-1.01)	0.05	1.09 (0.83-1.08)	0.51
Duration of illness, fever (days)	1.06 (1.04-1.09)	<0.0001	1.08 (1.04-1.12)	<0.0001	1.08 (1.04-1.12)	<0.0001	1.03 (0.98-1.48)	0.24
Biomass fuel	1.28 (1.05-1.57)	0.02	1.39 (1.10-1.76)	0.006	1.40 (1.14-1.88)	0.003	1.08 (0.79-1.45)	0.64
Malnutrition Status								
Normal ^{*Ref}								
Malnutrition*	1.16 (0.93-1.45)	0.20	1.19 (0.92-1.55)	0.19	1.19 (0.90-1.59)	0.22	1.06 (0.76-1.48)	0.69
Severe malnutrition*	1.64 (1.30-2.06)	<0.0001	1.80 (1.39-2.34)	<0.0001	1.86 (1.40-2.46)	<0.0001	1.33 (0.94-1.89)	<0.10

Abbreviations used: ^{Ref} Reference Category

Footnotes: [¶] No signs of pneumonia taken as a reference

*Normal-weight of age z score > -2SD; Malnutrition-weight of age z ≤ -2SD and Severe malnutrition-weight of age z ≤ -3SD

DISCUSSION

This prospective hospital-based surveillance study was conducted to assess the radiological abnormalities in children (2-59 months) residing in pre-specified districts of Uttar Pradesh and Bihar, India and hospitalized with CAP. The study was conducted from January 2015 to April 2017, prior to introduction of PCV in NIP of Government of India ⁹. In our study, among interpretable CXRs, we found 22.44% (635/2829) children had PEP alone or with infiltrates, other infiltrates only 12.09% (342/2829) and 65.46% (1852/2829) had normal CXRs findings. Our study used WHO case definition for CAP ¹⁸. A panel of three trained radiologists interpreted CXRs, adopting WHO recommended methodology ^{11 12}. These make our study methodology robust and results generalizable.

In our study, there were 88.54% (2829/3195) interpretable CXRs. This is similar to 83% (3587/3973) interpretable CXRs reported by Pneumonia Etiology Research for Child Health (PERCH) study conducted on 4232 children (1-59 months) to assess the etiology of CAP in nine sites of seven countries ²⁴. Consistent with PERCH findings, a vaccine probe trial conducted in Gambia found the proportion of interpretable CXRs among unvaccinated cases of pneumonia to be 84.32% (242/287) ²⁵.

There have been several studies in the past two decades, which have reported CXRs findings in hospitalized cases of CAP. Almost all of these were conducted before the introduction of PCV in their respective regions. A small prospective study conducted in Ethiopia reported radiological abnormality in CXRs to be 48.3% (95% CI 39.49-57.22) in 122 children (3 months-14 years) clinically diagnosed with WHO-defined severe pneumonia ²⁶. Similar findings were reported

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3 from the Gambian vaccine probe trial where the proportion of radiological abnormality was 45%
4 (95% CI: 43.35-46.46) among unvaccinated hospitalized cases of clinical pneumonia. PERCH
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6 (95% CI: 52.31-55.57) of CXRs among cases of CAP were abnormal ²⁴.
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8 In all of these studies, proportion of cases with abnormal CXRs is higher than 34.5% (95% CI
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10 32.8-36.3) found by us in the current study. However, our findings are similar to PERCH rural
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12 study site of Matlab, Bangladesh that reported radiological abnormality in 35.3% (95% CI:
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14 29.77-40.85) CXRs of hospitalized cases of CAP ²⁴. Another PERCH urban site of Dhaka,
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16 Bangladesh reported 63.10% (95% CI 56.18 -70.02) cases with abnormal CXRs ²⁴. In our study,
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18 radiological abnormalities in CXRs were higher in cases from largely urban districts of Patna and
19
20 Lucknow compared to rural districts of Darbhanga and Etawah. This is consistent with rural-
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22 urban differences in Bangladesh sites of PERCH. Variation in CXR findings among cases of
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24 CAP may be due to infecting organism, immune response of patient and prior duration of
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26 disease.
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35 In 2016, WHO's Department of Immunization, Vaccines and Biologicals standardized the
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37 categorization of radiological pneumonia and established that PEP can be taken as a good
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39 surrogate marker of SP in epidemiological and vaccine efficacy studies ¹². In our study, 22.44 %
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41 (95% C.I. 20.90 -23.98), CXRs were having PEP alone or with other infiltrates. This is similar to
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43 PERCH study that reported PEP alone or with other infiltrates in 27% (95% C.I. 25.50 -28.40)
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45 hospitalized cases of CAP ²⁴. Another study conducted in Gambia reported that 45% (95% CI:
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47 43.35-46.46) non-vaccinated children had PEP and/or other infiltrates ²⁵. PEP has been
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49 associated with increased risk of treatment failure (p=0.002), increased length of hospitalization
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3 (p=0.0003) and more days of respiratory support (p=0.002) in Botswana when compared with
4 cases reporting `no significant pathology` on CXRs ²⁷.
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10 In our study, female gender (p<0.001) was at the higher risk of developing radiological
11 abnormalities compared to males (**table 3**). The results are in concordance with a hospital-based
12 case-control study carried out in Brazil that reported male gender as a protective factor against
13 pneumonia (OR = 0.53; 95 % CI 0.39–0.72) ²⁸. Another study in Mozambique, Africa reported
14 that male gender was not significantly associated with presence of radiological abnormalities
15 (OR =0.77 (95 % CI 0.56–1.05) in children (0-59 months) suffering from severe pneumonia ²⁹.
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17 However, in contrast, a Gambian study reported male preponderance for all pneumonia that was
18 most marked for `other infiltrates/abnormalities` pneumonia ²⁵.
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31 A systematic review with meta-analysis conducted in 2019 suggests that no one clinical feature
32 is sufficient on its own to diagnose of radiological pneumonia ³⁰. However other socio-
33 demographic and clinical correlates of abnormal CXRs found by us (Model 1), which increased
34 the risk of radiological abnormalities, were presence of pallor, severe malnutrition, longer
35 duration of illness and exposure to biomass fuel. Exposure to biomass fuel at the time of cooking
36 is an important factor that impacts the severity of CAP in developing countries ³¹. In rural India,
37 majority of the households use biomass fuel like firewood, dung cakes and wood for cooking ³².
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39 Young children are at risk to adverse effects of exposure to biomass fuel as either the households
40 have no separate cooking space or have poor ventilation and sometimes young children stay with
41 their mother while she cooks.
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3 Specific correlates of PEP/Radiological Pneumonia (Models II and III) possibly due to SP, other
4 than those mentioned above, were presence of vomiting and ronchi on auscultation, both of
5 which were found to be protective. These symptoms/signs are more often reported in viral
6 pneumonia³³. No specific correlates of radiological abnormalities of `other infiltrates` (Model
7 IV) were found by us. Hence it is difficult to attribute radiological findings of other infiltrates to
8 either bacterial or viral etiology.
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19 Based on our study, almost two-third hospitalized cases of CAP had normal CXRs and this could
20 be perhaps of viral etiology. This is supported by a recent study that reported 61.4% (95% CI
21 57.3–65.6) cases to be viral³³. Among one-third of cases of CAP had abnormal CXRs and thus
22 were more likely to be bacterial in etiology, and two-thirds of which were possibly due to SP.
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31 CONCLUSION

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34 Among hospitalized cases of community-acquired pneumonia, almost one-third children had
35 abnormal chest radiographs of which about two-thirds had abnormalities related with possible
36 bacterial etiology (SP). Hence, the introduction of pneumococcal vaccination is likely to reduce
37 the burden of childhood pneumonia in India. Since the study was done prior to the introduction
38 of PCV in India, continued surveillance will be required to assess the impact of PCV on
39 radiological findings in cases admitted with CAP. The impact of introduction of PCV in NIP on
40 under-five mortality rate and burden of CAP needs to be assessed.
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45

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Supporting Information

S1 Appendix: Chest radiograph interpretation form

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Figure Legend

Figure 1: Flow diagram of cases of community acquired pneumonia recruited from participating districts before the introduction of pneumococcal conjugate vaccine (January 2015-April 2017)

Figure 1: Flow diagram of cases of community acquired pneumonia recruited from participating districts before introduction of pneumococcal conjugate vaccine (January 2015-April 2017)

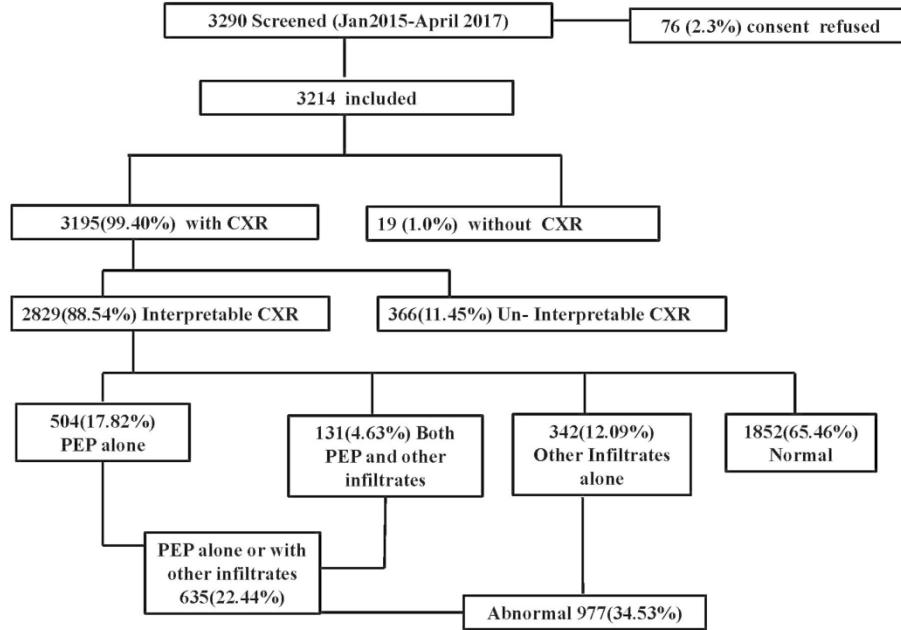


Figure 1: Flow diagram of cases of community acquired pneumonia recruited from participating districts before the introduction of pneumococcal conjugate vaccine (January 2015-April 2017)

254x190mm (300 x 300 DPI)

Childhood Pneumonia Surveillance
Department of Paediatrics, KGMU, Lucknow ,UP

Form-R
(RADIOLOGY REPORT FORM)

1	Drs_ID	[][][][]
	Radiology Report	Patient Details
2	IDNo:	[] / [] / [][][][][][] State /District / Unit / Subject number (For office use)
2	Date Of Report	[][]/[][]/[][][][] (DD/MM/YYYY)
	Report Details	Findings (tick one)
3	Image Quality	Adequate <input type="checkbox"/> Suboptimal <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
4	Significant Pathology	Yes <input type="checkbox"/> No <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
5	End Point Consolidation	
5a	Left	Yes <input type="checkbox"/> No <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
5b	Right	Yes <input type="checkbox"/> No <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
		Uninterpretable
6	Other Infiltrates/Abnormalities	
6a	Left	Yes <input type="checkbox"/> No <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
6b	Right	Yes <input type="checkbox"/> No <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
7	Pleural Fluid	
7a	Left	Yes <input type="checkbox"/> No <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
7b	Right	Yes <input type="checkbox"/> No <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
8	Comments:	<input type="text"/>
9	Conclusion:	a) Primary endpoint pneumonia only <input type="checkbox"/> b) Other infiltrate only <input type="checkbox"/> c) Both PEP and other infiltrate <input type="checkbox"/> d) Normal <input type="checkbox"/> e) Un-interpretable for any findings <input type="checkbox"/>

BMJ Open

Chest Radiograph Findings in children aged 2-59 months hospitalized with Community-Acquired Pneumonia, prior to the introduction of Pneumococcal Conjugate Vaccine in India- A Prospective Multisite Observational Study

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Title: *Chest Radiograph Findings in children aged 2-59 months hospitalized with Community-Acquired Pneumonia, prior to the introduction of Pneumococcal Conjugate Vaccine in India- A Prospective Multisite Observational Study*

Short Title: *Radiological Findings in Children hospitalized with Community-Acquired Pneumonia in India Pre-Pneumococcal Conjugate Vaccine introduction*

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ABSTRACT

Objectives: To assess radiological abnormalities in chest X-rays and to identify the demographic and clinical correlates of specific radiological abnormalities in children aged 2-59 months, hospitalized with World Health Organization defined community-acquired pneumonia, residing in pre-specified districts of Uttar Pradesh and Bihar, India.

Design: Prospective, hospital-based surveillance

Setting: Multi-site study conducted in a network of 117 secondary/tertiary care hospitals in four districts of Uttar Pradesh and Bihar, India.

Participants: Included were children aged 2-59 months hospitalized with community-acquired pneumonia, residing in project district, with duration of illness of <14 days and who were not hospitalized elsewhere for this episode nor had been recruited previously.

Main outcome measure: Radiological abnormalities in the chest X-rays, where there was concordance between two or more of the panel of three trained radiologists.

Results: From January 2015 to April 2017, 3214 cases were recruited and in 99.40 % (3195/3214) chest X-rays were available. Among 88.54 % (2829/3195) interpretable X-rays, 34.53 % (977/ 2829, 95% C.I. 32.78 -36.28) had some radiological abnormalities, while the rest were normal. Primary endpoint pneumonia alone or with other infiltrates was found in 22.44 % (635/2829, C.I. 20.90 %-23.98 %), other infiltrates only in 12.09% (342/ 2829; C.I. 10.88 %-13.29 %). There was a statistically significant inter-district variation in radiological abnormality. Statistically significantly higher proportion of abnormal chest X-ray was found among girls, those with weight-for-age z score ≤ -3 SD, longer duration of fever, pallor and with exposure to biomass fuel.

Conclusions: Among hospitalized cases of community-acquired pneumonia, almost one-third children had abnormal chest radiographs of which about two-thirds had abnormalities related with possible bacterial etiology (*Streptococcus pneumoniae*). Hence introduction of pneumococcal vaccination is likely to reduce burden of childhood pneumonia in India.

Key words: Chest radiographs, Hospitalized community-acquired pneumonia, under-five, *Streptococcus pneumoniae*, India

Strengths and Limitations of the Study

- Prospective, multisite recruitments from a large hospital surveillance network established for the project in four districts in two states of India that have high under-five mortality rates
- Standard World Health Organization definition was used for identifying hospitalized cases of clinical pneumonia
- Radiological abnormalities interpreted by a panel of three trained radiologists at locations out of the surveillance network, blinded to each other as well as clinical features of the case
- Since pre-existing X-rays machines were used in this pragmatic study, there was a variation in the quality of images obtained, which were minimized by digitizing them centrally
- Since the objective of the study was to assess the radiological abnormalities in chest X-rays of recruited cases, clinical data was recorded by pre-existing hospital staff, there could be some inter-observer variations.

1 INTRODUCTION

2 Community-acquired pneumonia (CAP) is the single largest infectious cause of death in young
3 children worldwide. Globally, pneumonia accounts for 16% of deaths in children under-five years of
4 age and results in almost one million deaths (0.9 million children in 2016) every year^{1 2}. Most
5 deaths due to pneumonia occur in low and middle income countries particularly in sub-Saharan
6 Africa and South Asia^{2 3}. In India, there were approximately 0.44 million under-five deaths due to
7 CAP in the year 2015⁴.

8
9 CAP could have viral or bacterial etiology^{5 -7}. Etiology varies from country to country and also
10 across different time periods. Pediatric bacterial pneumonia is predominantly caused by
11 *Streptococcus pneumoniae* (SP) and *Hemophilus influenzae Type B* (HiB) while Respiratory
12 syncytial virus and Influenza A or B virus are important contributors of pediatric viral
13 pneumonia^{5 6}. The World Health Organization (WHO) recommends the introduction of
14 Pneumococcal Conjugate Vaccine (PCV) in the national immunization programme of countries
15 with high child mortality rates, which includes India⁸. Consequently, PCV-13 was launched in
16 May 2017 under the national immunization programme of five Indian states (Uttar Pradesh,
17 Bihar, Rajasthan, Madhya Pradesh and Himachal Pradesh) in a phased manner⁹. It is expected to
18 be rolled out in other parts of the country in the near future. Vaccination against HiB is already
19 under the national immunization programme since 2011.

20
21 Differentiating bacterial from viral etiology of CAP on clinical features or by investigations
22 remains difficult^{7 10 11}. Several PCV probe trials have used radiographically confirmed alveolar

23 pneumonia, also called end-point pneumonia, to be an outcome for vaccine efficacy and this has
24 been endorsed by WHO ¹²⁻¹⁴.

26 The current study was a hospital-based surveillance to assess the radiological abnormalities in
27 chest X-rays (CXRs) and to identify the demographic and clinical correlates of specific
28 radiological abnormalities in children aged 2-59 months, hospitalized with WHO defined CAP,
29 residing in pre-specified districts of Uttar Pradesh and Bihar, India.

31 **METHODS**

32 **Study design and Setting**

33 This prospective multi-site observational study was conducted in Lucknow and Etawah districts
34 of Uttar Pradesh and Patna & Darbhanga districts of Bihar, India. Uttar Pradesh is the first most
35 populated and Bihar third most populated state of India^{15 16}. In Lucknow district 66.2% population
36 resides in urban areas and in Patna district 43.07% ^{15 16}. In contrast, only 22.3% population of
37 Etawah district and 9.74% population of Darbhanga district resides in urban areas ^{15 16}. All four
38 project districts have alarmingly high infant and child mortality indicators ¹⁵⁻¹⁷. The under-five
39 mortality rates of Lucknow (58/1000), Etawah (85/1000), Patna (46/1000) and Darbhanga
40 (77/1000) districts are above the national average (50/1000) ¹⁵⁻¹⁷. Similarly, the infant mortality
41 rates of Lucknow (44/1000), Etawah (56/1000), Patna (31/1000) and Darbhanga (44/1000)
42 districts are also higher than the national average (41/1000) ¹⁵⁻¹⁷.

44 **Study Population**

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2
3 45 A hospital-based surveillance system was established for this study^{17 18}. Included in the
4
5 46 surveillance were public and private hospitals of study districts which provided either secondary
6
7 47 or tertiary level care to admitted children. All children (2-59 months), hospitalized in network
8
9 48 hospitals between January 2015 to April 2017, with history of fast breathing with/without chest
10
11 49 in-drawing were screened¹⁸.
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17 51 Included were children hospitalized with symptoms of WHO defined CAP and residing in the
18
19 52 project district¹⁸. WHO has developed guidelines for hospital-based management of common
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21 53 childhood illness such as pneumonia¹⁹. According to these guidelines, fast breathing ≥ 50
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23 54 breaths/minute in a child aged 2–11 months and ≥ 40 breaths/minute in a child aged 12-59
24
25 55 months along with chest indrawing was categorized as having 'pneumonia'¹⁹. A child presenting
26
27 56 with cough or difficulty in breathing with: (a) oxygen saturation $< 90\%$ or central cyanosis (b)
28
29 57 severe respiratory distress (e.g. grunting, very severe chest indrawing) and (c) signs of
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31 58 pneumonia with a general danger sign (inability to breastfeed or drink, lethargy or reduced level
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33 59 of consciousness, convulsions) was categorized as having 'severe pneumonia'¹⁹. Excluded were
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35 60 children with cough for ≥ 14 days or those that had been hospitalized in last 14 days¹⁸.
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43 62 **Sample Size**

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45 63 We assumed that the incidence of radiological pneumonia is 3/100 child years of observations.
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47 64 Then for a margin of error of 1.5/100 child years of observation, incidence of pneumonia in the
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49 65 community of 20/100 child years of observation, alpha level of 0.05, and power of 90% when the
50
51 66 estimated population of children under-five years of age in Lucknow district²⁰ is 750,000; 693
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53 67 cases had to be included per district.
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68 **Data collection**

69 Data was collected by surveillance officers who had postgraduate degree in social sciences and
70 almost 10 years experience in community based health research. After recruitment, they were
71 imparted six-day centralized training on project procedures and logistics. Class-room as well as
72 practical skills-training was given by the coordinating centre in Lucknow. Pre and post tests were
73 conducted to ascertain knowledge and skills acquired by them through the training to ensure
74 quality in data collection. The coordinating centre provided annual refresher trainings to the
75 surveillance officers from all four sites in Lucknow.

77 After obtaining written, informed consent of the caregivers, data was collected through face-to-
78 face interviews with them as well as by abstraction from hospital records. Socio-demographic
79 data, obtained by interviewing caregivers, was: child's age, gender, residence, birth order,
80 immunization status, current breastfeeding status, parental education and occupation, smoking
81 status of parents, family type, housing infrastructure, use of biomass fuel etc. Caregivers were
82 also asked about the symptoms of disease and its duration in days.

84 Clinical data, recorded by pre-existing hospital staff at the time of hospitalization, was
85 abstracted. Where available, data was collected on anthropometry (weight and height), fever
86 (axillary temperature $\geq 37.5^{\circ}\text{C}$), oxygen saturation by pulse oxymetry, pallor, central cyanosis,
87 and danger signs of pneumonia and vital signs (heart rate and respiratory rate). Presence of
88 wheezing on auscultation of chest was abstracted, when recorded. At the hospitals, clinicians
89 generally used Integrated Management of Childhood Illness (IMCI) definitions²¹ to identify
90 pallor, cyanosis, wheeze on auscultation and general danger sign as it is incorporated in their

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3 91 medical undergraduate training. Most doctors of public health sector also receive a formal in-
4
5 92 service training on IMCI ²¹. Clinical outcome (survival or mortality) was noted from hospital
6
7
8 93 records on follow up.^{17 18}
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10 94

95 **Chest x-ray (CXR) image acquisition and archiving**

15 96 CXR (poster-anterior view) was done when advised by the treating physician. These CXRs were
16
17 97 obtained by the surveillance staff at the time of recruitment. CXRs were either analog or digital.
18
19 98 In case of digital CXRs, second copy was obtained where possible. If only single analog image
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21 99 was available, then the hardcopy of CXR was obtained from the caregiver after the child was
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24 100 discharged. If this could not be done, image of the hardcopy was captured. CXR machines were
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26
27 101 not provided through the project.
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29 102

31 103 CXRs of recruited cases were subsequently scanned and converted into digital format using a
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33 104 diagnostic-quality film image digitalizer (Microteck International Limited, model Medi 6000
34
35 105 plus) ²². CXRs obtained/converted into digital image were stored as per the standard operating
36
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38 106 procedure and were subsequently archived for web-based radiological interpretation. Digital
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40 107 images were stored in JPEG format at 300 dpi resolution. Each CXR file was anonymized and
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42
43 108 given a unique identification number. Digital CXRs were uploaded on online data management
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45 109 software, developed especially for the project.
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50 111 **Interpretation of radiological images**

52 112 A panel of radiologists was constituted for standardized interpretations of CXRs. Four
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54
55 113 radiologists were part of this panel, one of whom was Project co-investigator-Radiology (NK).
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3 114 All radiologists are faculty in medical teaching institutes and also look after pediatric radiology.
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5 115 They all have more than fifteen years experience in interpreting pediatric CXRs.
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10 117 Radiologists were trained according to the methodology developed by Department of
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12 118 Immunization, Vaccines, and Biologicals of the WHO ¹¹. An international WHO-certified
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14 119 trainer from the International Centre for Diarrhoeal Disease Research, Bangladesh imparted a
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16 120 two-day in-house training to the radiologists. Training objective was to standardize interpretation
17
18 121 and coding of CXRs, to develop a CXR reporting form [S1 Appendix] and to provide training
19
20 122 on web-based CXR retrieval and reporting system. During the training, 210 CXRs of WHO data
21
22 123 set were used. For assessing concordance post training, another set of 48 CXRs was provided for
23
24 124 interpretation to individual radiologists. Post-test agreement with WHO findings was calculated,
25
26 125 which was about 80%. Inter-observer variation was about 25% and was for minor interpretation
27
28 126 like quality of film, end point infiltrates etc. Repeat training was conducted on an additional set
29
30 127 of 44 CXRs provided by WHO to ensure standardization in interpretation. Thereafter,
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32 128 concordance achieved by the radiologists was reviewed quarterly by the study arbitrator.
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34 129 Radiologists met annually to review key concepts and discuss challenges faced in interpreting
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36 130 CXRs.
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45 132 After training, radiologists independently reviewed CXRs and registered their findings in an
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47 133 online standardized chest radiograph interpretation form [S1 Appendix]. For optimal viewing of
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49 134 CXRs, all radiologists used similar workstations. Specifications were provided for the computer
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51 135 monitor and hardware to be used. It was ensured that monitors had the correct brightness and
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53 136 contrast adjustment for optimal viewing.
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6 138 During online evaluation, radiologists recorded the quality of film, findings of CXRs and
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8 139 conclusion. Radiologists interpreted film quality as follows: (a) *'Adequate/optimal'* for features
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10 140 that allow confident interpretation of consolidation and pleural effusion as well as other
11
12 141 infiltrates; (b) *'Suboptimal'* for features that allow interpretation of consolidation and pleural
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14 142 effusion, but not of other infiltrates or findings and (c) *'Un-interpretable'* pertaining to features
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16 143 of the image that are not interpretable with respect to presence or absence of consolidation or
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18 144 pleural effusion without additional images¹².
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24 146 After interpreting film quality, radiologists interpreted the pathological findings. For each
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26 147 radiographic finding, there were two options to be chosen: 'yes' for the presence of pathological
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28 148 findings and 'no' for its absence. Pathological findings were classified into significant pathology
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30 149 (including pleural effusion) and the presence of consolidation and infiltrates. *'End-point*
31
32 150 *consolidation'* for CXRs was defined as dense or confluent opacity that occupies a portion or
33
34 151 whole of a lobe or the entire lung, that may or may not contain air bronchograms. Portion of the
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36 152 lung would mean the opacity covering the width of intercostal spaces plus the width of one
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38 153 adjacent rib. *'Other (non end-point) infiltrate'* for CXRs was defined as linear and patchy
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40 154 opacities (interstitial infiltrate) in a lacy pattern, featuring peri-bronchial thickening and multiple
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42 155 areas of atelectasis or minor patchy infiltrates that are not of sufficient magnitude to constitute
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44 156 endpoint consolidation, and small areas of atelectasis that in children may be difficult to
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46 157 distinguish from consolidation. *'Pleural effusion'* was defined as presence of fluid in the lateral
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48 158 pleural space between the lung and chest wall that is spatially associated with a pulmonary
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50 159 parenchymal infiltrate (including 'other infiltrate') or has obliterated enough of the hemithorax to
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3 160 obscure any infiltrate. In most cases, this will be seen at the costo-phrenic angle or as a layer of
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5 161 fluid adjacent to the lateral chest-wall. This does not include fluid seen in the horizontal or
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8 162 oblique fissures ¹².
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12 164 Final conclusions were categorised into: (a) *'Primary End Point Pneumonia only'* (PEP) on the
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14 165 presence of consolidation or pleural effusion; (b) *'Other (non end-point) infiltrate only'* on the
15
16 166 presence of other (non-consolidation) infiltrates as defined above in the absence of a pleural
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19 167 effusion (c) *'Both PEP and other infiltrate'* and (d) *'Normal'* when there were no findings
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21 168 consistent with 'endpoint consolidation' or 'other infiltrate' or 'pleural effusion' ¹².
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26 170 After radiological interpretation, online data was archived, stored and checked for
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28 171 inconsistencies and completeness by the data manager. CXRs with concordant and discordant
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30 172 interpretations were identified. Interpretations were considered concordant when there was an
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32 173 agreement between two or more radiologists and discordant if all the three radiologists disagreed.
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34 174 Discordant interpretations were forwarded to the study arbitrator (NK). Arbitrator assessed
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36 175 discordant CXRs online and her interpretation was taken as final.
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41 42 177 **Data management and statistical analysis**

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45 178 Clinical data of hospital surveillance network was entered online in customized software.
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47 179 Primary entry was done by the four participating sites. Secondary data entry was done by the
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49 180 coordinating site in separate customized software. Anonymized CXRs were uploaded on
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51 181 customized software. Each of the three panelists assessed the CXRs online, blind to peer
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182 assessments as well as clinical features of the case. CXR assessment data was downloaded from
183 the online software in MS Access database.

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185 Exploratory data analysis was performed for detection of outlier and missing observations for all
186 the variables. Descriptive statistics was calculated for continuous variables as mean \pm standard
187 deviation and categorical variables in percent. Un-interpretable CXRs were not analyzed. Among
188 interpretable CXRs, those radiological abnormalities where there was concordance between the
189 two radiologists, were taken as final. Weight-for-age (WAZ) z-score each child was calculated
190 using WHO Anthro Survey Analyser ²³. Weight of 7.59% (215/2829) children was missing in
191 our data. Missing weight of recruited children was estimated using regression based imputation
192 technique ²⁴. Kappa statistics was performed for agreement analysis among radiologists for
193 CXRs findings. Statistical analysis was performed using SPSS version 22.0 (Chicago, IL) ²⁵. A
194 p-value of <0.05 was taken as statistically significant using a two-tailed distribution.

195
196 Univariate analysis was performed to evaluate heterogeneity, stratified by four participating sites
197 for socio-demographic variables such as child's age, gender, residence, birth order,
198 immunization status, current breastfeeding status, parental education and occupation, smoking
199 status of parents, family type, housing infrastructure, use of biomass fuel and for clinical
200 variables such as weight, height, duration of fever and oxygen saturation.

201
202 We report proportions of radiological abnormalities among hospitalized children for CAP by
203 four districts. Univariate analysis was performed to assess association of socio-demographic
204 variables and clinical signs of CAP with radiological abnormalities. Chi-square test was used for

1
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3 205 categorical variables and student's t-test for continuous variables. ANOVA test was used for
4
5 206 more than two groups to test the significance of continuous variables. Multivariate unconditional
6
7 207 logistic regression was performed find association of presence of various radiological
8
9 208 abnormalities, controlling for district of residence and other variables that had univariate
10
11 209 association with radiological abnormalities (p value ≤ 0.2) and/or were clinically meaningful.
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16
17 211 We developed four models and in these four models dependent (outcome) were:

18
19 212 Model I: Abnormal vs. Normal

20
21 213 Model II: Primary End Point Pneumonia (PEP) alone or with infiltrates vs. Normal

22
23 214 Model III: Primary End Point Pneumonia (PEP) alone vs. Normal

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25 215 Model IV: Other infiltrates only vs. Normal

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27 216
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31 217 Independent variables that were kept across all the four models were : participating districts, age,
32
33 218 gender, use of biomass fuel, symptoms of CAP such as duration of illness, presence of wheeze
34
35 219 on auscultation, pallor, vomiting everything and malnutrition status of the case [$WAZ \leq -2$ SD
36
37 220 (malnourished) and $WAZ \leq -3$ SD (severely malnourished)].
38
39

40 221

41 42 222 **Patient and public involvement in research**

43
44
45 223 Patients or public were not involved in the development of research question, study design or
46
47 224 conducting the research. Reporting of this research conforms to the guidelines for Strengthening
48
49 225 the Reporting of Observational Studies in Epidemiology (STROBE)²⁶.
50
51

52 226

53 54 55 227 **RESULTS**

228 A total of 3290 hospitalized cases were screened in hospital surveillance network of Lucknow
 229 and Etawah districts of Uttar Pradesh and Patna & Darbhanga districts of Bihar. Out of these,
 230 3214 cases fulfilling the WHO diagnosis of CAP were included [Figure 1]. Among them, 3195
 231 (99.40%) cases were enrolled with CXRs and only in 19 (1.0%) cases CXRs were not done. Out
 232 of these 88.54% (2829/3195) CXRs were found interpretable and remaining 11.45% (366/3195)
 233 were found un-interpretable by radiologists. Among interpretable CXRs, we found 22.44%
 234 (635/2829) children had primary end point pneumonia (PEP) alone or with infiltrates, 12.09%
 235 (342/2829) other infiltrates only and 65.46% (1852/2829) had normal CXRs findings [Figure 1].
 236 Concordance among ≥ 2 radiologists for CXRs findings was 86.0%. Kappa statistics was
 237 calculated for agreement of CXRs findings between Reader 1 versus Reader 2 ($K_1=0.31$), Reader
 238 2 versus Reader 3 ($K_2=0.46$) and Reader 3 versus Reader 1 ($K_3=0.42$).

240 **Table 1** shows univariate distribution of socio-demographic and clinical variables among
 241 hospitalized cases across four participating districts. A statistically significant variation was
 242 observed in all socio-demographic variables such as place of residence, type of house, type of
 243 family, maternal and paternal education and occupation, use of biomass fuel and parental
 244 smoking status across the four districts. We also report clinical variables of recruited cases across
 245 the four districts in **table 1**. Oxygen saturation by pulse-oxymetry was statistically significantly
 246 different across the sites, the proportion of cases with oxygen saturation ≤ 90 % was found also
 247 found statistically significant in children across four districts ($p < 0.0001$).

248

249 **Table 1: Distribution of socio-demographic and clinical variables among hospitalized children for**
 250 **participating districts (Jan 2015-April 2017)**

Characteristics	Lucknow	Etawah	Patna	Darbhanga	Total	
Socio-demographic	n=1025	n=389	n=744	n=671	N=2829	p value

Characteristics	(%)	(%)	(%)	(%)	(%)	
Gender						
Male	659(64.29)	287(73.78)	557(74.87)	502(74.81)	2005(70.87)	<0.0001
Place of residence						
Rural	195(19.02)	279(71.72)	304(40.86)	614(91.51)	1392(49.20)	<0.0001
Urban	830(80.98)	110(28.28)	440(59.14)	57(8.49)	1437(50.80)	
Family Type						
Joint	688(67.12)	360(92.54)	707(95.03)	383(57.08)	2138(75.57)	<0.0001
Nuclear	337(32.88)	29(7.46)	37(4.97)	287(42.77)	690(24.39)	
House type						
Mud	64(6.24)	54(13.88)	123(16.53)	374(55.74)	615(21.74)	
Bricks	854(83.32)	256(65.81)	453(60.89)	85(12.67)	1648(58.25)	<0.0001
Combined	107(10.4)	79(20.31)	168(22.58)	212(31.59)	566(20.01)	
Mother's Education						
No formal education	203(19.80)	56(14.40)	328(44.09)	496(73.92)	1083(38.28)	
Class I-V	108(10.54)	28(7.20)	82(11.02)	38(5.66)	256(9.05)	<0.0001
Class VI-XII	379(36.98)	176(45.24)	243(33.66)	112(16.69)	910(32.17)	
Graduate/ Post graduation	335(32.68)	129(33.16)	91(12.23)	25(3.73)	580(20.50)	
Father's Education						
No formal education	167(16.29)	29(7.46)	153(20.56)	345(51.42)	694(24.53)	
Class I-V	85(8.29)	19(4.88)	91(12.23)	82(12.22)	277(9.79)	
Class VI-XII	437(42.63)	206(52.96)	328(44.09)	205(30.55)	1176(41.57)	<0.0001
Graduate/ Post graduation	336(32.78)	135(34.70)	172(23.12)	39(5.81)	682(24.11)	
Birth Order						
1 st	435(42.44)	187(48.07)	315(42.34)	192(28.61)	1129(39.91)	
2 nd	343(33.46)	120(30.85)	235(31.59)	258(38.45)	956(33.79)	<0.0001
3 rd	153(14.93)	47(12.08)	129(17.34)	137(20.42)	466(16.47)	
More than 3 rd	93(9.07)	35(9.00)	62(8.33)	83(12.37)	273(9.65)	
Immunization Status						
Complete for age	792(77.27)	300(77.12)	711(95.56)	544(81.07)	2347(82.96)	
Incomplete for age	220(21.46)	84(21.59)	25(3.36)	126(18.78)	455(16.08)	<0.0001
Unimmunized	13(1.27)	5(1.29)	8(1.08)	1(0.15)	27(0.95)	
Currently Breast Feeding						
Yes	653(63.71)	256(65.81)	589(79.17)	537(80.03)	2035(71.93)	<0.0001
No	372(36.29)	133(34.19)	155(20.83)	134(19.97)	794(28.07)	
Father's Occupation						
Unemployed	13(1.27)	20(5.14)	27(3.63)	63(9.39)	123(4.35)	
Daily wages	329(32.10)	81(20.82)	165(22.18)	474(70.64)	1049(37.08)	
Salaried/ Professional	397(38.73)	104(26.74)	245(32.93)	55(8.20)	801(28.31)	<0.0001
Self-Employment	286(27.90)	184(47.30)	307(41.26)	79(11.77)	856(30.26)	
Mother's Occupation						
Home maker	961(93.76)	376(96.66)	701(94.22)	484(72.13)	2522(89.15)	
Daily wages	17(1.66)	3(0.77)	17(2.28)	171(25.48)	208(7.35)	
Salaried/Professionals	47(4.59)	9(2.31)	18(2.42)	7(1.04)	81(2.86)	<0.0001
Self-Employment	0(0.0)	1(0.26)	8(1.08)	9(1.34)	18(0.64)	
Biomass fuel						
Yes	211(20.59)	245(62.98)	263(35.35)	609(90.76)	1328(46.94)	<0.0001
No	814(79.41)	144(37.02)	481(64.65)	62(9.24)	1501(53.06)	
Smoking Status-Father						

Yes	152(14.83)	45(11.57)	56(7.53)	59(8.79)	312(11.03)	<0.0001
No	873(85.17)	344(88.43)	688(92.47)	612(91.21)	2517(88.97)	
Indoor smoking-Father						
Yes	83(8.10)	21(5.40)	16(2.15)	43(6.41)	163(5.76)	<0.0001
No	942(91.90)	368(91.60)	728(97.85)	628(93.59)	2666(94.24)	
Smoking Status-Family member						
Yes	129(12.59)	55(14.14)	45(6.05)	102(15.20)	331(11.70)	<0.0001
No	896(87.41)	334(85.86)	699(93.95)	569(84.80)	2498(83.30)	
Indoor smoking – Family member						
Yes	84(8.20)	27(6.94)	27(3.63)	94(14.01)	232(8.20)	<0.0001
No	941(91.80)	362(93.06)	717(96.37)	577(85.99)	2597(91.80)	
Clinical Variables at the time of admission at hospital						
	n, Mean± SD	n, Mean± SD	n, Mean± SD	n, Mean± SD	n, Mean± SD	p value
Age (months)	1025, 14.53±13.88	389, 10.69±10.95	744, 10.26±11.35	671, 12.30±13.29	2829, 12.35±12.85	<0.0001
Height (cm)	303, 68.61±13.78	324, 70.66±13.75	34, 64.38±10.25	266, 70.46±12.14	927, 69.70±13.26	<0.018
Weight (Kg)	1025, 7.96±2.97	389, 7.34±2.73	744, 7.11±2.78	671, 7.78±2.93	2829, 7.61±2.90	<0.0001
Fever Duration (days)	929, 4.46±2.71	321, 3.59±2.37	689, 4.25±2.52	569, 3.54±2.47	2508, 4.08±2.59	<0.0001
Oxygen saturation done n (%)	528(51.51)	343(88.17)	236(34.25)	319(56.06)	1426(50.40)	<0.0001
Oxygen Saturation ≤90 % n (%)	90 (17.04)	86 (26.79)	76(32.20)	49(15.36)	301(20.58)	<0.0001

251

252 **Table 2** shows proportions of radiological pneumonia among cases hospitalized for CAP in four

253 participating districts. We observed statistically significant district-wise heterogeneity in

254 radiological abnormalities. We found higher proportion of radiological abnormalities in Patna

255 and Lucknow districts, which have a larger urban population, and lower proportion in Etawah

256 and Darbhanga districts, which in contrast have a larger rural population. We also observed

257 correspondingly higher proportion of PEP alone or with other infiltrates in districts of Lucknow

258 and Patna and lower in districts of Etawah and Darbhanga.

259

Table 2 also describes univariate distribution of socio-demographic and clinical factors of CAP among hospitalized children (2-59 months). Statistically significantly higher proportion of females hospitalized for CAP had radiologically abnormal CXR. Likewise, statistically significantly higher proportion of abnormal versus normal CXRs findings were reported in hospitalized cases who had symptoms of fever, pallor, wheezing on auscultation, vomiting everything or were malnourished.

Table 2: Distribution of socio-demographic and clinical factors by chest radiograph findings among hospitalized children from January 2015-April 2017

	Interpretable chest X rays				Abnormal chest X rays		
	N=2829	Normal 1852 n (%)	Abnormal 977 n (%)	p value	PEP* alone or with other infiltrate 635 n (%)	Other infiltrates 342 n (%)	p value
Participating site (row %)							
Lucknow	1025	636 (62.05)	389 (37.95)	<0.0001	282 (72.49)	107 (27.51)	<0.0001
Etawah	389	275 (70.69)	114 (29.31)		73 (64.04)	41 (35.96)	
Patna	744	457 (61.42)	287 (38.58)		184 (64.11)	103 (35.89)	
Darbhangha	671	484 (72.13)	187 (27.87)		96 (51.34)	91 (48.66)	
Socio-demographic & clinical factors (column %)							
Age-group (months)							
2-11	1865	1223 (66.04)	642 (65.71)	0.86	409 (64.41)	233 (68.13)	0.26
12-59	964	629 (33.96)	335 (34.29)		226 (35.59)	109 (31.87)	
Gender							

Male	2005	1354 (73.11)	651 (66.63)	<0.0001	426 (67.09)	225 (65.79)	0.72
Female	824	498 (26.89)	326 (33.37)		209 (32.91)	117 (34.21)	
Place of residence							
Rural	1392	921 (49.73)	471 (48.21)	0.44	299 (47.09)	172 (50.29)	0.34
Urban	1437	931 (50.27)	506 (51.79)		336 (52.91)	170 (49.71)	
Biomass fuel							
Yes	1501	867 (46.81)	461 (47.19)	0.44	294 (42.30)	167 (48.83)	0.24
No	1328	985 (53.19)	516 (52.81)		341 (53.70)	175 (51.17)	
Immunization status							
Complete for age	2347	1546 (83.48)	801 (81.99)	0.32	516 (81.26)	285 (83.33)	0.54
Incomplete	482	306 (16.52)	176 (18.01)		119 (18.74)	57 (16.67)	
Symptoms of pneumonia							
Fever	2499	1616 (87.26)	883 (90.38)	0.014	575 (90.55)	308 (90.06)	0.82
Cyanosis	62	39 (2.11)	23 (2.35)	0.34	16 (2.52)	7 (2.05)	0.64
Pallor	764	465 (25.11)	299 (30.60)	0.002	200 (31.50)	99 (28.95)	0.41
Wheeze on auscultation	2054	1377 (74.35)	677 (69.29)	0.005	415 (65.35)	262 (76.61)	0.0003
Duration of illness fever [days] (n, Mean ± SD)	2499	1611 3.91±2.51	888, 4.40±2.70	<0.0001	577, 4.57±2.82	342, 4.08±2.44	0.011
Respiratory Rate and Fast Breathing							
Respiratory Rate [2-11 months] (n, Mean ± SD)	1865	1243, 55.52±11.29	642, 57.99±11.70	<0.0001	409, 58.12±11.88	233, 57.74±11.40	0.69
Respiratory Rate [12-59 months] (n, Mean ± SD)	964	629, 49.78±12.41	335, 51.28±13.37	0.08	226, 51.35±13.31	109, 51.12±13.35	0.88
Fast Breathing for age (2-11 months)	1735	1130 (61.02)	605 (61.92)	0.11	384 (60.47)	221 (64.62)	0.69
Fast Breathing for	862	562	300	0.92	204	96	0.53

age (12-59 months)		(30.35)	(30.71)		(32.13)	(28.07)	
Danger Signs of pneumonia							
Lethargy	1101	732 (39.52)	369 (37.77)	0.39	247 (38.90)	122 (35.67)	0.33
Inability to drink	937	612 (33.05)	325 (33.27)	0.46	211 (33.23)	114 (33.33)	0.97
Convulsion	148	98 (5.29)	50 (5.12)	0.93	33 (5.20)	17 (4.97)	0.87
Cyanosis	42	27 (1.46)	15 (1.54)	0.87	12 (1.89)	3 (0.88)	0.28
Malnutrition Status							
Normal *	1880	1293 (69.82)	587 (60.08)	< 0.0001	367 (57.80)	220 (64.33)	0.06
Malnutrition*	517	333 (17.98)	184 (18.83)		122 (19.21)	62 (18.13)	
Severe malnutrition*	432	226 (12.20)	206 (21.08)		146 (22.99)	60 (17.54)	

*Normal-weight of age z score > -2SD; Malnutrition-weight-for-age z ≤ -2SD and Severe malnutrition-weight-for-age z ≤ -3SD

Table 3 describes four multivariate unconditional logistic regression models to find associates of abnormal CXR findings. After controlling for age, gender, symptoms of pneumonia, duration of illness, biomass fuel and malnutrition status of cases, statistically significant district-wise heterogeneity remained in the first three models. Models I, II and III had similar associates for radiological abnormalities whereas Model IV was different. Across all the four models, female gender and those with severe malnutrition had statistically significantly higher risk for having abnormal CXRs. A higher risk of radiological abnormalities was also observed in those children with longer duration of illness.

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284 **Table 3: Independent Associations between Chest Radiograph Findings and demographic**
 285 **and clinical factors, among hospitalized children January 2015-April 2017**

Variables	Model – I Abnormal/Normal ^{Ref}		Model – II PEP alone or with other infiltrate /Normal ^{Ref}		Model – III PEP alone / Normal ^{Ref}		Model – IV Other infiltrate / Normal ^{Ref}	
	Adjusted Odd Ratio (95%CI)	p value	Adjusted Odd Ratio (95%CI)	p value	Adjusted Odd Ratio (95%CI)	p value	Adjusted Odd Ratio (95%CI)	P value
Districts								
Lucknow vs. Others	1.58 (1.20-2.10)	<0.0001	2.07 (1.48-2.89)	<0.0001	2.20 (1.52-3.19)	<0.0001	0.98 (0.65-1.47)	0.93
Etawah vs. Others	1.22 (0.88-1.70)	0.23	1.30 (0.87-1.95)	0.19	1.49 (0.95-2.30)	0.07	1.17 (0.74-1.87)	0.50
Patna vs. Others	1.67 (1.27-2.20)	<0.0001	1.89 (1.36-2.64)	<0.0001	2.25 (1.56-3.24)	<0.0001	1.39 (0.95-2.07)	0.09
Age – Group (months)								
2-11 ^{Ref}								
12-59	0.92 (0.77-1.10)	0.34	0.95 (0.77-1.17)	0.62	1.03 (0.82-1.29)	0.79	0.86 (0.66-1.13)	0.27
Gender								
Male ^{Ref}								
Female	1.39 (1.16-1.66)	<0.0001	1.34 (1.08-1.65)	0.008	1.28 (1.01-1.61)	0.03	1.48 (1.14-1.92)	0.004
Symptoms of pneumonia[¶]								
Wheezing	0.83 (0.68-1.01)	0.06	0.72 (0.57-0.90)	0.005	0.75 (0.59-0.96)	0.02	1.14 (0.83-1.55)	0.42
Pallor	1.30 (1.08-1.58)	0.006	1.28 (1.03-1.60)	0.02	1.22 (0.95-1.55)	0.12	1.34 (1.01-1.77)	0.04
Vomiting everything	0.90 (0.75-1.09)	0.28	0.80 (0.64-0.99)	0.04	0.78 (0.62-1.01)	0.05	1.09 (0.83-1.08)	0.51
Duration of illness, fever (days)	1.06 (1.04-1.09)	<0.0001	1.08 (1.04-1.12)	<0.0001	1.08 (1.04-1.12)	<0.0001	1.03 (0.98-1.48)	0.24
Biomass fuel	1.28 (1.05-1.57)	0.02	1.39 (1.10-1.76)	0.006	1.40 (1.14-1.88)	0.003	1.08 (0.79-1.45)	0.64
Malnutrition Status								
Normal ^{*Ref}								
Malnutrition*	1.18 (0.93-1.45)	0.15	1.17 (0.91-1.52)	0.23	1.17 (0.88-1.55)	0.27	1.12 (0.82-1.52)	0.47
Severe malnutrition*	1.65 (1.31-2.09)	<0.0001	1.82 (1.34-2.36)	<0.0001	1.87 (1.41-2.47)	<0.0001	1.62 (1.71-2.23)	0.003

286 **Abbreviations used:** ^{Ref} Reference Category

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288 **Footnotes:** [¶] No signs of pneumonia taken as a reference

289 *Normal: weight-for-age z score > -2SD; Malnutrition: weight-for -age z ≤ -2SD; Severe

290 malnutrition: weight-for-age z ≤ -3SD

291 **DISCUSSION**

292 This prospective hospital-based surveillance study was conducted to assess the radiological
293 abnormalities in children (2-59 months) residing in pre-specified districts of Uttar Pradesh and
294 Bihar, India and hospitalized with CAP. The study was conducted from January 2015 to April
295 2017, prior to introduction of PCV in the national immunization programme of the Government
296 of India⁹.

297
298 In our study, among interpretable CXRs, we found 22.44% (635/2829) children had PEP alone
299 or with infiltrates, other infiltrates only 12.09%(342/2829) and 65.46% (1852/2829) had normal
300 CXRs findings. Our study used WHO case definition for CAP¹⁹. A panel of three trained
301 radiologists interpreted CXRs, adopting WHO recommended methodology^{11 12}. These make our
302 study methodology robust and results generalizable.

303
304 There were 88.54% (2829/3195) interpretable CXRs in the current study. This is similar to 83%
305 (3587/3973) interpretable CXRs reported by Pneumonia Etiology Research for Child Health
306 (PERCH) study conducted on 4232 children (1-59 months) to assess the etiology of CAP in nine
307 sites of seven countries²⁷. Consistent with PERCH findings, a vaccine probe trial conducted in
308 Gambia found the proportion of interpretable CXRs among unvaccinated cases of pneumonia to
309 be 84.32% (242/287)²⁸.

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311 There have been several studies in the past two decades, which have reported CXRs findings in
312 hospitalized cases of CAP. Almost all of these were conducted before the introduction of PCV in
313 their respective regions. A small prospective study conducted in Ethiopia reported radiological

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3 314 abnormality in CXRs in 48.3% (95% CI 39.49-57.22) among 122 children (3 months-14 years)
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5 315 clinically diagnosed with WHO-defined severe pneumonia²⁹. Similar findings were reported
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7 316 from the Gambian vaccine probe trial where the proportion of radiological abnormality was 45%
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10 317 (95% CI: 43.35-46.46) among unvaccinated hospitalized cases of clinical pneumonia²⁸. PERCH
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12 318 study found that 54% (95% CI: 52.31-55.57) of CXRs among cases of CAP were abnormal ²⁷.
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14 319 In all of these studies, proportion of cases with abnormal CXRs is higher than 34.5% (95% CI
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16 320 32.8-36.3) found by us in the current study. However, our findings are similar to PERCH rural
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18 321 study site of Matlab, Bangladesh that reported radiological abnormality in 35.3% (95% CI:
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20 322 29.77-40.85) CXRs of hospitalized cases of CAP ²⁷. Another PERCH urban site of Dhaka,
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22 323 Bangladesh reported 63.10% (95% CI 56.18 -70.02) cases with abnormal CXRs ²⁷. In our study,
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24 324 radiological abnormalities in CXRs were higher in cases from largely urban districts of Patna and
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26 325 Lucknow compared to rural districts of Darbhanga and Etawah. This is consistent with rural-
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28 326 urban differences in Bangladesh sites of PERCH. Variation in CXR findings among cases of
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30 327 CAP may be due to infecting organism, immune response of patient and prior duration of
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32 328 disease.

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40 330 In 2016, WHO's Department of Immunization, Vaccines and Biologicals standardized the
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42 331 categorization of radiological pneumonia and established that PEP can be taken as a good
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44 332 surrogate marker of SP in epidemiological and vaccine efficacy studies¹². In our study, 22.44 %
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46 333 (95% C.I. 20.90 -23.98), CXRs were having PEP alone or with other infiltrates. This is similar to
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48 334 PERCH study that reported PEP alone or with other infiltrates in 27% (95% C.I. 25.50 -28.40)
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50 335 hospitalized cases of CAP²⁷. Another study conducted in Gambia reported that 45% (95% CI:
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52 336 43.35-46.46) non-vaccinated children had PEP and/or other infiltrates ²⁸. PEP has been

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3 337 associated with increased risk of treatment failure ($p=0.002$), increased length of hospitalization
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5 338 ($p=0.0003$) and more days of respiratory support ($p=0.002$) in Botswana when compared with
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8 339 cases reporting 'no significant pathology' on CXRs³⁰.
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12 341 In our study, female gender ($p<0.001$) was at the higher risk of developing radiological
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14 342 abnormalities compared to males (**table 3**). The results are in concordance with a hospital-based
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16 343 case-control study carried out in Brazil that reported male gender as a protective factor against
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18 344 pneumonia (OR = 0.53; 95 % CI 0.39–0.72)³¹. Another study in Mozambique, Africa reported
19
20 345 that male gender was not significantly associated with presence of radiological abnormalities
21
22 346 (OR =0.77; 95 % CI 0.56–1.05) in children (0-59 months) suffering from severe pneumonia³².
23
24 347 However, in contrast, a Gambian study reported male preponderance for all pneumonia that was
25
26 348 most marked for 'other infiltrates/abnormalities' pneumonia²⁸.
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33 350 In our study, it was observed that there was differential care-seeking by gender for CAP in all
34
35 351 four project sites. Although females admitted with CAP were at higher risk of having
36
37 352 radiological abnormalities, lower proportion were hospitalized for it. Gender inequality in health
38
39 353 care seeking for females is common in India, as in other South Asian countries^{33 34}. Since there
40
41 354 is no health-care financing or health insurance provision in India, in case of severe illness,
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43 355 parents are less likely to incur out-of-pocket expenditure or incur debts to pay expenses on
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45 356 medical treatment of their daughters compared to sons³⁵. Another Indian study found that male
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47 357 children were five times more likely to be taken early for medical care and three times more
48
49 358 likely to be seen by qualified medical doctors compared to female children³⁶. We also found
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3 359 that majority of hospitalized cases of pneumonia were from urban areas, in contrast with
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5 360 observations of other researchers who report poor health care seeking from rural areas³⁷.
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10 362 A systematic review with meta-analysis conducted in 2019 suggests that no one clinical feature
11
12 363 is sufficient on its own to diagnose radiological pneumonia ³⁸. However other socio-
13
14 364 demographic and clinical correlates of abnormal CXRs found by us (Model 1), which increased
15
16 365 the risk of radiological abnormalities, were presence of pallor, severe malnutrition, longer
17
18 366 duration of illness and exposure to biomass fuel. Exposure to biomass fuel used for cooking is an
19
20 367 important factor that increases the risk of CAP in developing countries³⁹. In rural India, majority
21
22 368 of the households use biomass fuel like firewood, dung cakes and wood for cooking ⁴⁰. Young
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24 369 children are at risk to adverse effects of exposure to biomass fuel as either the households have
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26 370 no separate cooking space or have poor ventilation and sometimes young children stay with their
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28 371 mother while she cooks.
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34 373 Other correlates of PEP/Radiological Pneumonia (Models II and III) possibly due to SP, besides
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36 374 those found in Model I, were presence of vomiting everything and wheeze on auscultation, both
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38 375 of which were found to be protective. These symptoms/signs are more often reported in viral
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40 376 pneumonia⁴¹. Correlates of radiological abnormalities of `other infiltrates` (Model IV), which
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42 377 increased the risk, were again female gender, pallor and severe malnutrition. Hence it is difficult
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44 378 to attribute radiological findings of other infiltrates to either bacterial or viral etiology.
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51 380 Based on our study, almost two-third hospitalized cases of CAP had normal CXRs and this could
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53 381 be perhaps of viral etiology. This is supported by a recent study that reported 61.4% (95% CI
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382 57.3–65.6) cases to be viral⁴¹. Among one-third of cases of CAP had abnormal CXRs and thus
383 were more likely to be bacterial in etiology, two-thirds of which were possibly due to SP.

384
385 In India, 13-valent PCV is given using a three dose schedule (2 primary and one booster) at 6
386 weeks, 14 weeks and 9 months of age. PCV 13 provides coverage against 13 serotypes (1, 3, 4,
387 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) causing pneumococcal pneumonia⁴². Several
388 studies have assessed serotype distribution of pneumococcal disease among children in India. A
389 study conducted in Vellore, India found that the most common serotypes causing invasive
390 infections among under-five children were 14, 19F, 5, 6A and 6B, all of which were covered by
391 the 13-valent PCV ⁴³. Another population-based surveillance study conducted in rural
392 Bangladesh found that the most common serotypes were 1, 5, 14, 18C and 19A and 38 and these
393 comprised more than three-fourth of the *S. pneumoniae* isolates ⁴⁴. A systematic review and
394 meta-analysis of data collected on Invasive Pneumococcal Disease serotypes from under-five
395 children during the pre-PCV period (between 1980–2007) found that serotypes included in both
396 the 10-valent and 13-valent PCVs accounted for 10 million cases and 600,000 deaths
397 worldwide⁴⁵.

398
399 Several strengths of the study are worth-noting. This was a prospective, multi-site study where
400 recruitments were done from a large hospital surveillance network established especially for the
401 study in four districts of two Indian states that have high under-five mortality rates. Standard
402 WHO definition was used to identify hospitalized cases of CAP. Radiological abnormalities
403 were interpreted by a panel of three trained radiologists at locations out of the surveillance
404 network, blinded to each other as well as clinical features of the case. Despite these strengths,

our study findings have certain limitations. First, in our study, pre-existing x-rays machines which were not of uniform specification, were used. This might have caused variation in quality of CXR images, though this error was minimized by digitizing the CXR images centrally. Secondly, in our study, clinical data collection was recorded by physicians in the network hospitals and this could be subject to observer bias. However, the primary outcome of the study was radiological findings of CXRs of cases admitted with CAP. This was not subject to bias. In this study, we have not collected information on use of antibiotic prior to hospitalization; as such information is not available reliably. However, in another study, done in one of the network hospitals of Lucknow in the recent past, it was found that 70.5% children tested positive for antibiotics on urine examination⁴⁶.

415

416 CONCLUSION

417 Among hospitalized cases of community-acquired pneumonia, almost one-third children had
418 abnormal chest radiographs of which about two-thirds had abnormalities related with possible
419 bacterial etiology (SP). Hence, the introduction of pneumococcal vaccination is likely to reduce
420 the burden of childhood pneumonia in India. Since the study was done prior to the introduction
421 of PCV in India, continued surveillance will be required to assess the impact of PCV on
422 radiological findings in cases admitted with CAP. The impact of introduction of PCV in the
423 national immunization programme on under-five mortality rate and burden of CAP needs to be
424 assessed.

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29
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31
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33
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35
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37
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45
46 447 manuscript.

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8
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15

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18 456 shally07@gmail.com
19

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34 463 **Supporting Information**

35 464 S1 Appendix: Chest radiograph interpretation form
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5 604 **Figure Legend**
6
7 605 Figure 1: Flow diagram of cases of community acquired pneumonia recruited from participating
8 606 districts before the introduction of pneumococcal conjugate vaccine (January 2015-April 2017)
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For peer review only

Figure 1: Flow diagram of cases of community acquired pneumonia recruited from participating districts before introduction of pneumococcal conjugate vaccine (January 2015-April 2017)

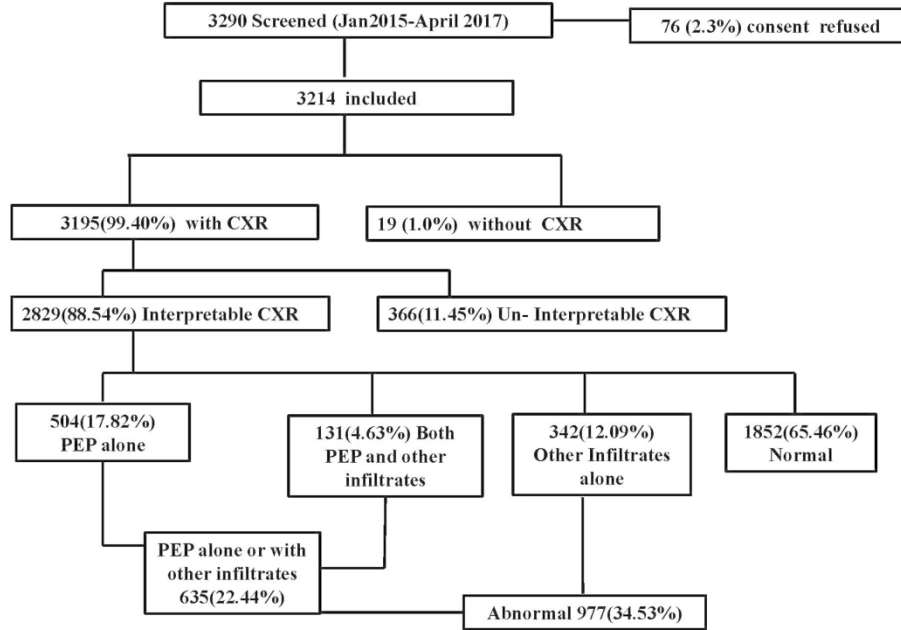


Figure 1: Flow diagram of cases of community acquired pneumonia recruited from participating districts before the introduction of pneumococcal conjugate vaccine (January 2015-April 2017)

254x190mm (300 x 300 DPI)

Childhood Pneumonia Surveillance
Department of Paediatrics, KGMU, Lucknow ,UP

Form-R
(RADIOLOGY REPORT FORM)

1	Drs_ID	[][][][]
	Radiology Report	Patient Details
2	IDNo:	[] / [] / [][][][][][] State /District / Unit / Subject number (For office use)
2	Date Of Report	[][]/[][]/[][][][] (DD/MM/YYYY)
	Report Details	Findings (tick one)
3	Image Quality	Adequate <input type="checkbox"/> Suboptimal <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
4	Significant Pathology	Yes <input type="checkbox"/> No <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
5	End Point Consolidation	
5a	Left	Yes <input type="checkbox"/> No <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
5b	Right	Yes <input type="checkbox"/> No <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
		Uninterpretable
6	Other Infiltrates/Abnormalities	
6a	Left	Yes <input type="checkbox"/> No <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
6b	Right	Yes <input type="checkbox"/> No <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
7	Pleural Fluid	
7a	Left	Yes <input type="checkbox"/> No <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
7b	Right	Yes <input type="checkbox"/> No <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
8	Comments:	<input type="text"/>
9	Conclusion:	a) Primary endpoint pneumonia only <input type="checkbox"/> b) Other infiltrate only <input type="checkbox"/> c) Both PEP and other infiltrate <input type="checkbox"/> d) Normal <input type="checkbox"/> e) Un-interpretable for any findings <input type="checkbox"/>

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60STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page Number
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	25
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11-13
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	11-13
		(b) Describe any methods used to examine subgroups and interactions	Table 1, 2 & 3
		(c) Explain how missing data were addressed	12 reference 24
		(d) If applicable, describe analytical methods taking account of sampling strategy	11-13
		(e) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	14
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	14-15 Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Figure 1

Outcome data	15*	Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3 (adjusted odds ratio)
		(b) Report category boundaries when continuous variables were categorized	Table 3
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA (calculated only odds ratio)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	21-23
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	25-26
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	21-23
Generalisability	21	Discuss the generalisability (external validity) of the study results	21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	27

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Chest Radiograph Findings in children aged 2-59 months hospitalized with Community-Acquired Pneumonia, prior to the introduction of Pneumococcal Conjugate Vaccine in India- A Prospective Multisite Observational Study

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Keywords:	Chest radiographs, Hospitalized community-acquired pneumonia, under-five, Streptococcus pneumoniae, India

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Title: *Chest Radiograph Findings in children aged 2-59 months hospitalized with Community-Acquired Pneumonia, prior to the introduction of Pneumococcal Conjugate Vaccine in India- A Prospective Multisite Observational Study*

Short Title: *Radiological Findings in Children hospitalized with Community-Acquired Pneumonia in India Pre-Pneumococcal Conjugate Vaccine introduction*

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ABSTRACT

Objectives: To assess radiological abnormalities in chest X-rays and to identify the demographic and clinical correlates of specific radiological abnormalities in children aged 2-59 months, hospitalized with World Health Organization defined community-acquired pneumonia, residing in pre-specified districts of Uttar Pradesh and Bihar, India.

Design: Prospective, hospital-based surveillance

Setting: Multi-site study conducted in a network of 117 secondary/tertiary care hospitals in four districts of Uttar Pradesh and Bihar, India.

Participants: Included were children aged 2-59 months hospitalized with community-acquired pneumonia, residing in project district, with duration of illness of <14 days and who were not hospitalized elsewhere for this episode nor had been recruited previously.

Main outcome measure: Radiological abnormalities in the chest X-rays, where there was concordance between two or more of the panel of three trained radiologists.

Results: From January 2015 to April 2017, 3214 cases were recruited and in 99.40 % (3195/3214) chest X-rays were available. Among 88.54 % (2829/3195) interpretable X-rays, 34.53 % (977/ 2829, 95% C.I. 32.78 -36.28) had some radiological abnormalities, while the rest were normal. Primary endpoint pneumonia alone or with other infiltrates was found in 22.44 % (635/2829, C.I. 20.90 %-23.98 %), other infiltrates only in 12.09% (342/ 2829; C.I. 10.88 %-13.29 %). There was a statistically significant inter-district variation in radiological abnormality. Statistically significantly higher proportion of abnormal chest X-ray was found among girls, those with weight-for-age z score ≤ -3 SD, longer duration of fever, pallor and with exposure to biomass fuel.

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3 **Conclusions:** Among hospitalized cases of community-acquired pneumonia, almost one-third
4 children had abnormal chest radiographs, which were higher in females, malnourished children
5 and those with longer illnesses; and an intra-district variation was observed.
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12 **Key words:** Chest radiographs, Hospitalized community-acquired pneumonia, under-five,
13 *Streptococcus pneumoniae*, India
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17 **Strengths and Limitations of the Study**

- 21 • Prospective, multisite recruitments from a large hospital surveillance network established for
22 the project in four districts in two states of India that have high under-five mortality rates
23
- 24 • Standard World Health Organization definition was used for identifying hospitalized cases of
25 clinical pneumonia
26
- 27 • Radiological abnormalities interpreted by a panel of three trained radiologists at locations out
28 of the surveillance network, blinded to each other as well as clinical features of the case
29
- 30 • Since pre-existing X-rays machines were used, there was a variation in the quality of images
31 obtained, which were minimized by digitizing them centrally
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- 33 • Since data of clinical examination was abstracted from hospital records, it could have resulted
34 in inter-observer variation.
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1 INTRODUCTION

2 Community-acquired pneumonia (CAP) is the single largest infectious cause of death in young
3 children worldwide. Globally, pneumonia accounts for 16% of deaths in children under-five years of
4 age and results in almost one million deaths (0.9 million children in 2016) every year^{1 2}. Most
5 deaths due to pneumonia occur in low and middle income countries particularly in sub-Saharan
6 Africa and South Asia^{2 3}. In India, there were approximately 0.44 million under-five deaths due to
7 CAP in the year 2015⁴.

8
9 CAP could have viral or bacterial etiology^{5 - 7}. Etiology varies from country to country and also
10 across different time periods. Pediatric bacterial pneumonia is predominantly caused by
11 *Streptococcus pneumoniae* and *Hemophilus influenzae Type B* while Respiratory syncytial virus
12 and Influenza A or B virus are important contributors of pediatric viral pneumonia^{5 6}. The World
13 Health Organization (WHO) recommends the introduction of Pneumococcal Conjugate Vaccine
14 (PCV) in the national immunization programme of countries with high child mortality rates,
15 which includes India⁸. Consequently, PCV-13 was launched in May 2017 under the national
16 immunization programme of five Indian states (Uttar Pradesh, Bihar, Rajasthan, Madhya Pradesh
17 and Himachal Pradesh) in a phased manner⁹. It is expected to be rolled out in other parts of the
18 country in the near future. Vaccination against *Hemophilus influenzae Type B* is already under
19 the national immunization programme since 2011.

20
21 Differentiating bacterial from viral etiology of CAP on clinical features or by investigations
22 remains difficult^{7 10 11}. Several PCV probe trials have used radiographically confirmed end-
23 point pneumonia, to be an outcome for vaccine efficacy and this has been endorsed by WHO¹²⁻¹⁴.

24
25 The current study was a hospital-based surveillance to assess the radiological abnormalities in
26 chest X-rays (CXRs) and to identify the demographic and clinical correlates of specific
27 radiological abnormalities in children aged 2-59 months, hospitalized with WHO defined CAP,
28 residing in pre-specified districts of Uttar Pradesh and Bihar, India.

29

30 **METHODS**

31 **Study design and Setting**

32 This prospective multi-site observational study was conducted in Lucknow and Etawah districts
33 of Uttar Pradesh and Patna & Darbhanga districts of Bihar, India. Uttar Pradesh is the first most
34 populated and Bihar third most populated state of India^{15 16}. In Lucknow district 66.2% population
35 resides in urban areas and in Patna district 43.07%^{15 16}. In contrast, only 22.3% population of
36 Etawah district and 9.74% population of Darbhanga district resides in urban areas^{15 16}. All four
37 project districts have alarmingly high infant and child mortality indicators¹⁵⁻¹⁷. The under-five
38 mortality rates of Lucknow (58/1000), Etawah (85/1000), Patna (46/1000) and Darbhanga
39 (77/1000) districts are above the national average (50/1000)¹⁵⁻¹⁷. Similarly, the infant mortality
40 rates of Lucknow (44/1000), Etawah (56/1000), Patna (31/1000) and Darbhanga (44/1000)
41 districts are also higher than the national average (41/1000)¹⁵⁻¹⁷.

42

43 **Study Population**

44 A prospective, active, hospital-based surveillance system was established for this study^{17 18}.
45 Included in the surveillance were 117 public and private hospitals of four study districts which

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3 46 provided either secondary or tertiary level care to admitted children. Surveillance officers visited
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5 47 the hospital every 48-72 hours to screen and recruit eligible cases. In between the visits they
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7 48 telephonically contacted the hospitals and made additional visits, if required. All children (2-59
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9 49 months), hospitalized in network hospitals between January 2015 to April 2017, with history of
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11 50 fast breathing with/without chest in-drawing were screened ¹⁸.
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18 52 Included were children hospitalized with symptoms of WHO defined CAP and residing in the
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20 53 project district ¹⁸. WHO has developed guidelines for hospital-based management of common
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22 54 childhood illness such as pneumonia ¹⁹. According to these guidelines, fast breathing ≥ 50
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24 55 breaths/minute in a child aged 2–11 months and ≥ 40 breaths/minute in a child aged 12-59
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26 56 months along with chest indrawing was categorized as having `pneumonia`¹⁹. A child presenting
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28 57 with cough or difficulty in breathing plus atleast one of the following: (a) oxygen saturation <
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30 58 90% or central cyanosis or (b) severe respiratory distress (e.g. grunting, very severe chest
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32 59 indrawing) or (c) signs of pneumonia with a general danger sign (inability to breastfeed or drink,
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34 60 lethargy or reduced level of consciousness, convulsions) was categorized as having `severe
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36 61 pneumonia`¹⁹. Excluded were children with cough for ≥ 14 days or those that had been
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38 62 hospitalized in last 14 days ¹⁸.
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64 **Sample Size**

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48 65 We assumed that the incidence of radiological pneumonia is 3/100 child years of observations.
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50 66 Then for a margin of error of 1.5/100 child years of observation, incidence of pneumonia in the
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52 67 community of 20/100 child years of observation, alpha level of 0.05, and power of 90% when the
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3 68 estimated population of children under-five years of age in Lucknow district ²⁰ is 750,000; 693
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5 69 cases had to be included per district.
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11 **Data collection**

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13 72 Data was collected by surveillance officers who had postgraduate degree in social sciences and
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15 73 atleast 10 years experience in community based health research. After recruitment, they were
16
17 74 imparted six-day centralized training on project procedures and logistics. Class-room as well as
18
19 75 practical skills-training was given by the coordinating centre in Lucknow. Pre and post tests were
20
21 76 conducted to ascertain knowledge and skills acquired by them through the training to ensure
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23 77 quality in data collection. The coordinating centre provided annual refresher trainings to the
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25 78 surveillance officers from all four sites in Lucknow.
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33 80 After obtaining written, informed consent of the caregivers, data was collected through face-to-
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35 81 face interviews with them as well as by abstraction from hospital records. Socio-demographic
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37 82 data, obtained by interviewing caregivers, was: child's age, gender, residence, birth order,
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39 83 immunization status, current breastfeeding status, parental education and occupation, smoking
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41 84 status of parents, family type, housing infrastructure, use of biomass fuel etc. Caregivers were
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43 85 also asked about the symptoms of disease and its duration in days.
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49 87 Clinical data, recorded by pre-existing hospital staff at the time of hospitalization, was
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51 88 abstracted. Data was collected on anthropometry (weight and height), fever (axillary temperature
52
53 89 $\geq 37.5^{\circ}\text{C}$), oxygen saturation by pulse oxymetry, pallor, central cyanosis, signs of pneumonia
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55 90 with a general danger sign and vital signs (heart rate and respiratory rate). Presence of wheezing
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2
3 91 on auscultation of chest was abstracted or inquired from the treating physician. At the hospitals,
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5 92 clinicians generally used Integrated Management of Childhood Illness (IMCI) definitions²¹ to
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7 93 identify pallor, cyanosis, wheeze on auscultation and general danger sign as it is incorporated in
8
9 94 their medical undergraduate training. Most doctors of public health sector also receive a formal
10
11 95 in-service training on IMCI ²¹. Clinical outcome (survival or mortality) was noted from hospital
12
13 96 records on follow up.^{17 18}
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19 98 **Chest x-ray (CXR) image acquisition and archiving**

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22 99 CXR (poster-anterior view) was done when advised by the treating physician. These CXRs were
23
24 100 obtained by the surveillance staff at the time of recruitment. CXRs were either analog or digital.
25
26 101 In case of digital CXRs, second copy was obtained where possible. If only single analog image
27
28 102 was available, then the hardcopy of CXR was obtained from the caregiver after the child was
29
30 103 discharged. If the caregiver was not ready to give the hardcopy of CXR (in <1% cases), image of
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32 104 the same was captured by surveillance officers using 16 megapixel cell phone camera and
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34 105 portable CXR view-box.
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40 107 CXRs of recruited cases were subsequently scanned and converted into digital format using a
41
42 108 diagnostic-quality film image digitalizer (Microteck International Limited, model Medi 6000
43
44 109 plus) ²². CXRs obtained/converted into digital image were stored as per the standard operating
45
46 110 procedure and were subsequently archived for web-based radiological interpretation. Digital
47
48 111 images were stored in JPEG format at 300 dpi resolution. Each CXR file was anonymized and
49
50 112 given a unique identification number. Digital CXRs were uploaded on online data management
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52 113 software, developed especially for the project.
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115 **Interpretation of radiological images**

116 A panel of radiologists was constituted for standardized interpretations of CXRs. Four
117 radiologists were part of this panel, one of whom was Project co-investigator-Radiology (NK).

118 All radiologists are faculty in medical teaching institutes and also look after pediatric radiology.

119 They all have more than fifteen years experience in interpreting pediatric CXRs.

120

121 Radiologists were trained according to the methodology developed by Department of

122 Immunization, Vaccines, and Biologicals of the WHO for research purpose ¹¹. An international

123 WHO-certified trainer from the International Centre for Diarrhoeal Disease Research,

124 Bangladesh imparted a two-day in-house training to the radiologists. Training objective was to

125 standardize interpretation and coding of CXRs, to develop a CXR reporting form [S1 Appendix]

126 and to provide training on web-based CXR retrieval and reporting system. During the training,

127 210 CXRs of WHO data set were used. For assessing concordance post training, another set of

128 48 CXRs was provided for interpretation to individual radiologists. Post-test agreement with

129 WHO findings was calculated, which was about 80%. Inter-observer variation was about 25%

130 and was for minor interpretation like quality of film, end point infiltrates etc. Repeat training

131 was conducted on an additional set of 44 CXRs provided by WHO to ensure standardization in

132 interpretation. Thereafter, concordance achieved by the radiologists was reviewed quarterly by

133 the study arbitrator. Radiologists met annually to review key concepts and discuss challenges

134 faced in interpreting CXRs.

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3 136 After training, radiologists independently reviewed CXRs and registered their findings in an
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5 137 online standardized chest radiograph interpretation form [S1 Appendix]. For optimal viewing of
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8 138 CXRs, all radiologists used similar workstations. Specifications were provided for the computer
9
10 139 monitor and hardware to be used. It was ensured that monitors had the correct brightness and
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12 140 contrast adjustment for optimal viewing.
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16
17 142 During online evaluation, radiologists reported the quality of film as *'interpretable'* or *'un-*
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19 143 *'interpretable'*. Radiologists categorized *'interpretable'* CXRs as either *'adequate/optimal'* for
20
21 144 features that allowed confident interpretation of consolidation and pleural effusion as well as
22
23 145 other infiltrates or *'suboptimal'* for features that allowed interpretation of consolidation and
24
25 146 pleural effusion, but not of other infiltrates or findings. In *'un-interpretable'* CXRs, no comment
26
27 147 was possible for radiological abnormality with respect to presence or absence of consolidation or
28
29 148 pleural effusion or other infiltrates ¹².
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35 150 After interpreting film quality, radiologists evaluated interpretable CXRs for abnormal
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37 151 radiological findings. For each CXR evaluated, radiological abnormality could be presence of
38
39 152 consolidation, other infiltrates or pleural effusion. *'Consolidation'* was defined as a dense or
40
41 153 confluent opacity that occupies a portion or whole of a lobe or the entire lung, that may or may
42
43 154 not contain air bronchograms. *'Other infiltrates'* were defined as linear and patchy opacities
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45 155 (interstitial infiltrate) in a lacy pattern, featuring peri-bronchial thickening and multiple areas of
46
47 156 atelectasis; also including minor patchy infiltrates that are not of sufficient magnitude to
48
49 157 constitute endpoint consolidation, and small areas of atelectasis that in children may be difficult
50
51 158 to distinguish from consolidation. *'Pleural effusion'* was defined as the fluid in the lateral
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3 159 pleural space between the lung and chest wall that is spatially associated with a pulmonary
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5 160 parenchymal infiltrate (including `other infiltrates`) or has obliterated enough of the hemithorax
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8 161 to obscure any infiltrates. In most cases, this will be seen at the costo-phrenic angle or as a layer
9
10 162 of fluid adjacent to the lateral chest-wall and this does not include fluid seen in the horizontal or
11
12 163 oblique fissures¹². Primary end point pneumonia (PEP) for research purpose was the presence
13
14 164 of consolidation or pleural effusion which could be with or without other infiltrates.
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18
19 166 Final conclusions were categorised as: (a) “*Abnormal*” when it was `PEP only` or `Other
20
21 167 *infiltrates only*` or `Both PEP and other infiltrates` and (b) `Normal` when no findings were
22
23 168 abnormal¹².
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26 169

27
28 170 After radiological interpretation, online data was archived, stored and checked for
29
30 171 inconsistencies and completeness by the data manager. CXRs with concordant and discordant
31
32 172 interpretations were identified. Interpretations were considered concordant when there was an
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34 173 agreement between two or more radiologists on final conclusions and discordant if all the three
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36 174 radiologists disagreed. Discordant interpretations were forwarded to the study arbitrator (NK).
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38 175 Arbitrator assessed discordant CXRs online and her interpretation was taken as final.
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45 177 **Data management and statistical analysis**

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47 178 Clinical data of hospital surveillance network was entered online in customized software.
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49 179 Primary entry was done by the four participating sites. Secondary data entry was done by the
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51 180 coordinating site in separate customized software. Anonymized CXRs were uploaded on
52
53 181 customized software. Each of the three panelists assessed the CXRs online, blind to peer
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182 assessments as well as clinical features of the case. CXR assessment data was downloaded from
183 the online software in MS Access database.

184
185 Exploratory data analysis was performed for detection of outlier and missing observations for all
186 the variables. Descriptive statistics was calculated for continuous variables as mean \pm standard
187 deviation and categorical variables in percent. Un-interpretable CXRs were not analyzed. Among
188 interpretable CXRs, those radiological abnormalities where there was concordance between the
189 two radiologists, were taken as final. Weight-for-age (WAZ) z-score each child was calculated
190 using WHO Anthro Survey Analyser ²³. Weight of 7.59% (215/2829) children was missing in
191 our data. Missing weight of recruited children was estimated using regression based imputation
192 technique ²⁴. Kappa statistics was performed for agreement analysis among radiologists for
193 CXRs findings. Statistical analysis was performed using SPSS version 22.0 (Chicago, IL) ²⁵. A
194 p-value of <0.05 was taken as statistically significant using a two-tailed distribution.

195
196 Univariate analysis was performed to evaluate heterogeneity, stratified by four participating sites
197 for socio-demographic variables such as child's age, gender, residence, birth order,
198 immunization status, current breastfeeding status, parental education and occupation, smoking
199 status of parents, family type, housing infrastructure, use of biomass fuel and for clinical
200 variables such as weight, height, duration of fever and oxygen saturation.

201
202 We report proportions of radiological abnormalities among hospitalized children for CAP by
203 four districts. Univariate analysis was performed to assess association of socio-demographic
204 variables and clinical signs of CAP with radiological abnormalities. Chi-square test was used for

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3 205 categorical variables and student's t-test for continuous variables. ANOVA test was used for
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5 206 more than two groups to test the significance of continuous variables. Multivariate unconditional
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7 207 logistic regression was performed find association of presence of various radiological
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9 208 abnormalities, controlling for district of residence and other variables that had univariate
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11 209 association with radiological abnormalities (p value ≤ 0.2) and/or were clinically meaningful.
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17 211 We developed four models and in these four models dependent (outcome) were:

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19 212 Model I: Abnormal vs. Normal

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21 213 Model II: Primary End Point Pneumonia alone or with other infiltrates vs. Normal

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23 214 Model III: Primary End Point Pneumonia alone vs. Normal

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25 215 Model IV: Other infiltrates only vs. Normal

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31 217 Independent variables that were kept across all the four models were : participating districts, age,
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33 218 gender, use of biomass fuel, symptoms of CAP such as duration of illness, presence of wheeze
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35 219 on auscultation, pallor, vomiting everything and malnutrition status of the case [$WAZ \leq -2$ SD
36
37 220 (malnourished) and $WAZ \leq -3$ SD (severely malnourished)].
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41 42 222 **Patient and public involvement in research**

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44
45 223 Patients or public were not involved in the development of research question, study design or
46
47 224 conducting the research. Reporting of this research conforms to the guidelines for Strengthening
48
49 225 the Reporting of Observational Studies in Epidemiology (STROBE)²⁶.
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53 54 55 227 **RESULTS**

228 A total of 3290 hospitalized cases were screened in hospital surveillance network of Lucknow
229 and Etawah districts of Uttar Pradesh and Patna & Darbhanga districts of Bihar. Out of these,
230 3214 cases fulfilling the WHO diagnosis of CAP were included [Figure 1]. Among them, 3195
231 (99.40%) cases were enrolled with CXRs and only in 19 (1.0%) cases CXRs were not done. Out
232 of these 88.54% (2829/3195) CXRs were found interpretable and remaining 11.45% (366/3195)
233 were found un-interpretable by radiologists. Among interpretable CXRs, 99.11 % (2804/2829)
234 children had 'severe pneumonia' as per the WHO criteria¹⁹.

235
236 Among interpretable CXRs, we found 22.44% (635/2829) children had PEP alone or with
237 infiltrates, 12.09% (342/2829) had other infiltrates only and 65.46% (1852/2829) had normal
238 CXRs findings [Figure 1]. Concordance among ≥ 2 radiologists on final conclusion of CXRs
239 findings was 86.0%. Kappa statistics was calculated for agreement of CXRs findings between
240 Reader 1 versus Reader 2 ($K_1=0.31$), Reader 2 versus Reader 3 ($K_2=0.46$) and Reader 3 versus
241 Reader 1 ($K_3=0.42$).

242
243 **Table 1** shows univariate distribution of socio-demographic and clinical variables among
244 hospitalized cases across four participating districts. A statistically significant variation was
245 observed in all socio-demographic variables such as place of residence, type of house, type of
246 family, maternal and paternal education and occupation, use of biomass fuel and parental
247 smoking status across the four districts. We also report other clinical variables of recruited cases
248 across the four districts in **table 1**. Oxygen saturation by pulse-oxymetry was statistically
249 significantly different across the sites, the proportion of cases with oxygen saturation < 90 % was
250 found also found statistically significant in children across four districts ($p < 0.0001$).

251

252 **Table 1: Distribution of socio-demographic and clinical variables among hospitalized children for**
 253 **participating districts (Jan 2015-April 2017)**

Characteristics	Lucknow	Etawah	Patna	Darbhanga	Total
Socio-demographic Characteristics	n=1025 (%)	n=389 (%)	n=744 (%)	n=671 (%)	N=2829 (%)
Gender					
Male	659(64.29)	287(73.78)	557(74.87)	502(74.81)	2005(70.87)
Place of residence					
Rural	195(19.02)	279(71.72)	304(40.86)	614(91.51)	1392(49.20)
Urban	830(80.98)	110(28.28)	440(59.14)	57(8.49)	1437(50.80)
Family Type					
Joint	688(67.12)	360(92.54)	707(95.03)	383(57.08)	2138(75.57)
Nuclear	337(32.88)	29(7.46)	37(4.97)	287(42.77)	690(24.39)
House type					
Mud	64(6.24)	54(13.88)	123(16.53)	374(55.74)	615(21.74)
Bricks	854(83.32)	256(65.81)	453(60.89)	85(12.67)	1648(58.25)
Combined	107(10.4)	79(20.31)	168(22.58)	212(31.59)	566(20.01)
Mother's Education					
No formal education	203(19.80)	56(14.40)	328(44.09)	496(73.92)	1083(38.28)
Class I-V	108(10.54)	28(7.20)	82(11.02)	38(5.66)	256(9.05)
Class VI-XII	379(36.98)	176(45.24)	243(33.66)	112(16.69)	910(32.17)
Graduate/ Post graduation	335(32.68)	129(33.16)	91(12.23)	25(3.73)	580(20.50)
Father's Education					
No formal education	167(16.29)	29(7.46)	153(20.56)	345(51.42)	694(24.53)
Class I-V	85(8.29)	19(4.88)	91(12.23)	82(12.22)	277(9.79)
Class VI-XII	437(42.63)	206(52.96)	328(44.09)	205(30.55)	1176(41.57)
Graduate/ Post graduation	336(32.78)	135(34.70)	172(23.12)	39(5.81)	682(24.11)
Birth Order					
1 st	435(42.44)	187(48.07)	315(42.34)	192(28.61)	1129(39.91)
2 nd	343(33.46)	120(30.85)	235(31.59)	258(38.45)	956(33.79)
3 rd	153(14.93)	47(12.08)	129(17.34)	137(20.42)	466(16.47)
More than 3 rd	93(9.07)	35(9.00)	62(8.33)	83(12.37)	273(9.65)
Immunization Status					
Complete for age	792(77.27)	300(77.12)	711(95.56)	544(81.07)	2347(82.96)
Incomplete for age	220(21.46)	84(21.59)	25(3.36)	126(18.78)	455(16.08)
Unimmunized	13(1.27)	5(1.29)	8(1.08)	1(0.15)	27(0.95)
Currently Breast Feeding					
Yes	653(63.71)	256(65.81)	589(79.17)	537(80.03)	2035(71.93)
No	372(36.29)	133(34.19)	155(20.83)	134(19.97)	794(28.07)
Father's Occupation					
Unemployed	13(1.27)	20(5.14)	27(3.63)	63(9.39)	123(4.35)
Daily wages	329(32.10)	81(20.82)	165(22.18)	474(70.64)	1049(37.08)
Salaried/ Professional	397(38.73)	104(26.74)	245(32.93)	55(8.20)	801(28.31)

Self-Employment	286(27.90)	184(47.30)	307(41.26)	79(11.77)	856(30.26)
Mother's Occupation					
Home maker	961(93.76)	376(96.66)	701(94.22)	484(72.13)	2522(89.15)
Daily wages	17(1.66)	3(0.77)	17(2.28)	171(25.48)	208(7.35)
Salaried/Professionals	47(4.59)	9(2.31)	18(2.42)	7(1.04)	81(2.86)
Self-Employment	0(0.0)	1(0.26)	8(1.08)	9(1.34)	18(0.64)
Biomass fuel					
Yes	211(20.59)	245(62.98)	263(35.35)	609(90.76)	1328(46.94)
No	814(79.41)	144(37.02)	481(64.65)	62(9.24)	1501(53.06)
Smoking Status-Father					
Yes	152(14.83)	45(11.57)	56(7.53)	59(8.79)	312(11.03)
No	873(85.17)	344(88.43)	688(92.47)	612(91.21)	2517(88.97)
Indoor smoking-Father					
Yes	83(8.10)	21(5.40)	16(2.15)	43(6.41)	163(5.76)
No	942(91.90)	368(91.60)	728(97.85)	628(93.59)	2666(94.24)
Smoking Status-Family member					
Yes	129(12.59)	55(14.14)	45(6.05)	102(15.20)	331(11.70)
No	896(87.41)	334(85.86)	699(93.95)	569(84.80)	2498(83.30)
Indoor smoking – Family member					
Yes	84(8.20)	27(6.94)	27(3.63)	94(14.01)	232(8.20)
No	941(91.80)	362(93.06)	717(96.37)	577(85.99)	2597(91.80)
Clinical Variables at the time of admission at hospital	n Mean± SD	n Mean± SD	n Mean± SD	n Mean± SD	n Mean± SD
Age (in months)	1025 14.53±13.88	389 10.69±10.95	744 10.26±11.35	671 12.30±13.29	2829 12.35±12.85
Height (in cm)	303 68.61±13.78	324 70.66±13.75	34 64.38±10.25	266 70.46±12.14	927 69.70±13.26
Weight (in kg)	1025 7.96±2.97	389 7.34±2.73	744 7.11±2.78	671 7.78±2.93	2829 7.61±2.90
Fever Duration (in days)	929 4.46±2.71	321 3.59±2.37	689 4.25±2.52	569 3.54±2.47	2508 4.08±2.59
Respiratory Rate					
Respiratory Rate [2-11 months]	602 53.38±14.05	272 60.87±9.60	540 53.82±10.16	451 60.78±7.26	1864 56.37±11.49
Respiratory Rate [12-59 months]	423 47.75±14.17	117 53.22±13.17	204 45.59±10.11	220 58.03±6.83	964 50.30±12.76
	n (%)	n (%)	n (%)	n (%)	n (%)
Oxygen saturation done	528 (51.51)	343 (88.17)	236 (34.25)	319 (56.06)	1426 (50.40)
Oxygen saturation < 90%	61 (11.53)	57 (16.61)	49 (20.76)	43 (13.47)	210 (14.72)

Grunting	461 (44.98)	353 (90.75)	687 (92.34)	649 (96.72)	2150 (76.00)
Very severe chest in-drawing	953 (92.97)	352 (90.49)	739 (99.33)	651 (97.02)	2695 (95.26)
Signs of Pneumonia with a general danger sign					
Lethargy or reduced level of consciousness	423 (41.27)	259 (66.58)	6 (0.81)	412 (61.40)	1100 (38.88)
Inability to breastfeed or drink	291 (28.39)	259 (66.58)	75 (10.08)	312 (46.50)	937 (33.12)
Convulsions	16 (1.56)	19 (4.58)	13 (1.75)	100 (14.90)	148 (5.23)
Central cyanosis	15 (1.46)	7 (1.80)	26 (3.49)	14 (2.09)	62 (2.19)

254

255 **Table 2** shows proportions of radiological pneumonia which includes PEP alone or with other
 256 infiltrate and other infiltrates among cases hospitalized for CAP in four participating districts.
 257 We observed statistically significant district-wise heterogeneity in radiological abnormalities.
 258 We found higher proportion of radiological abnormalities in Patna and Lucknow districts, which
 259 have a larger urban population, and lower proportion in Etawah and Darbhanga districts, which
 260 in contrast have a larger rural population. We also observed correspondingly higher proportion of
 261 PEP alone or with other infiltrates in districts of Lucknow and Patna and lower in districts of
 262 Etawah and Darbhanga.

263

264 **Table 2** also describes univariate distribution of socio-demographic and clinical factors of CAP
 265 among hospitalized children (2-59 months). Statistically significantly higher proportion of
 266 females hospitalized for CAP had radiologically abnormal CXR. Likewise, statistically
 267 significantly higher proportion of abnormal versus normal CXRs findings were reported in

268 hospitalized cases who had symptoms of fever, pallor, wheezing on auscultation, vomiting
 269 everything or were malnourished.

270

271 **Table 2: Distribution of socio-demographic and clinical factors by chest radiograph**
 272 **findings among hospitalized children from January 2015-April 2017**

	Interpretable chest X rays			Abnormal chest X rays			
	N=2829	Normal 1852 n (%)	Abnormal 977 n (%)	p value	PEP* alone or with other infiltrate 635 n (%)	Other infiltrates 342 n (%)	p value
Participating site (row %)							
Lucknow	1025	636 (62.05)	389 (37.95)	<0.0001	282 (72.49)	107 (27.51)	<0.0001
Etawah	389	275 (70.69)	114 (29.31)		73 (64.04)	41 (35.96)	
Patna	744	457 (61.42)	287 (38.58)		184 (64.11)	103 (35.89)	
Darbhanga	671	484 (72.13)	187 (27.87)		96 (51.34)	91 (48.66)	
Socio-demographic & clinical factors (column %)							
Age-group (months)							
2-11	1865	1223 (66.04)	642 (65.71)	0.86	409 (64.41)	233 (68.13)	0.26
12-59	964	629 (33.96)	335 (34.29)		226 (35.59)	109 (31.87)	
Gender							
Male	2005	1354 (73.11)	651 (66.63)	<0.0001	426 (67.09)	225 (65.79)	0.72
Female	824	498 (26.89)	326 (33.37)		209 (32.91)	117 (34.21)	
Place of residence							
Rural	1392	921 (49.73)	471 (48.21)	0.44	299 (47.09)	172 (50.29)	0.34
Urban	1437	931 (50.27)	506 (51.79)		336 (52.91)	170 (49.71)	

Biomass fuel							
Yes	1501	867 (46.81)	461 (47.19)	0.44	294 (42.30)	167 (48.83)	0.24
No	1328	985 (53.19)	516 (52.81)		341 (53.70)	175 (51.17)	
Immunization status							
Complete for age	2347	1546 (83.48)	801 (81.99)	0.32	516 (81.26)	285 (83.33)	0.54
Incomplete	482	306 (16.52)	176 (18.01)		119 (18.74)	57 (16.67)	
Clinical Features							
Fever	2499	1616 (87.26)	883 (90.38)	0.014	575 (90.55)	308 (90.06)	0.82
Pallor	764	465 (25.11)	299 (30.60)	0.002	200 (31.50)	99 (28.95)	0.41
Wheeze on auscultation	2054	1377 (74.35)	677 (69.29)	0.005	415 (65.35)	262 (76.61)	0.0003
Duration of illness fever [days] (n, Mean ± SD)	2499	1611 3.91±2.51	888, 4.40±2.70	<0.0001	577, 4.57±2.82	342, 4.08±2.44	0.011
Respiratory Rate							
Respiratory Rate [2-11 months] (n, Mean ± SD)	1865	1243 55.52±11.29	642 57.99±11.70	<0.0001	409 58.12±11.88	233 57.74±11.40	0.69
Respiratory Rate [12-59 months] (n, Mean ± SD)	964	629 49.78±12.41	335 51.28±13.37	0.08	226 51.35±13.31	109 51.12±13.35	0.88
Fast Breathing for age [2-11 months]	1735	1130 (61.02)	605 (61.92)	0.11	384 (60.47)	221 (64.62)	0.69
Fast Breathing for age [12-59 months]	862	562 (30.35)	300 (30.71)	0.92	204 (32.13)	96 (28.07)	0.53
Signs of Pneumonia with a general danger sign n (%)							
Lethargy or reduced level of consciousness	1101	732 (39.52)	369 (37.77)	0.39	247 (38.90)	122 (35.67)	0.33
Inability to breastfeed or drink	937	612 (33.05)	325 (33.27)	0.46	211 (33.23)	114 (33.33)	0.97
Convulsions	148	98 (5.29)	50 (5.12)	0.93	33 (5.20)	17 (4.97)	0.87
Central Cyanosis	62	39	23	0.34	16	7	0.64

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		(2.11)	(2.35)		(2.52)	(2.05)	
Malnutrition Status							
Normal *	1880	1293 (69.82)	587 (60.08)	< 0.0001	367 (57.80)	220 (64.33)	0.06
Malnutrition*	517	333 (17.98)	184 (18.83)		122 (19.21)	62 (18.13)	
Severe malnutrition*	432	226 (12.20)	206 (21.08)		146 (22.99)	60 (17.54)	

273 *Normal-weight of age z score > -2SD; Malnutrition-weight-for-age z ≤ -2SD and Severe
274 malnutrition-weight-for- age z ≤ -3SD

275

276 **Table 3** describes four multivariate unconditional logistic regression models to find associates of
277 abnormal CXR findings. After controlling for age, gender, symptoms of pneumonia, duration of
278 illness, biomass fuel and malnutrition status of cases, statistically significant district-wise
279 heterogeneity remained in the first three models. Models I, II and III had similar associates for
280 radiological abnormalities whereas Model IV was different. Across all the four models, female
281 gender and those with severe malnutrition had statistically significantly higher risk for having
282 abnormal CXRs. A higher risk of radiological abnormalities was also observed in those children
283 with longer duration of illness.

284
285 **Table 3: Independent Associations between Chest Radiograph Findings and demographic**
286 **and clinical factors, among hospitalized children January 2015-April 2017**

Variables	Model – I Abnormal/Normal ^{Ref}		Model – II PEP alone or with other infiltrate /Normal ^{Ref}		Model – III PEP alone / Normal ^{Ref}		Model – IV Other infiltrate / Normal ^{Ref}	
	Adjusted Odd Ratio (95%CI)	p value	Adjusted Odd Ratio (95%CI)	p value	Adjusted Odd Ratio (95%CI)	p value	Adjusted Odd Ratio (95%CI)	p value
Districts								
Lucknow vs. Others	1.58 (1.20-2.10)	<0.0001	2.07 (1.48-2.89)	<0.0001	2.20 (1.52-3.19)	<0.0001	0.98 (0.65-1.47)	0.93
Etawah vs. Others	1.22 (0.88-1.70)	0.23	1.30 (0.87-1.95)	0.19	1.49 (0.95-2.30)	0.07	1.17 (0.74-1.87)	0.50
Patna vs. Others	1.67 (1.27-2.20)	<0.0001	1.89 (1.36-2.64)	<0.0001	2.25 (1.56-3.24)	<0.0001	1.39 (0.95-2.07)	0.09

Age – Group (months)								
2-11 ^{Ref}								
12-59	0.92 (0.77-1.10)	0.34	0.95 (0.77-1.17)	0.62	1.03 (0.82-1.29)	0.79	0.86 (0.66-1.13)	0.27
Gender								
Male ^{Ref}								
Female	1.39 (1.16-1.66)	<0.0001	1.34 (1.08-1.65)	0.008	1.28 (1.01-1.61)	0.03	1.48 (1.14-1.92)	0.004
Symptoms of pneumonia[†]								
Wheezing	0.83 (0.68-1.01)	0.06	0.72 (0.57-0.90)	0.005	0.75 (0.59-0.96)	0.02	1.14 (0.83-1.55)	0.42
Pallor	1.30 (1.08-1.58)	0.006	1.28 (1.03-1.60)	0.02	1.22 (0.95-1.55)	0.12	1.34 (1.01-1.77)	0.04
Vomiting everything	0.90 (0.75-1.09)	0.28	0.80 (0.64-0.99)	0.04	0.78 (0.62-1.01)	0.05	1.09 (0.83-1.08)	0.51
Duration of illness, fever (days)	1.06 (1.04-1.09)	<0.0001	1.08 (1.04-1.12)	<0.0001	1.08 (1.04-1.12)	<0.0001	1.03 (0.98-1.48)	0.24
Biomass fuel	1.28 (1.05-1.57)	0.02	1.39 (1.10-1.76)	0.006	1.40 (1.14-1.88)	0.003	1.08 (0.79-1.45)	0.64
Malnutrition Status								
Normal ^{*Ref}								
Malnutrition*	1.18 (0.93-1.45)	0.15	1.17 (0.91-1.52)	0.23	1.17 (0.88-1.55)	0.27	1.12 (0.82-1.52)	0.47
Severe malnutrition*	1.65 (1.31-2.09)	<0.0001	1.82 (1.34-2.36)	<0.0001	1.87 (1.41-2.47)	<0.0001	1.62 (1.71-2.23)	0.003

287 **Abbreviations used:**^{Ref} Reference Category

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 289 **Footnotes:** [†] No signs of pneumonia taken as a reference
 290 *Normal: weight-for-age z score > -2SD; Malnutrition: weight-for-age z ≤ -2SD; Severe
 291 malnutrition: weight-for-age z ≤ -3SD

292 DISCUSSION

293 This active, prospective hospital-based surveillance study was conducted to assess the
 294 radiological abnormalities in children (2-59 months) residing in pre-specified districts of Uttar
 295 Pradesh and Bihar, India and hospitalized with CAP. The study was conducted from January
 296 2015 to April 2017, prior to introduction of PCV in the national immunization programme of the
 297 Government of India⁹.

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3 299 In our study, among interpretable CXRs, we found that 22.44% (635/2829) children had PEP
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5 300 alone or with infiltrates, 12.09% (342/2829) had other infiltrates only and 65.46% (1852/2829)
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7 301 had normal CXRs findings. Our study used WHO case definition for CAP¹⁹. A panel of three
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9 302 trained radiologists interpreted CXRs, adopting WHO recommended methodology^{11 12}. These
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11 303 make our study methodology robust and results generalizable.
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17 305 There were 88.54% (2829/3195) interpretable CXRs in the current study. This is similar to 83%
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19 306 (3587/3973) interpretable CXRs reported by Pneumonia Etiology Research for Child Health
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21 307 (PERCH) study conducted on 4232 children (1-59 months) to assess the etiology of CAP in nine
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23 308 sites of seven countries²⁷. Consistent with PERCH findings, a vaccine probe trial conducted in
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25 309 Gambia found the proportion of interpretable CXRs among unvaccinated cases of pneumonia to
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27 310 be 84.32% (242/287)²⁸.
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33 312 There have been several studies in the past two decades, which have reported CXRs findings in
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35 313 hospitalized cases of CAP. Almost all of these were conducted before the introduction of PCV in
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37 314 their respective regions. A small prospective study conducted in Ethiopia reported radiological
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39 315 abnormality in CXRs in 48.3% (95% CI 39.49-57.22) among 122 children (3 months-14 years)
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41 316 clinically diagnosed with WHO-defined severe pneumonia²⁹. Similar findings were reported
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43 317 from the Gambian vaccine probe trial where the proportion of radiological abnormality was 45%
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45 318 (95% CI: 43.35-46.46) among unvaccinated hospitalized cases of clinical pneumonia²⁸. PERCH
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47 319 study found that 54% (95% CI: 52.31-55.57) of CXRs among cases of CAP were abnormal²⁷.
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49 320 In all of these studies, proportion of cases with abnormal CXRs is higher than 34.5% (95% CI
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51 321 32.8-36.3) found by us in the current study. However, our findings are similar to PERCH rural
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3 322 study site of Matlab, Bangladesh that reported radiological abnormality in 35.3% (95% CI:
4 29.77-40.85) CXRs of hospitalized cases of CAP²⁷. Another PERCH urban site of Dhaka,
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8 324 Bangladesh reported 63.10% (95% CI 56.18 -70.02) cases with abnormal CXRs²⁷. In our study,
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10 325 radiological abnormalities in CXRs were higher in cases from largely urban districts of Patna and
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12 326 Lucknow compared to rural districts of Darbhanga and Etawah. This is consistent with rural-
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14 327 urban differences in Bangladesh sites of PERCH. Variation in CXR findings among cases of
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16 328 CAP may be due to infecting organism, immune response of patient and prior duration of
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18 329 disease.
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24 331 In 2016, WHO's Department of Immunization, Vaccines and Biologicals standardized the
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26 332 categorization of radiological pneumonia and established that PEP can be taken as a good
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28 333 surrogate marker of bacterial pneumonia in epidemiological and vaccine efficacy studies¹². In
29
30 334 our study, 22.44 % (95% C.I. 20.90 -23.98), CXRs were having PEP alone or with other
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32 335 infiltrates. This is similar to PERCH study that reported PEP alone or with other infiltrates in
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34 336 27% (95% C.I. 25.50 -28.40) hospitalized cases of CAP²⁷. Another study conducted in Gambia
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36 337 reported that 45% (95% CI: 43.35-46.46) non-vaccinated children had PEP and/or other
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38 338 infiltrates²⁸. PEP has been associated with increased risk of treatment failure (p=0.002),
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40 339 increased length of hospitalization (p=0.0003) and more days of respiratory support (p=0.002) in
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42 340 Botswana when compared with cases reporting `no significant pathology` on CXRs³⁰.
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49 342 In our study, female gender (p<0.001) was at the higher risk of developing radiological
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51 343 abnormalities compared to males (**table 3**). The results are in concordance with a hospital-based
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53 344 case-control study carried out in Brazil that reported male gender as a protective factor against
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3 345 pneumonia (OR = 0.53; 95 % CI 0.39–0.72)³¹. Another study in Mozambique, Africa reported
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5 346 that male gender was not significantly associated with presence of radiological abnormalities
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8 347 (OR =0.77; 95 % CI 0.56–1.05) in children (0-59 months) suffering from severe pneumonia³².
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10 348 However, in contrast, a Gambian study reported male preponderance for all pneumonia that was
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12 349 most marked for `other infiltrates/abnormalities` pneumonia²⁸.

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16
17 351 In our study, it was observed that there was differential care-seeking by gender for CAP in all
18
19 352 four project sites. Although females admitted with CAP were at higher risk of having
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21 353 radiological abnormalities, lower proportion were hospitalized for it. Gender inequality in health
22
23 354 care seeking for females is common in India, as in other South Asian countries^{33 34}. Since there
24
25 355 is no health-care financing or health insurance provision in India, in case of severe illness,
26
27 356 parents are less likely to incur out-of-pocket expenditure or incur debts to pay expenses on
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29 357 medical treatment of their daughters compared to sons³⁵. Another Indian study found that male
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31 358 children were five times more likely to be taken early for medical care and three times more
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33 359 likely to be seen by qualified medical doctors compared to female children³⁶. We also found
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37 360 that majority of hospitalized cases of pneumonia were from urban areas, in contrast with
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39 361 observations of other researchers who report poor health care seeking from rural areas³⁷.

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44 363 A systematic review with meta-analysis conducted in 2019 suggests that no one clinical feature
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46 364 is sufficient on its own to diagnose radiological pneumonia³⁸. However other socio-
47
48 365 demographic and clinical correlates of abnormal CXRs found by us (Model 1), which increased
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50 366 the risk of radiological abnormalities, were presence of pallor, severe malnutrition, longer
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52 367 duration of illness and exposure to biomass fuel. Exposure to biomass fuel used for cooking is an

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3 368 important factor that increases the risk of CAP in developing countries³⁹. In rural India, majority
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5 369 of the households use biomass fuel like firewood, dung cakes and wood for cooking ⁴⁰. Young
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7 370 children are at risk to adverse effects of exposure to biomass fuel as either the households have
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9 371 no separate cooking space or have poor ventilation and sometimes young children stay with their
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11 372 mother while she cooks.
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17 374 Other correlates of PEP/Radiological Pneumonia (Models II and III), besides those found in
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19 375 Model I, were presence of vomiting everything and wheeze on auscultation, both of which were
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21 376 found to be protective. These symptoms/signs are more often reported in viral pneumonia⁴¹.
22
23 377 Correlates of radiological abnormalities of 'other infiltrates' (Model IV), which increased the
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25 378 risk, were again female gender, pallor and severe malnutrition. Hence it is difficult to attribute
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27 379 radiological findings of other infiltrates to either bacterial or viral etiology.
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33 381 Based on our study, almost two-third hospitalized cases of CAP had normal CXRs and this could
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35 382 be perhaps of viral etiology. This is supported by a recent study that reported 61.4% (95% CI
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37 383 57.3–65.6) cases to be viral⁴¹. Among one-third of cases of CAP had abnormal CXRs and thus
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39 384 were more likely to be bacterial in etiology.
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45 386 In India, 13-valent PCV is given using a three dose schedule (2 primary and one booster) at 6
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47 387 weeks, 14 weeks and 9 months of age. PCV 13 provides coverage against 13 serotypes (1, 3, 4,
48
49 388 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) causing pneumococcal pneumonia⁴². Several
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51 389 studies have assessed serotype distribution of pneumococcal disease among children in India. A
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53 390 study conducted in Vellore, India found that the most common serotypes causing invasive
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3 391 infections among under-five children were 14, 19F, 5, 6A and 6B, all of which were covered by
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5 392 the 13-valent PCV ⁴³. Another population-based surveillance study conducted in rural
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8 393 Bangladesh found that the most common serotypes were 1, 5, 14, 18C and 19A and 38 and these
9
10 394 comprised more than three-fourth of the *S. pneumoniae* isolates ⁴⁴. A systematic review and
11
12 395 meta-analysis of data collected on Invasive Pneumococcal Disease serotypes from under-five
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14 396 children during the pre-PCV period (between 1980–2007) found that serotypes included in both
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16 397 the 10-valent and 13-valent PCVs accounted for 10 million cases and 600,000 deaths
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19 398 worldwide⁴⁵.

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25 400 Several strengths of the study are worth-noting. This was an active, prospective, multi-site study
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27 401 where recruitments were done from a large hospital surveillance network established especially
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29 402 for the study in four districts of two Indian states that have high under-five mortality rates.
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31 403 Standard WHO definition was used to identify hospitalized cases of CAP. Radiological
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33 404 abnormalities were interpreted by a panel of three trained radiologists at locations out of the
34
35 405 surveillance network, blinded to each other as well as clinical features of the case. Despite these
36
37 406 strengths, our study findings have certain limitations. First, in our study, pre-existing x-rays
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39 407 machines which were not of uniform specification, were used. This might have caused variation
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41 408 in quality of CXR images, though this error was minimized by digitizing the CXR images
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43 409 centrally. Secondly, in our study, clinical data collection was recorded by physicians in the
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45 410 network hospitals and this could be subject to observer bias. This could also have lead to
46
47 411 possibly over reporting of presence of wheezing. In this study, we have not collected information
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49 412 on use of antibiotic prior to hospitalizations, as such information is not available reliably.
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52 413 However, in another study, done in one of the network hospitals of Lucknow in the recent past, it

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3 414 was found that 70.5% children tested positive for antibiotics on urine examination⁴⁶. Prior use of
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5 415 antibiotics could have possibly lead to underestimation of radiological pneumonia. We also
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7 416 observed that pulse oxymetry was routinely done in the network hospitals. This could have an
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9 417 impact on the case management but would not have affected the radiological findings of CXRs.
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16 419 CONCLUSION

19 420 Among hospitalized cases of community-acquired pneumonia, almost one-third children had
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21 421 abnormal chest radiographs of which about two-thirds had abnormalities related with possible
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23 422 bacterial etiology (*Streptococcus pneumoniae*). Hence, the introduction of pneumococcal
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25 423 vaccination is likely to reduce the burden of childhood pneumonia in India. Since the study was
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27 424 done prior to the introduction of PCV in India, continued surveillance will be required to assess
28
29 425 the impact of PCV on radiological findings in cases admitted with CAP. The impact of
30
31 426 introduction of PCV in the national immunization programme on under-five mortality rate and
32
33 427 burden of CAP needs to be assessed.
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38 428

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49
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16
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18
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20
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22
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30
31 450 manuscript.

32
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34
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36
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40
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42
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3 458 **Data sharing statement:** The data contained within this study can be obtained by writing to
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5 459 shally07@gmail.com

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21 466 **Supporting Information**

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24 467 S1 Appendix: Chest radiograph interpretation form
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607 **Figure Legend**

608 Figure 1: Flow diagram of cases of community acquired pneumonia recruited from participating
609 districts before the introduction of pneumococcal conjugate vaccine (January 2015-April 2017)

Figure 1: Flow diagram of cases of community acquired pneumonia recruited from participating districts before introduction of pneumococcal conjugate vaccine (January 2015-April 2017)

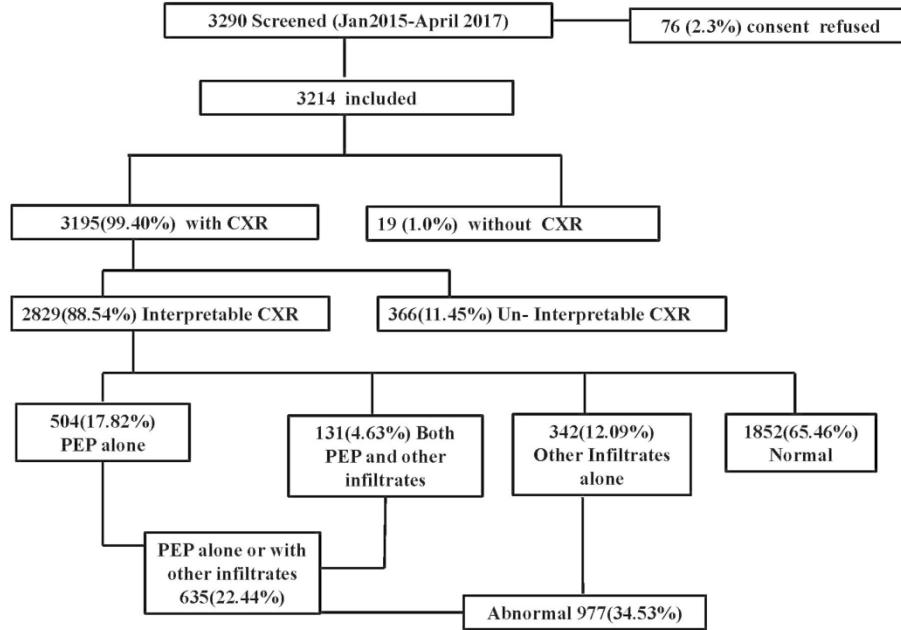


Figure 1: Flow diagram of cases of community acquired pneumonia recruited from participating districts before the introduction of pneumococcal conjugate vaccine (January 2015-April 2017)

254x190mm (300 x 300 DPI)

Childhood Pneumonia Surveillance
Department of Paediatrics, KGMU, Lucknow ,UP

Form-R
(RADIOLOGY REPORT FORM)

1	Drs_ID	[][][][]
	Radiology Report	Patient Details
2	IDNo:	[] / [] / [][][][][][] State /District / Unit / Subject number (For office use)
2	Date Of Report	[][]/[][]/[][][][] (DD/MM/YYYY)
	Report Details	Findings (tick one)
3	Image Quality	Adequate <input type="checkbox"/> Suboptimal <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
4	Significant Pathology	Yes <input type="checkbox"/> No <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
5	End Point Consolidation	
5a	Left	Yes <input type="checkbox"/> No <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
5b	Right	Yes <input type="checkbox"/> No <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
		Uninterpretable
6	Other Infiltrates/Abnormalities	
6a	Left	Yes <input type="checkbox"/> No <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
6b	Right	Yes <input type="checkbox"/> No <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
7	Pleural Fluid	
7a	Left	Yes <input type="checkbox"/> No <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
7b	Right	Yes <input type="checkbox"/> No <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
8	Comments:	<input style="width: 100%; height: 15px;" type="text"/>
9	Conclusion:	a) Primary endpoint pneumonia only <input type="checkbox"/> b) Other infiltrate only <input type="checkbox"/> c) Both PEP and other infiltrate <input type="checkbox"/> d) Normal <input type="checkbox"/> e) Un-interpretable for any findings <input type="checkbox"/>

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60STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page Number
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	25
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11-13
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	11-13
		(b) Describe any methods used to examine subgroups and interactions	Table 1, 2 & 3
		(c) Explain how missing data were addressed	12 reference 24
		(d) If applicable, describe analytical methods taking account of sampling strategy	11-13
		(e) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	14
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	14-15 Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Figure 1

Outcome data	15*	Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3 (adjusted odds ratio)
		(b) Report category boundaries when continuous variables were categorized	Table 3
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA (calculated only odds ratio)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	21-23
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	25-26
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	21-23
Generalisability	21	Discuss the generalisability (external validity) of the study results	21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	27

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Chest Radiograph Findings in children aged 2-59 months hospitalized with Community-Acquired Pneumonia, prior to the introduction of Pneumococcal Conjugate Vaccine in India- A Prospective Multisite Observational Study

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Title: *Chest Radiograph Findings in children aged 2-59 months hospitalized with Community-Acquired Pneumonia, prior to the introduction of Pneumococcal Conjugate Vaccine in India - A Prospective Multisite Observational Study*

Short Title: *Radiological Findings in Children hospitalized with Community-Acquired Pneumonia in India Pre-Pneumococcal Conjugate Vaccine introduction*

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ABSTRACT

Objectives: The current study was a hospital-based surveillance of cases hospitalized with World Health Organization defined community-acquired pneumonia in children, aged 2-59 months, to assess the radiological abnormalities in chest X-rays and to identify the demographic and clinical correlates of specific radiological abnormalities, in residents of pre-specified districts of Uttar Pradesh and Bihar, India.

Design: Prospective, active, hospital-based surveillance.

Setting: Multisite study conducted in a network of 117 secondary/tertiary care hospitals in four districts of Uttar Pradesh and Bihar, India.

Participants: Included were children aged 2-59 months, hospitalized with community-acquired pneumonia, residing in the project district, with duration of illness <14 days and who had not been hospitalized elsewhere for this episode nor had been recruited previously.

Main outcome measure: Concordant radiological abnormalities in the chest X-rays.

Results: From January 2015 to April 2017, 3214 cases were recruited and in 99.40 % (3195/3214) chest X-rays were available, among which 88.54 % (2829/3195) were interpretable. Relevant radiological abnormalities were found in 34.53 % (977/ 2829, 95% C.I. 32.78 -36.28). These were primary end-point pneumonia alone or with other infiltrates in 22.44 % (635/2829, C.I. 20.90 %-23.98 %) and other infiltrates in 12.09% (342/ 2829; C.I. 10.88 %- 13.29 %). There was a statistically significant inter-district variation in radiological abnormalities. Statistically significantly higher proportion of abnormal chest X-ray were found in girls, those with weight-for-age z score ≤ -3 SD, longer duration of fever, pallor and with exposure to biomass fuel.

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2
3 **Conclusions:** Among hospitalized cases of community-acquired pneumonia, almost one-third
4 children had abnormal chest radiographs, which were higher in females, malnourished children
5 and those with longer illnesses; and an intra-district variation was observed.
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12 **Key words:** Chest radiographs, Hospitalized community-acquired pneumonia, under-five,
13 *Streptococcus pneumoniae*, India
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17 **Strengths and Limitations of the Study**

- 18 • Prospective, multisite study recruiting cases from a large hospital surveillance network
19 established for the project in four districts in two states of India that have high under-five
20 mortality rates.
- 21 • World Health Organization definition of clinical pneumonia was used for identifying
22 hospitalized cases for generalizability.
- 23 • Radiological abnormalities were interpreted by a panel of three independent, trained
24 radiologists outside the surveillance network, blinded to each other as well as clinical features of
25 the case.
- 26 • Since pre-existing X-rays machines were used, there were variations in the quality of images,
27 which was, however, minimized by digitizing them centrally.
- 28 • Since data of clinical examination was abstracted from hospital records, inter-observer
29 variation in documentation was possible.
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1 INTRODUCTION

2 Community-acquired pneumonia (CAP) is the leading cause of death in young children
3 worldwide. Globally, pneumonia accounts for 16% of deaths in children under-five years of age,
4 which translates into almost one million deaths annually, with 0.9 million deaths reported in
5 2016.^{1 2} Most deaths due to pneumonia occur in low and middle income countries, particularly
6 in sub-Saharan Africa and South Asia.^{2 3} In India, there were approximately 0.44 million under-
7 five deaths due to CAP in the year 2015.⁴

8
9 CAP could be of either viral or bacterial etiology.⁵⁻⁷ In young children, bacteria associated with
10 pneumonia are predominantly *Streptococcus pneumoniae* and *Hemophilus influenzae Type B*,
11 while viruses are Respiratory Syncytial Virus and Influenza A or B.⁶ However, etiology varies
12 from country to country and also across different time periods. To reduce the incidence of
13 bacterial pneumonia, vaccination against *Hemophilus influenzae Type B* is already under the
14 national immunization programme of India since 2011. Thereafter, World Health Organization
15 (WHO) introduced Pneumococcal Conjugate Vaccine (PCV) in countries, such as India, with
16 high child mortality rates.⁸ Consequently, PCV-13 was launched in May 2017 under the national
17 immunization programme of five Indian states (Uttar Pradesh, Bihar, Rajasthan, Madhya Pradesh
18 and Himachal Pradesh) in a phased manner.⁹ It is expected to be rolled out in other parts of the
19 country in the near future.

20
21 Differentiating bacterial from viral etiology of CAP based on clinical features or investigations
22 remains difficult.^{7 10 11} Therefore, several PCV probe trials have used radiographically

23 confirmed end-point pneumonia to be a surrogate marker of bacterial etiology and hence used
24 this as an outcome measure for vaccine efficacy. This approach has been endorsed by WHO.¹²⁻¹⁴

26 The current study was conducted to assess the radiological abnormalities in chest X-rays (CXRs)
27 and to identify the demographic and clinical correlates of specific radiological abnormalities in
28 children aged 2-59 months, hospitalized with WHO defined CAP, residing in pre-specified
29 districts of Uttar Pradesh and Bihar.

31 **METHODS**

32 **Study design and Setting**

33 This was a prospective, multisite observational study conducted in the northern Indian states of
34 Uttar Pradesh and Bihar. Uttar Pradesh is the first most populated and Bihar third most populated
35 state of the country.^{15 16} This study was conducted in Lucknow and Etawah districts of Uttar
36 Pradesh and Patna and Darbhanga districts of Bihar, India. In Lucknow district 66.2% population
37 is urban and in Patna district 43.07%.^{15 16} In contrast, only 22.3% population of Etawah district
38 and 9.74% population of Darbhanga district is urban.^{15 16} All four project districts have high
39 infant and child mortality rates.¹⁵⁻¹⁷ Infant mortality rate per 1000 live births of Lucknow district
40 is 44, Etawah district 56, Patna district 31 and Darbhanga district 44, all being higher than the
41 national average 41.¹⁵⁻¹⁷ Similarly, under-five mortality rates per 1000 live births of districts
42 included in this study are above the national average 50, being 58 for Lucknow, 85 for Etawah,
43 46 for Patna and 77 for Darbhanga.¹⁵⁻¹⁷

45 Study Population

46 This study was conducted after obtaining institutional ethical clearance from all four
47 participating academic institutions, one in each district. Each institution then established a
48 prospective, active, hospital-based surveillance system for this study.^{17 18} After obtaining written
49 informed consent from the private hospital management and district administration for public
50 hospitals, included in the surveillance were 117 public and private hospitals of four study
51 districts which provided either secondary or tertiary level care to admitted children.

52 Surveillance officers of the project visited these hospitals every 48-72 hours to screen and
53 recruit eligible cases. In between the scheduled visits they telephonically contacted the hospitals
54 daily to inquire about hospitalization of any potentially eligible case and made additional visits,
55 if required. All children between the ages of 2-59 months, hospitalized in network hospitals with
56 history of fast breathing with/without chest in-drawing were screened.¹⁸

57
58 Included were children hospitalized with symptoms of WHO defined CAP and residing in the
59 project district.¹⁸ WHO defined CAP was categorized into pneumonia and severe pneumonia.

60 Fast breathing ≥ 50 breaths/minute in a child aged 2–11 months and ≥ 40 breaths/minute in a
61 child aged 12-59 months, with or without chest in-drawing was categorized as `pneumonia`.¹⁹

62 Cough or difficulty in breathing plus at least one of the following: (a) oxygen saturation $< 90\%$
63 or central cyanosis or (b) severe respiratory distress (e.g. grunting, very severe chest in-drawing)
64 or (c) signs of pneumonia with a general danger sign (inability to breastfeed or drink, lethargy or
65 reduced level of consciousness, convulsions) was categorized as `severe pneumonia`.¹⁹ Excluded
66 were children with cough for ≥ 14 days or those that had been hospitalized in last 14 days.¹⁸

67

68 **Sample Size**

69 We assumed that the incidence of radiological pneumonia is 3/100 child years of observations.
70 Then for a margin of error of 1.5/100 child years of observation, incidence of pneumonia in the
71 community of 20/100 child years of observation, alpha level of 0.05, and power of 90% when the
72 estimated population of children under-five years of age in Lucknow district ²⁰ is 750,000; 693
73 cases had to be included per district.

75 **Data collection**

76 Data was collected by surveillance officers hired for the project at each of the four district sites.
77 They had postgraduate degree in social sciences and at least 10 years experience in community
78 based health research. After recruitment, they were imparted six-day centralized training on
79 project procedures and logistics. Classroom as well as practical skills training in real life setting
80 was given by the coordinating centre in Lucknow. Pre and post tests were conducted to ascertain
81 knowledge. Skills acquired by them were assessed during field observations. The coordinating
82 centre provided annual refresher training to the surveillance officers from all four district sites in
83 Lucknow. This was done to ensure quality of data collected.

84 After obtaining written, informed consent of the caregivers, data was collected through face-to-
85 face interviews with caregivers, as well as by abstraction from hospital records. Socio-
86 demographic data obtained by interviewing caregivers was: child's age, gender, residence, birth
87 order, immunization status, current breastfeeding status, parental education and occupation,
88 smoking status of parents, family type, housing infrastructure, use of biomass fuel etc.
89 Caregivers were also asked about the symptoms of disease and its duration in days.

90
91 Clinical data, recorded by pre-existing hospital staff at the time of hospitalization, was abstracted
92 by surveillance officers. Data was collected on anthropometry (weight and height), fever
93 (axillary temperature $\geq 37.5^{\circ}\text{C}$), oxygen saturation by pulse oxymetry where done, pallor, central
94 cyanosis, signs of pneumonia along with general danger sign and vital signs (heart rate and
95 respiratory rate). Presence of auscultatory wheeze was abstracted or inquired from the treating
96 clinician. In case information on a clinical variable was missing in the medical chart, the
97 surveillance officers contacted the clinician and obtained the same. Thus, there was no missing
98 data for clinical variables reported in this manuscript.

99
100 At the hospitals, clinicians generally used Integrated Management of Childhood Illness
101 definitions²¹ to identify pallor, cyanosis, wheeze on auscultation and general danger sign as it is
102 incorporated in their medical undergraduate training. Most clinicians of public health sector had
103 also received a formal in-service training on Integrated Management of Childhood Illness.²¹
104 Clinical outcome (survival or mortality) was noted from the hospital records on follow up.^{17 18}

106 **Chest x-ray (CXR) image acquisition and archiving**

107 CXR (poster-anterior view) was done on the advice of treating physician. These CXRs were
108 obtained by the surveillance officers at the time of recruitment. CXRs were either analog or
109 digital. In case of digital CXRs, second copy was obtained where possible. If only single analog
110 image was available, then the hardcopy of CXR was obtained from the caregiver after the child
111 was discharged. If the caregiver was not ready to give the hardcopy of CXR (in <1% cases),

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3 112 image of the same was captured by surveillance officers using 16 megapixel cell phone camera
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5 113 and portable CXR view-box.
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10 115 CXRs of recruited cases were subsequently scanned and converted into digital format using a
11
12 116 diagnostic quality film image digitizer (Microteck International Limited[®], Medi 6000 plus).²²
13
14 117 These were archived for web-based radiological interpretation. Digital images were stored in
15
16 118 JPEG format at 300 dpi resolution. Each CXR file was anonymized and given a unique
17
18 119 identification number. Digital CXRs were uploaded on customized online data management
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20 120 software.
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26 122 **Interpretation of radiological images**

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29 123 A panel of radiologists was constituted for standardized interpretations of CXRs. Four
30
31 124 radiologists were part of this panel, one of whom was Project co-investigator-Radiology (NK).
32
33 125 All radiologists are faculty in medical teaching institutes and also look after pediatric radiology.
34
35 126 They have more than fifteen years experience in interpreting pediatric CXRs.
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40 128 Radiologists were trained according to the methodology developed by Department of
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42 129 Immunization, Vaccines and Biologicals of the WHO for research purpose.¹¹ An international
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44 130 WHO-certified trainer from the International Centre for Diarrhoeal Disease Research,
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46 131 Bangladesh imparted two-day in-house training to the radiologists. The objectives of this training
47
48 132 were to standardize interpretation and coding of CXRs, to develop a CXR reporting form [S1
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50 133 **Appendix]** and to provide training on web-based CXR retrieval and reporting system. During the
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52 134 training, 210 CXRs of the WHO data set were used. For assessing post training concordance,
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3 135 another set of 48 CXRs was provided for interpretation to individual radiologists. Post-test
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5 136 agreement with WHO findings was about 80%. Inter-observer variation was about 25% and was
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7 137 for only minor interpretations such as quality of film, end-point infiltrates etc. Repeat training
8
9 138 was conducted on an additional set of 44 CXRs provided by the WHO to ensure standardization
10
11 139 in interpretation. Thereafter, concordance achieved by the radiologists was reviewed quarterly by
12
13 140 the study arbitrator. Radiologists met annually to review key concepts and discuss challenges
14
15 141 faced in interpreting CXRs.
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21 143 After training, radiologists independently reviewed CXRs and registered their findings in an
22
23 144 online standardized chest radiograph interpretation form [S1 Appendix]. For optimal viewing of
24
25 145 CXRs, all radiologists used similar workstations. Specifications were provided for the computer
26
27 146 monitor and hardware to be used. It was ensured that computer monitors had the correct
28
29 147 brightness and contrast adjustment for optimal viewing.
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35 149 During online evaluation, radiologists reported the quality of film as *'interpretable'* or *'un-*
36
37 150 *'interpretable'*. Further, they categorized *'interpretable'* CXRs as either *'adequate/optimal'*
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39 151 which allowed for confident interpretation of consolidation and pleural effusion as well as other
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41 152 infiltrates or *'suboptimal'* which allowed interpretation of only consolidation and pleural
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43 153 effusion, but not of other infiltrates. In *'un-interpretable'* CXRs, no comment was possible for
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45 154 radiological abnormality such as consolidation, pleural effusion or other infiltrates.¹²
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51 156 After interpreting film quality, radiologists evaluated interpretable CXRs for abnormal
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53 157 radiological findings. For each CXR evaluated, radiological abnormality could be presence of
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3 158 consolidation, other infiltrates or pleural effusion. *Consolidation* was defined as a dense or
4
5 159 confluent opacity that occupied a portion or whole of a lobe or the entire lung that may or may
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8 160 not contain air bronchograms. *Other infiltrates* were defined as linear and patchy opacities
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10 161 (interstitial infiltrate) in a lacy pattern, featuring peri-bronchial thickening and multiple areas of
11
12 162 atelectasis, also including minor patchy infiltrates that were not of sufficient magnitude to
13
14 163 constitute end-point consolidation, and small areas of atelectasis which may be difficult to
15
16 164 distinguish from consolidation. *Pleural effusion* was defined as the fluid in the lateral pleural
17
18 165 space between the lung and chest wall that was spatially associated with a pulmonary
19
20 166 parenchymal infiltrate (including *other infiltrates*) or had obliterated enough of the hemithorax
21
22 167 to obscure any infiltrates. In most cases, this was to be seen at the costo-phrenic angle or as a
23
24 168 layer of fluid adjacent to the lateral chest-wall and this does not include fluid seen in the
25
26 169 horizontal or oblique fissures.¹² Primary end-point pneumonia (PEP) for research purpose was
27
28 170 the presence of consolidation or pleural effusion which could be with or without other infiltrates.
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35 172 Final conclusions were categorised as: (a) *Abnormal* when it was *PEP only* or *other*
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37 173 *infiltrates only* or *Both PEP and other infiltrates* and (b) *Normal* when no abnormal findings
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39 174 were seen.¹²
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44 176 Data manager checked for inconsistencies and completeness after online evaluation of CXRs by
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46 177 individual radiologists. Thereafter, CXRs with concordant and discordant interpretations were
47
48 178 identified. Interpretations were considered concordant when there was an agreement between
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50 179 two or more radiologists on final conclusions and discordant if all the three radiologists
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3 180 disagreed. Discordant interpretations were forwarded to the study arbitrator (NK). Arbitrator
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5 181 assessed discordant CXRs online and her interpretation was taken as final.
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183 **Data management and statistical analysis**

184 Clinical data of hospital surveillance network was entered online in customized software.
185 Primary entry was done by the four participating sites. Secondary data entry was done by the
186 coordinating site in separate customized software. Anonymized CXRs were uploaded on
187 customized software. Each of the three panelists assessed the CXRs online, blind to peer
188 assessments as well as clinical features of the case. CXR assessment data was downloaded from
189 the online software in MS Access database.
190

191 Exploratory data analysis was performed for detection of outlier and missing observations for all
192 the variables. Un-interpretable CXRs were not analyzed. Among interpretable CXRs, concordant
193 radiological abnormalities were taken as final. Weight-for-age (WAZ) z-score each child was
194 calculated using WHO Anthro Survey Analyser.²³ Weight of 7.59% (215/2829) children was
195 missing. Missing weight was estimated using regression based imputation technique.²⁴ Kappa
196 statistics was performed for agreement analysis among radiologists for CXRs findings. Statistical
197 analysis was performed using SPSS version 22.0 (Chicago, IL).²⁵ A p-value of <0.05 was taken
198 as statistically significant using a two-tailed distribution.
199

200 Univariate analysis was performed to evaluate heterogeneity, stratified by four participating
201 districts for socio-demographic variables such as child's age, gender, residence, birth order,
202 immunization status, current breastfeeding status, parental education and occupation, smoking

203 status of parents, family type, housing infrastructure, use of biomass fuel and for clinical
204 variables such as weight, height, duration of fever and oxygen saturation.

205
206 We report proportions of radiological abnormalities among children hospitalized for CAP by
207 four districts. Univariate analysis was performed to assess association of socio-demographic
208 variables and clinical signs of CAP with radiological abnormalities. Chi-square test was used for
209 categorical variables and student's t-test for continuous variables. ANOVA was used to test the
210 significance of continuous variables when there were more than two groups. Multivariate
211 unconditional logistic regression was performed to find association of presence of various
212 radiological abnormalities with other variables that had univariate association with radiological
213 abnormalities (p value ≤ 0.2) and/or were clinically meaningful, controlling for district of
214 residence.

215
216 We developed four models in which the dependent (outcome) were different CXR findings and
217 these were as follows:

218 Model I: Abnormal versus Normal

219 Model II: Primary End-Point Pneumonia alone or with Other Infiltrates versus Normal

220 Model III: Primary End-Point Pneumonia alone versus Normal

221 Model IV: Other Infiltrates only versus Normal

222
223 Independent variables were the same in all the four models. These were participating districts,
224 age, gender, use of biomass fuel, symptoms of CAP such as duration of illness, presence of

225 wheeze on auscultation, pallor, vomiting everything and malnutrition status of the case [$WAZ \leq -$
226 2 SD (malnourished) and $WAZ \leq -3$ SD (severely malnourished)].

227

228 **Patient and public involvement in research**

229 Patients or public were not involved in the development of research question, study design or
230 conducting the research. Reporting of this research conforms to the guidelines for Strengthening
231 the Reporting of Observational Studies in Epidemiology (STROBE)²⁶.

232

233 **RESULTS**

234 From January 2015 to April 2017, 3290 cases were screened in hospital surveillance network of
235 four districts. Out of these, 3214 were eligible and consenting for inclusion [**Figure 1**]. Among
236 them, in 3195 (99.40%) CXR was done and only in 19 (1.0%) cases CXR not done. However,
237 only 88.54% (2829/3195) CXRs were interpretable and remaining 11.45% (366/3195) were un-
238 interpretable. In cases with interpretable CXRs, 99.11 % (2804/2829) had `severe pneumonia` as
239 per the WHO criteria¹⁹.

240

241 Concordance among ≥ 2 radiologists on final conclusion of CXRs findings was 86.0%. Kappa
242 statistics was calculated for agreement of CXRs findings between Reader 1 versus Reader 2
243 ($K_1=0.31$), Reader 2 versus Reader 3 ($K_2=0.46$) and Reader 3 versus Reader 1 ($K_3=0.42$). Among
244 interpretable CXRs, 22.44% (635/2829) cases had PEP alone or with other infiltrates, 12.09%
245 (342/2829) had other infiltrates only and 65.46% (1852/2829) were normal [**figure 1**].

246

247 **Table 1** shows univariate distribution of socio-demographic and clinical variables among
 248 hospitalized cases across participating districts. A variation was observed in socio-demographic
 249 variables such as place of residence, type of house, type of family, maternal and paternal
 250 education and occupation, use of biomass fuel and parental smoking status across the four
 251 districts. We also report clinical variables of recruited cases across the four districts in **table 1**.
 252 Among those where pulse-oximetry was done, the proportion of cases with oxygen saturation <
 253 90 % was found to be different across four districts.

255 **Table 1: Distribution of socio-demographic and clinical variables among hospitalized children for**
 256 **participating districts (January 2015-April 2017)**

Characteristics	Lucknow	Etawah	Patna	Darbhanga	Total
Socio-demographic Characteristics	n=1025	n=389	n=744	n=671	N=2829
	(%)	(%)	(%)	(%)	(%)
Gender					
Male	659(64.29)	287(73.78)	557(74.87)	502(74.81)	2005(70.87)
Place of residence					
Rural	195(19.02)	279(71.72)	304(40.86)	614(91.51)	1392(49.20)
Urban	830(80.98)	110(28.28)	440(59.14)	57(8.49)	1437(50.80)
Family Type					
Joint	688(67.12)	360(92.54)	707(95.03)	383(57.08)	2138(75.57)
Nuclear	337(32.88)	29(7.46)	37(4.97)	287(42.77)	690(24.39)
House type					
Mud	64(6.24)	54(13.88)	123(16.53)	374(55.74)	615(21.74)
Bricks	854(83.32)	256(65.81)	453(60.89)	85(12.67)	1648(58.25)
Combined	107(10.4)	79(20.31)	168(22.58)	212(31.59)	566(20.01)
Mother's Education					
No formal education	203(19.80)	56(14.40)	328(44.09)	496(73.92)	1083(38.28)
Class I-V	108(10.54)	28(7.20)	82(11.02)	38(5.66)	256(9.05)
Class VI-XII	379(36.98)	176(45.24)	243(33.66)	112(16.69)	910(32.17)
Graduate/ Post graduation	335(32.68)	129(33.16)	91(12.23)	25(3.73)	580(20.50)
Father's Education					
No formal education	167(16.29)	29(7.46)	153(20.56)	345(51.42)	694(24.53)
Class I-V	85(8.29)	19(4.88)	91(12.23)	82(12.22)	277(9.79)
Class VI-XII	437(42.63)	206(52.96)	328(44.09)	205(30.55)	1176(41.57)
Graduate/ Post graduation	336(32.78)	135(34.70)	172(23.12)	39(5.81)	682(24.11)

Birth Order					
1 st	435(42.44)	187(48.07)	315(42.34)	192(28.61)	1129(39.91)
2 nd	343(33.46)	120(30.85)	235(31.59)	258(38.45)	956(33.79)
3 rd	153(14.93)	47(12.08)	129(17.34)	137(20.42)	466(16.47)
More than 3 rd	93(9.07)	35(9.00)	62(8.33)	83(12.37)	273(9.65)
Immunization Status					
Complete for age	792(77.27)	300(77.12)	711(95.56)	544(81.07)	2347(82.96)
Incomplete for age	220(21.46)	84(21.59)	25(3.36)	126(18.78)	455(16.08)
Unimmunized	13(1.27)	5(1.29)	8(1.08)	1(0.15)	27(0.95)
Currently Breast Feeding					
Yes	653(63.71)	256(65.81)	589(79.17)	537(80.03)	2035(71.93)
No	372(36.29)	133(34.19)	155(20.83)	134(19.97)	794(28.07)
Father's Occupation					
Unemployed	13(1.27)	20(5.14)	27(3.63)	63(9.39)	123(4.35)
Daily wages	329(32.10)	81(20.82)	165(22.18)	474(70.64)	1049(37.08)
Salaried/ Professional	397(38.73)	104(26.74)	245(32.93)	55(8.20)	801(28.31)
Self-Employment	286(27.90)	184(47.30)	307(41.26)	79(11.77)	856(30.26)
Mother's Occupation					
Home maker	961(93.76)	376(96.66)	701(94.22)	484(72.13)	2522(89.15)
Daily wages	17(1.66)	3(0.77)	17(2.28)	171(25.48)	208(7.35)
Salaried/Professional	47(4.59)	9(2.31)	18(2.42)	7(1.04)	81(2.86)
Self-Employment	0(0.0)	1(0.26)	8(1.08)	9(1.34)	18(0.64)
Biomass fuel					
Yes	211(20.59)	245(62.98)	263(35.35)	609(90.76)	1328(46.94)
No	814(79.41)	144(37.02)	481(64.65)	62(9.24)	1501(53.06)
Smoking Status-Father					
Yes	152(14.83)	45(11.57)	56(7.53)	59(8.79)	312(11.03)
No	873(85.17)	344(88.43)	688(92.47)	612(91.21)	2517(88.97)
Indoor smoking-Father					
Yes	83(8.10)	21(5.40)	16(2.15)	43(6.41)	163(5.76)
No	942(91.90)	368(91.60)	728(97.85)	628(93.59)	2666(94.24)
Smoking Status-Family member					
Yes	129(12.59)	55(14.14)	45(6.05)	102(15.20)	331(11.70)
No	896(87.41)	334(85.86)	699(93.95)	569(84.80)	2498(83.30)
Indoor smoking – Family member					
Yes	84(8.20)	27(6.94)	27(3.63)	94(14.01)	232(8.20)
No	941(91.80)	362(93.06)	717(96.37)	577(85.99)	2597(91.80)
Clinical Variables at	n	n	n	n	n

the time of admission at hospital	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD
Age (months)	1025 14.53±13.88	389 10.69±10.95	744 10.26±11.35	671 12.30±13.29	2829 12.35±12.85
Height (cm)	303 68.61±13.78	324 70.66±13.75	34 64.38±10.25	266 70.46±12.14	927 69.70±13.26
Weight (kg)	1025 7.96±2.97	389 7.34±2.73	744 7.11±2.78	671 7.78±2.93	2829 7.61±2.90
Fever Duration (days)	929 4.46±2.71	321 3.59±2.37	689 4.25±2.52	569 3.54±2.47	2508 4.08±2.59
Respiratory Rate					
Respiratory Rate (2-11 months)	602 53.38±14.05	272 60.87±9.60	540 53.82±10.16	451 60.78±7.26	1864 56.37±11.49
Respiratory Rate (12-59 months)	423 47.75±14.17	117 53.22±13.17	204 45.59±10.11	220 58.03±6.83	964 50.30±12.76
Oxygen saturation done (n, %)	528 (51.51)	343 (88.17)	236 (34.25)	319 (56.06)	1426 (50.40)
Oxygen saturation < 90% (n, %)	61(11.53)	57(16.61)	49 (20.76)	43(13.47)	210 (14.72)
Grunting (n, %)	461(44.98)	353 (90.75)	687 (92.34)	649 (96.72)	2150 (76.00)
Very severe chest in-drawing (n, %)	953 (92.97)	352 (90.49)	739 (99.33)	651 (97.02)	2695 (95.26)
Signs of Pneumonia with a general danger sign					
Lethargy or reduced level of consciousness (n, %)	423 (41.27)	259 (66.58)	6 (0.81)	412 (61.40)	1100(38.88)
Inability to breastfeed or drink (n, %)	291(28.39)	259 (66.58)	75 (10.08)	312 (46.50)	937(33.12)
Convulsions (n, %)	16 (1.56)	19 (4.58)	13 (1.75)	100 (14.90)	148(5.23)
Central cyanosis (n,%)	15 (1.46)	7 (1.80)	26 (3.49)	14 (2.09)	62 (2.19)

257

258 Among those with interpretable CXRs, 34.5% (977/2829) had radiological abnormalities, which
 259 were PEP alone or with other infiltrates in 64.9% (635/977) and other infiltrates in 35.1%
 260 (342/977) (**table 2**). In the same table, we report these findings by district as well as socio-
 261 demographical and clinical associates of normal versus abnormal CXR as well among those with
 262 abnormal CXRs, in those with PEP alone or with other infiltrates versus other infiltrates only.

263

264 We observed statistically significant district-wise heterogeneity in radiological abnormalities

265 (**table 2**). We found higher proportion of radiological abnormalities as well as PEP alone or with

266 other infiltrates in Patna and Lucknow districts, and lower proportion in Etawah and Darbhanga

267 districts. Statistically significant higher proportion of females hospitalized for CAP had

268 radiologically abnormal CXR (**table 2**). Likewise, statistically significantly higher proportion of

269 abnormal CXR findings were reported in hospitalized cases who had symptoms of fever, pallor,

270 wheezing on auscultation, vomiting everything or were malnourished (**table 2**). Among cases

271 with abnormal CXRs, statistically significantly higher proportion of cases with other infiltrates

272 had wheezing on auscultation.

273

274 **Table 2: Distribution of socio-demographic and clinical factors by chest radiograph**

275 **findings among hospitalized children from January 2015-April 2017**

	Interpretable chest X rays			Abnormal chest X rays			
	N=2829	Normal 1852 n (%)	Abnormal 977 n (%)	p value	PEP* alone or with other infiltrates 635 n (%)	Other infiltrates 342 n (%)	p value
Participating site (row %)							
Lucknow	1025	636 (62.05)	389 (37.95)	<0.0001	282 (72.49)	107 (27.51)	<0.0001
Etawah	389	275 (70.69)	114 (29.31)		73 (64.04)	41 (35.96)	
Patna	744	457 (61.42)	287 (38.58)		184 (64.11)	103 (35.89)	
Darbhangha	671	484 (72.13)	187 (27.87)		96 (51.34)	91 (48.66)	
Socio-demographic & clinical factors (column %)							

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Age-group (months)							
2-11	1865	1223 (66.04)	642 (65.71)	0.86	409 (64.41)	233 (68.13)	0.26
12-59	964	629 (33.96)	335 (34.29)		226 (35.59)	109 (31.87)	
Gender							
Male	2005	1354 (73.11)	651 (66.63)	<0.0001	426 (67.09)	225 (65.79)	0.72
Female	824	498 (26.89)	326 (33.37)		209 (32.91)	117 (34.21)	
Place of residence							
Rural	1392	921 (49.73)	471 (48.21)	0.44	299 (47.09)	172 (50.29)	0.34
Urban	1437	931 (50.27)	506 (51.79)		336 (52.91)	170 (49.71)	
Biomass fuel							
Yes	1501	867 (46.81)	461 (47.19)	0.44	294 (42.30)	167 (48.83)	0.24
No	1328	985 (53.19)	516 (52.81)		341 (53.70)	175 (51.17)	
Immunization status							
Complete for age	2347	1546 (83.48)	801 (81.99)	0.32	516 (81.26)	285 (83.33)	0.54
Incomplete	482	306 (16.52)	176 (18.01)		119 (18.74)	57 (16.67)	
Clinical Features							
Fever	2499	1616 (87.26)	883 (90.38)	0.014	575 (90.55)	308 (90.06)	0.82
Pallor	764	465 (25.11)	299 (30.60)	0.002	200 (31.50)	99 (28.95)	0.41
Wheeze on auscultation	2054	1377 (74.35)	677 (69.29)	0.005	415 (65.35)	262 (76.61)	0.0003
Duration of illness fever [days] (n, Mean ± SD)	2499	1611 3.91±2.51	888, 4.40±2.70	<0.0001	577, 4.57±2.82	342, 4.08±2.44	0.011
Respiratory Rate							
Respiratory Rate [2-11 months] (n, Mean ± SD)	1865	1243 55.52±11.29	642 57.99±11.70	<0.0001	409 58.12±11.88	233 57.74±11.40	0.69
Respiratory Rate [12-59 months] (n, Mean ± SD)	964	629 49.78±12.41	335 51.28±13.37	0.08	226 51.35±13.31	109 51.12±13.35	0.88
Fast Breathing for	1735	1130	605	0.11	384	221	0.69

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age [2-11 months]		(61.02)	(61.92)		(60.47)	(64.62)	
Fast Breathing for age [12-59 months]	862	562 (30.35)	300 (30.71)	0.92	204 (32.13)	96 (28.07)	0.53
Signs of Pneumonia with a general danger sign n (%)							
Lethargy or reduced level of consciousness	1101	732 (39.52)	369 (37.77)	0.39	247 (38.90)	122 (35.67)	0.33
Inability to breastfeed or drink	937	612 (33.05)	325 (33.27)	0.46	211 (33.23)	114 (33.33)	0.97
Convulsions	148	98 (5.29)	50 (5.12)	0.93	33 (5.20)	17 (4.97)	0.87
Central Cyanosis	62	39 (2.11)	23 (2.35)	0.34	16 (2.52)	7 (2.05)	0.64
Malnutrition Status							
Normal *	1880	1293 (69.82)	587 (60.08)	< 0.0001	367 (57.80)	220 (64.33)	0.06
Malnutrition*	517	333 (17.98)	184 (18.83)		122 (19.21)	62 (18.13)	
Severe malnutrition*	432	226 (12.20)	206 (21.08)		146 (22.99)	60 (17.54)	

276 *Normal-weight of age z score > -2SD; Malnutrition-weight-for-age z ≤ -2SD and Severe
277 malnutrition-weight-for- age z ≤ -3SD

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279 **Table 3** describes four multivariate unconditional logistic regression models to find associates of
280 various abnormal CXR findings. After controlling for age, gender, symptoms of pneumonia,
281 duration of illness, biomass fuel and malnutrition status of cases, statistically significant district-
282 wise heterogeneity remained in the first three models. Model I, which compared abnormal versus
283 normal CXRs, II, which compared CXRs with PEP alone or with other infiltrates versus normal
284 and III, which compared CXRs with PEP alone versus normal, had similar associates for
285 radiological abnormalities whereas Model IV, which compared CXRs with other infiltrates only
286 versus normal, was different. Across all the four models, female gender and those with severe

malnutrition had statistically significantly higher risk for having abnormal CXRs. A higher risk of radiological abnormalities was also observed in those children with longer duration of illness.

Table 3: Independent Associations between Chest Radiograph findings and demographic and clinical variables among hospitalized children of Community Acquired Pneumonia, using Unconditional Logistic Regression

Variables	Model – I Abnormal/Normal ^{Ref}		Model – II PEP alone or with other infiltrates /Normal ^{Ref}		Model – III PEP alone / Normal ^{Ref}		Model – IV Other infiltrates Normal ^{Ref}	
	Adjusted Odd Ratio (95%CI)	p value	Adjusted Odd Ratio (95%CI)	p value	Adjusted Odd Ratio (95%CI)	p value	Adjusted Odd Ratio (95%CI)	p value
Districts								
Lucknow vs. Others	1.58 (1.20-2.10)	<0.0001	2.07 (1.48-2.89)	<0.0001	2.20 (1.52-3.19)	<0.0001	0.98 (0.65-1.47)	0.9
Etawah vs. Others	1.22 (0.88-1.70)	0.23	1.30 (0.87-1.95)	0.19	1.49 (0.95-2.30)	0.07	1.17 (0.74-1.87)	0.5
Patna vs. Others	1.67 (1.27-2.20)	<0.0001	1.89 (1.36-2.64)	<0.0001	2.25 (1.56-3.24)	<0.0001	1.39 (0.95-2.07)	0.0
Age – Group (months)								
2-11 ^{Ref}								
12-59	0.92 (0.77-1.10)	0.34	0.95 (0.77-1.17)	0.62	1.03 (0.82-1.29)	0.79	0.86 (0.66-1.13)	0.2
Gender								
Male ^{Ref}								
Female	1.39 (1.16-1.66)	<0.0001	1.34 (1.08-1.65)	0.008	1.28 (1.01-1.61)	0.03	1.48 (1.14-1.92)	0.00
Symptoms of pneumonia[¶]								
Wheezing	0.83 (0.68-1.01)	0.06	0.72 (0.57-0.90)	0.005	0.75 (0.59-0.96)	0.02	1.14 (0.83-1.55)	0.4
Pallor	1.30 (1.08-1.58)	0.006	1.28 (1.03-1.60)	0.02	1.22 (0.95-1.55)	0.12	1.34 (1.01-1.77)	0.0
Vomiting everything	0.90 (0.75-1.09)	0.28	0.80 (0.64-0.99)	0.04	0.78 (0.62-1.01)	0.05	1.09 (0.83-1.08)	0.5
Duration of illness, fever (days)								
	1.06 (1.04-1.09)	<0.0001	1.08 (1.04-1.12)	<0.0001	1.08 (1.04-1.12)	<0.0001	1.03 (0.98-1.48)	0.2
Biomass fuel								
	1.28 (1.05-1.57)	0.02	1.39 (1.10-1.76)	0.006	1.40 (1.14-1.88)	0.003	1.08 (0.79-1.45)	0.6

Malnutrition Status								
Normal *Ref								
Malnutrition*	1.18 (0.93-1.45)	0.15	1.17 (0.91-1.52)	0.23	1.17 (0.88-1.55)	0.27	1.12 (0.82-1.52)	0.4
Severe malnutrition*	1.65 (1.31-2.09)	<0.0001	1.82 (1.34-2.36)	<0.0001	1.87 (1.41-2.47)	<0.0001	1.62 (1.71-2.23)	0.00

294 **Abbreviations:** ^{Ref} : Reference Category; PEP: Primary End-Point Pneumonia

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 296 **Footnotes:** ¶ No signs of pneumonia taken as a reference
 297 *Normal: weight-for-age z score > -2SD; Malnutrition: weight-for-age z ≤ -2SD; Severe
 298 malnutrition: weight-for-age z ≤ -3SD

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300 DISCUSSION

301 This active, prospective, hospital-based surveillance study was conducted to assess radiological
 302 abnormalities in CXRs and to identify the demographic and clinical correlates of specific
 303 radiological abnormalities in children aged 2-59 months, hospitalized with WHO defined CAP,
 304 residing in pre-specified districts of Uttar Pradesh and Bihar. The study was conducted from
 305 January 2015 to April 2017, prior to the introduction of PCV in the national immunization
 306 programme of the Government of India.⁹

307 In our study, among interpretable CXRs, we found that 22.44% (635/2829) cases had PEP alone
 308 or with infiltrates, 12.09% (342/2829) had other infiltrates only and 65.46% (1852/2829) had
 309 normal findings. Our study used WHO case definition for CAP.¹⁹ A panel of three trained
 310 radiologists interpreted CXRs, adopting WHO recommended methodology.^{11 12} These make our
 311 study methodology robust and results generalizable.

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313 There were 88.54% (2829/3195) interpretable CXRs in the current study. This is similar to 83%
 314 (3587/3973) interpretable CXRs reported by Pneumonia Etiology Research for Child Health

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3 315 (PERCH) study conducted on 4232 children (1-59 months) in nine sites in seven countries.²⁷

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5 316 Consistent with PERCH findings, a vaccine probe trial conducted in Gambia found proportion of
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7 317 interpretable CXRs among unvaccinated cases of pneumonia to be 84.32% (242/287).²⁸

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12 319 There have been several studies in the past two decades, which have reported CXRs findings in

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15 320 hospitalized cases of pediatric CAP. Almost all of these were conducted before the introduction

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17 321 of PCV in their respective regions. A small prospective study conducted in Ethiopia reported

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19 322 radiological abnormality in CXRs in 48.3% (95% CI 39.49-57.22) among 122 children aged 3

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21 323 months to 14 years with clinically diagnosed WHO-defined severe pneumonia.²⁹ Similar

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23 324 findings were reported from the Gambian vaccine probe trial where the proportion of

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25 325 radiological abnormality was 45% (95% CI: 43.35-46.46) among unvaccinated hospitalized

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27 326 cases of clinical pneumonia.²⁸ Likewise, PERCH study found that 54% (95% CI: 52.31-55.57)

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29 327 of CXRs among cases of CAP were abnormal.²⁷ In all of these studies, proportion of cases with

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31 328 abnormal CXRs is higher than 34.5% (95% CI 32.8-36.3) found by us in the current study.

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33 329 However, our findings are similar to PERCH rural study site of Matlab, Bangladesh that reported

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35 330 radiological abnormality in 35.3% (95% CI: 29.77-40.85) CXRs of hospitalized cases of CAP.²⁷

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37 331 Another PERCH urban site of Dhaka, Bangladesh reported 63.10% (95% CI 56.18 -70.02) cases

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39 332 with abnormal CXRs.²⁷ In our study, radiological abnormalities in CXRs were higher in cases

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41 333 from largely urban districts of Patna and Lucknow compared to rural districts of Darbhanga and

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43 334 Etawah. This is consistent with rural-urban differences in Bangladesh sites of PERCH.²⁷

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45 335 Variation in CXR findings among cases of CAP may be due to place of residence, infecting

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47 336 organism, immune response of patient and prior duration of disease.

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3 338 In 2016, WHO's Department of Immunization, Vaccines and Biologicals standardized the
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5 339 categorization of radiological pneumonia and established that PEP can be taken as a good
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7 340 surrogate marker of bacterial pneumonia in epidemiological and vaccine efficacy studies.¹¹ In
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9 341 our study, 22.44 % (95% C.I. 20.90 -23.98), CXRs had PEP alone or with other infiltrates and
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11 342 hence were probably bacterial in etiology. This is similar to findings of PERCH study that
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13 343 reported PEP alone or with other infiltrates in 27% (95% C.I. 25.50 -28.40) hospitalized cases of
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15 344 CAP.²⁷ However, a study conducted in Gambia reported that 45% (95% CI: 43.35-46.46) non-
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17 345 vaccinated children had PEP and/or other infiltrates²⁸ which is higher than that found by us or
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19 346 the PERCH study. PEP in CXR has been associated with increased risk of treatment failure
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21 347 (p=0.002), increased length of hospitalization (p=0.0003) and more days of respiratory support
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23 348 (p=0.002) in Botswana when compared with cases reporting `no significant pathology` on
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25 349 CXRs.³⁰

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33 351 In our study, female gender (p<0.001) was at the higher risk of developing radiological
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35 352 abnormalities compared to males (**table 3**). The results are in concordance with a hospital-based
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37 353 case-control study carried out in Brazil that reported male gender as a protective factor against
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39 354 pneumonia (OR=0.53; 95%CI 0.39–0.72).³¹ However, a study in Mozambique, Africa reported
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41 355 that male gender was not significantly associated with presence of radiological abnormalities
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43 356 (OR =0.77; 95%CI 0.56–1.05) in children (0-59 months) suffering from severe pneumonia.³² In
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45 357 contrast, a Gambian study reported male preponderance for all pneumonia that was most marked
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47 358 for those whose CXRs showed `other infiltrates/abnormalities`.²⁸

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3 360 In our study, we observed differential care-seeking by gender for CAP in all four project
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5 361 districts. Although females admitted with CAP were at higher risk of having radiological
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7 362 abnormalities, lower proportions were hospitalized. Gender inequality in health care seeking for
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9 363 females is common in India, as in other South Asian countries.^{33 34} Since there is no health-care
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11 364 financing or provision of health insurance in India, in case of severe illness, parents are less
12
13 365 likely to incur out-of-pocket expenditure or incur debts to pay expenses on medical treatment of
14
15 366 their daughters as compared to sons.³⁵ Another Indian study found that male children were five
16
17 367 times more likely to be taken early for medical care and three times more likely to be seen by
18
19 368 qualified medical doctors compared to female children.³⁶ We also found that large proportion of
20
21 369 hospitalized cases of pneumonia were from urban areas, as there is poor health-care seeking from
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23 370 rural areas.³⁷
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31 372 A systematic review with meta-analysis conducted in 2019 suggests that no one clinical feature
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33 373 is sufficient on its own to diagnose radiological pneumonia.³⁸ However other socio-demographic
34
35 374 and clinical correlates of abnormal CXRs found by us in Model 1 (abnormal versus normal),
36
37 375 which increased the risk of radiological abnormalities were presence of pallor, severe
38
39 376 malnutrition, longer duration of illness and exposure to biomass fuel. In developing countries
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41 377 exposure to biomass fuel used for cooking has been reported as an important risk factor for
42
43 378 CAP.³⁹ In rural India, majority of the households use biomass fuel like firewood, dung cakes and
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45 379 wood for cooking.⁴⁰ Young children are at risk to adverse effects of exposure to biomass fuel as
46
47 380 either the households have no separate cooking space or have poor ventilation and sometimes
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49 381 young children stay with their mother while she cooks.
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3 383 Other correlates of PEP/radiological pneumonia, which were more likely to be bacterial in
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5 384 etiology, as found in Model II, which compared PEP alone or with other infiltrates versus
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8 385 normal, and Model III, which compared PEP alone versus normal (**table 3**), besides those found
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10 386 in Model I, were presence of vomiting everything and wheeze on auscultation, both of which
11
12 387 were found to be protective. These symptoms/signs are more often reported in viral pneumonia.⁴¹
13
14 388 Correlates of radiological abnormalities of `other infiltrates` (Model IV which compared other
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16 389 infiltrates with normal), which increased the risk, were again female gender, pallor and severe
17
18 390 malnutrition. Hence it is difficult to attribute radiological findings of other infiltrates to either
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20 391 bacterial or viral etiology.
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26 393 Based on our study, almost two-third hospitalized cases of CAP had normal CXRs and could be
27
28 394 perhaps of viral etiology. This is supported by a recent study that reported 61.4% (95% CI 57.3–
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30 395 65.6) cases to be viral.⁴¹ One-third of cases of CAP had abnormal CXRs and thus were more
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32 396 likely to be bacterial in etiology.
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38 398 In India, 13-valent PCV has been introduced in May 2017. A three dose schedule is followed
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40 399 with two primary and one booster, at 6 weeks, 14 weeks and 9 months of age, respectively. PCV
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42 400 13 provides coverage against 13 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and
43
44 401 23F).⁴² Several studies have assessed serotype distribution of pneumococcal disease among
45
46 402 children in India. A study conducted in Vellore, India, found that the most common serotypes
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48 403 causing invasive infections among under-five children were 14, 19F, 5, 6A and 6B, all of which
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50 404 are covered by the 13-valent PCV.⁴³ Another population-based surveillance study conducted in
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52 405 rural Bangladesh found that the most common serotypes of *S. pneumoniae* were 1, 5, 14, 18C
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3 406 and 19A and 38 which caused invasive disease and all but one were covered by the 13 valent
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5 407 vaccine.⁴⁴ A systematic review and meta-analysis of data collected on Invasive Pneumococcal
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7 408 Disease serotypes from under-five children during the pre-PCV period (between 1980-2007)
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10 409 found that serotypes included in both the 10-valent and 13-valent PCVs accounted for 10 million
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12 410 cases and 600,000 deaths worldwide.⁴⁵
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18 412 Several strengths of the study are worth-noting. This was an active, prospective, multisite study
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20 413 where recruitments were done from a large hospital surveillance network established especially
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22 414 for the study in four districts of two Indian states that have high under-five mortality rates.
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24 415 Standard WHO definition was used to identify hospitalized cases of CAP. Radiological
25
26 416 abnormalities were interpreted by a panel of three trained radiologists at locations out of the
27
28 417 surveillance network, blinded to each other as well as clinical features of the case. Despite these
29
30 418 strengths, our study findings have certain limitations. First, in our study, pre-existing x-rays
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32 419 machines which were not of uniform specification were used. This might have caused variation
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34 420 in quality of CXR images, though this error was minimized by digitizing the CXR images
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36 421 centrally. Secondly, in our study, clinical data collection was recorded by clinicians in the
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38 422 network hospitals and there could be observer bias. This could also have lead to possibly over
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40 423 reporting of presence of wheezing. In this study, we have not collected information on use of
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42 424 antibiotic prior to hospitalizations; as such information is not available reliably. However, in
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44 425 another study, done in one of the network hospitals of Lucknow in the recent past, it was found
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46 426 that 70.5% children tested positive for antibiotics on urine examination.⁴⁶ Prior use of antibiotics
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48 427 could have possibly lead to under-estimation of radiological pneumonia. We also observed that
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428 pulse oxymetry was not routinely done in the network hospitals. This could have an impact on
429 the case management but would not have affected the radiological findings of CXRs.

430

431 CONCLUSION

432 Among hospitalized cases of CAP, almost one-third children had abnormal chest radiographs of
433 which about two-thirds had abnormalities related with possible bacterial etiology (*Streptococcus*
434 *pneumonia*). Hence, the introduction of pneumococcal vaccination is likely to reduce the burden
435 of childhood pneumonia in India. Since the study was done prior to the introduction of PCV in
436 India, continued surveillance will be required to assess the impact of PCV on radiological
437 findings in cases admitted with CAP. The impact of introduction of PCV in the national
438 immunization programme on under-five mortality rate and burden of CAP needs to be assessed
439 too.

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13
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15
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17
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19
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27
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32
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36
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38
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40
41 468 approval for conduct of study.

42
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46
47 471 shally07@gmail.com

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17 478 **Supporting Information**

18
19 479 S1 Appendix: Chest radiograph interpretation form
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616 **Figure Legend**

617 Figure 1: Flow diagram of cases of community acquired pneumonia recruited from participating
618 districts before the introduction of pneumococcal conjugate vaccine (January 2015-April 2017)

Figure 1: Flow diagram of cases of community acquired pneumonia recruited from participating districts before introduction of pneumococcal conjugate vaccine (January 2015-April 2017)

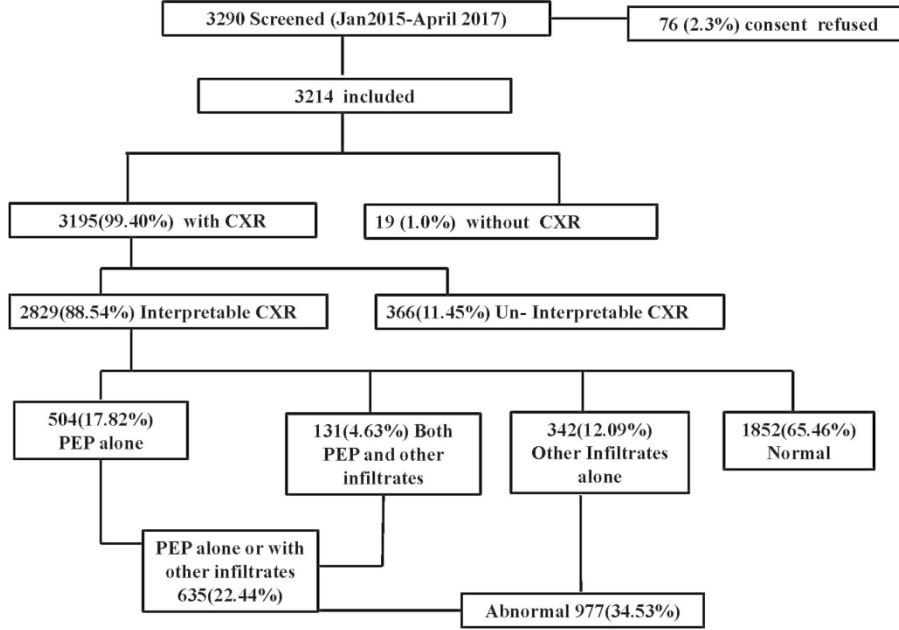


Figure 1: Flow diagram of cases of community acquired pneumonia recruited from participating districts before the introduction of pneumococcal conjugate vaccine (January 2015-April 2017)

254x190mm (300 x 300 DPI)

Childhood Pneumonia Surveillance
Department of Paediatrics, KGMU, Lucknow ,UP

Form-R
(RADIOLOGY REPORT FORM)

1	Drs_ID	[][][][]
	Radiology Report	Patient Details
2	IDNo:	[] / [] / [][][][][][] State /District / Unit / Subject number (For office use)
2	Date Of Report	[][]/[][]/[][][][] (DD/MM/YYYY)
	Report Details	Findings (tick one)
3	Image Quality	Adequate <input type="checkbox"/> Suboptimal <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
4	Significant Pathology	Yes <input type="checkbox"/> No <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
5	End Point Consolidation	
5a	Left	Yes <input type="checkbox"/> No <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
5b	Right	Yes <input type="checkbox"/> No <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
		Uninterpretable
6	Other Infiltrates/Abnormalities	
6a	Left	Yes <input type="checkbox"/> No <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
6b	Right	Yes <input type="checkbox"/> No <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
7	Pleural Fluid	
7a	Left	Yes <input type="checkbox"/> No <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
7b	Right	Yes <input type="checkbox"/> No <input type="checkbox"/> Un-interpretable <input type="checkbox"/>
8	Comments:	<input style="width: 100%; height: 15px;" type="text"/>
9	Conclusion:	a) Primary endpoint pneumonia only <input type="checkbox"/> b) Other infiltrate only <input type="checkbox"/> c) Both PEP and other infiltrate <input type="checkbox"/> d) Normal <input type="checkbox"/> e) Un-interpretable for any findings <input type="checkbox"/>

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page Number
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	25
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11-13
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	11-13
		(b) Describe any methods used to examine subgroups and interactions	Table 1, 2 & 3
		(c) Explain how missing data were addressed	12 reference 24
		(d) If applicable, describe analytical methods taking account of sampling strategy	11-13
		(e) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	14
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	14-15 Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Figure 1

Outcome data	15*	Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3 (adjusted odds ratio)
		(b) Report category boundaries when continuous variables were categorized	Table 3
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA (calculated only odds ratio)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	21-23
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	25-26
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	21-23
Generalisability	21	Discuss the generalisability (external validity) of the study results	21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	27

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.