Chest Radiograph Findings in Childhood Pneumonia Cases From the Multisite PERCH Study


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Background. Chest radiographs (CXRs) are frequently used to assess pneumonia cases. Variations in CXR appearances between epidemiological settings and their correlation with clinical signs are not well documented.

Methods. The Pneumonia Etiology Research for Child Health project enrolled 4232 cases of hospitalized World Health Organization (WHO)–defined severe and very severe pneumonia from 9 sites in 7 countries (Bangladesh, the Gambia, Kenya, Mali, South Africa, Thailand, and Zambia). At admission, each case underwent a standardized assessment of clinical signs and pneumonia risk factors by trained health personnel, and a CXR was taken that was interpreted using the standardized WHO methodology. CXRs were categorized as abnormal (consolidation and/or other infiltrate), normal, or uninterpretable.

Results. CXRs were interpretable in 3587 (85%) cases, of which 1935 (54%) were abnormal (site range, 35%–64%). Cases with abnormal CXRs were more likely than those with normal CXRs to have hypoxemia (45% vs 26%), crackles (69% vs 62%), tachypnea (85% vs 80%), or fever (20% vs 16%) and less likely to have wheeze (30% vs 38%; all P < .05). CXR consolidation was associated with a higher case fatality ratio at 30-day follow-up (13.5%) compared to other infiltrate (4.7%) or normal (4.9%) CXRs.

Conclusions. Clinically diagnosed pneumonia cases with abnormal CXRs were more likely to have signs typically associated with pneumonia. However, CXR-normal cases were common, and clinical signs considered indicative of pneumonia were present in substantial proportions of these cases. CXR-consolidation cases represent a group with an increased likelihood of death at 30 days post-discharge.

Keywords: chest radiograph; pneumonia; pediatrics; signs and symptoms; mortality.

The diagnosis of pneumonia in children is challenging because there is no single method with high sensitivity and high specificity [1, 2]. Clinical assessments for diagnosing pneumonia are sensitive but nonspecific, resulting in the inclusion of many nonpneumonia cases [3–5]. The use of chest radiographs (CXRs) to identify pneumonia cases is also imperfect but understood to identify fewer false-positive cases, especially for Haemophilus influenzae type b (Hib) and Streptococcus pneumoniae disease [6, 7]. How accurately standardized CXR definitions correlate to clinical signs and risk factors for pneumonia is less well described, especially in differing geographic areas where the predominant pathogens can vary. We aimed to
describe the CXR findings of clinically diagnosed pneumonia cases in the Pneumonia Etiology Research for Child Health (PERCH) study and determine if there were differences in findings by geography, epidemiological setting, particular clinical signs, or pneumonia risk factors.

METHODS

Data Collection

The PERCH study is a multicountry, standardized, case-control study of the causes and risk factors of childhood pneumonia. Nine study sites were located in 7 countries: Dhaka and Matlab, Bangladesh; Basse, the Gambia; Kilifi, Kenya; Bamako, Mali; Soweto, South Africa; Nakhon Phanom and Sa Kaeo, Thailand; and Lusaka, Zambia. These sites include the geographic regions where the vast majority of severe and fatal pneumonia cases occur and represent a diverse range of epidemiological contexts [8].

Cases were hospitalized children aged 1–59 months with World Health Organization (WHO)–defined severe or very severe pneumonia [5, 9]. Severe pneumonia was defined as having cough and/or difficulty in breathing and lower chest wall indrawing. Very severe pneumonia was defined as having cough and/or difficulty in breathing and at least 1 of the following “danger signs”: central cyanosis, difficulty breastfeeding/drinking, vomiting everything, convulsions, lethargy, unconsciousness, or head nodding. Case exclusion criteria were hospitalization within the previous 14 days, having been discharged as a PERCH case within the past 30 days, not residing in the study catchment area, or resolution of lower chest wall indrawing following bronchodilator therapy for those with severe pneumonia and wheeze. Standardization of clinical procedures used for participant enrollment and collection of PERCH data was achieved and maintained through on-site training for health-worker personnel, the use of a training website and training materials, and intermittent evaluations and competency assessments throughout the study [10].

A CXR was obtained from each case as soon as possible after clinical evaluation and study enrollment. All sites underwent a prestudy assessment of radiography facilities and procedures to review quality and safety and to standardize the collection of CXRs. Most sites used digital CXR imaging equipment, except Zambia and Matlab where analog techniques were used; analog images were scanned into digital format and all files managed according to a standardized operating procedure. Standardized methods for the collection and interpretation of chest radiographs are detailed elsewhere [11]. Each CXR was randomly assigned to be assessed by 2 members of a reading panel, comprised of 14 radiologists and pediatricians from study sites trained in the WHO methodology for the standardized interpretation of pediatric CXRs [7]. Two randomly selected members of a 4-person arbitration panel, consisting of experienced radiologists, resolved discordant interpretations by further blinded interpretations and a final consensus discussion if needed. Readers and arbitrators were unaware of the clinical and demographic information associated with each CXR, and readers did not interpret CXRs from their own site. Conclusions for CXRs were (1) consolidation (ie, alveolar consolidation, including pleural effusion if present) only; (2) other infiltrate only; (3) both consolidation and other infiltrate; (4) normal (no consolidation or infiltrate); and (5) uninterpretable for consolidation and/or other infiltrate. Additional conclusions derived from these 5 categories were (a) abnormal (1, 2, or 3), (b) any consolidation (1 or 3), and (c) any other infiltrate (2 or 3). For cases with multiple CXRs, the conclusion of the first interpretable CXR was used. CXR conclusions were excluded if the CXR was taken more than 72 hours after admission to avoid bias from possible nosocomial complications.

Analyses

Results from the 2 Thailand sites were combined because they had similar epidemiologic and demographic characteristics. Results from sites with a high prevalence of human immunodeficiency virus (HIV) infection (South Africa and Zambia) were stratified by HIV status where relevant. HIV status was assumed to be negative for 385 cases where HIV status was unknown (HIV testing was not performed and/or there was no record of the child’s HIV history or maternal HIV history). Age was categorized as 1–5 months, 6–11 months, 12–23 months, and 24–59 months. Vaccination status was defined based on the number of doses a child received and the age at first dose or age at vaccine introduction in the community. Complete vaccination for pneumococcal conjugate vaccine was defined as 3 or more doses, or as 2 doses if there was at least 8 weeks between doses and the child was aged <9 months at enrollment or >12 months at the time of the first dose, or 1 or more doses if the age at any of the doses, or age at introduction, was ≥24 months. Complete vaccination for Hib conjugate vaccine was defined as 3 or more doses, or 1 or more doses for a child aged >12 months at first dose. Antibiotic pretreatment was defined by having either a positive serum bioassay or documented administration of antibiotics on the day of admission at the referral or study hospital prior to blood culture collection. Severe malnutrition was defined as a weight-for-age z score less than −3 below the median of the WHO child growth standards (WHO Anthro, version 3.2.2, January 2011). Moderate malnutrition was defined as a z score between −3 and −2 below the median of the WHO child growth standards. Tachypnea was defined as a respiratory rate ≥60 breaths per minute for children aged <2 months, ≥50 for children 2–11 months, and ≥40 for children 12–59 months. Tachycardia was defined as >160 beats per minute (bpm) for children aged 1–11 months, >150 bpm for children 12–35 months, and >140 bpm for children 36–59 months. Hypoxemia at admission was defined as either a room air pulse oximetry reading of <90% at the 2 sites at elevation (Zambia and South Africa) or <92% at all other sites or...
as a child treated with supplemental oxygen on admission but without a room air pulse oximetry reading. Nonpneumonia admission diagnoses were recorded.

Analyses were restricted to cases with interpretable CXRs. Distributions of categorical variables were compared using the Pearson χ² statistic. Logistic regression was used to estimate odds ratios of CXR outcomes for predictors of clinical signs and risk factors, first in univariate models stratified by site to evaluate heterogeneity, and then overall adjusted for site, age, pneumonia severity, and HIV status. To assess the independent effects of variables potentially correlated with each other, such as findings on clinical examination (eg, tachypnea and hypoxemia) or nonpneumonia admission diagnoses (eg, bronchiolitis and asthma), multivariable logistic regression models were examined including all variables for danger signs and clinical signs (for very severe cases), clinical signs, and admission diagnoses. Analyses were completed using Stata 12.1 (Stata Corporation, College Station, Texas).

**Ethical Considerations**

The institutional review board or ethical review committee at each study site institution and at the Johns Hopkins Bloomberg School of Public Health approved the PERCH study protocol. Parents or guardians of all participants provided written informed consent.

**RESULTS**

A total of 3973/4232 (94%) cases had a CXR conclusion and of these 386 (10%) were uninterpretable (range, 4% in Gambia and Thailand to 20% in Zambia), leaving 3587 cases for analyses (Figure 1). Overall, 54% of interpretable CXRs were abnormal (site range from 35% in Matlab to 64% in HIV-negative cases from South Africa; Figure 2 and Table 1). Of these, 50% had consolidation (either alone or with other infiltrate) and 50% had other infiltrate only. Those with abnormal CXRs were more likely to be HIV infected (19% vs 5%) and aged <24 months (88% vs 83%; Table 1). However, the relationship between age and CXR outcome differed by severity strata. Among severe pneumonia cases, the youngest children (aged 1–5 months) were less likely to have an abnormal CXR compared to those in older age categories, and among very severe pneumonia cases, the youngest children were more likely to have an abnormal CXR (Supplemental Table 1).

We evaluated differences between cases with abnormal and normal CXRs to assess the likelihood that those with normal CXRs truly had pneumonia. Cases with abnormal CXRs were significantly more likely to have central cyanosis, tachypnea, hypoxemia, crackles, nasal flaring, or temperature ≥38.5°C and were less likely to have vomiting, convulsions, or wheeze than cases with normal CXRs (all P ≤ .001; Table 1). Results were similar after controlling for site, age, pneumonia severity, and HIV (Supplemental Table 2). Cases with moderate and severe malnutrition, as measured by weight-for-age, had higher odds of an abnormal CXR compared to those without malnutrition (Supplemental Table 2). Despite these statistically significant differences, high proportions of the 1652 CXR-normal cases had clinical signs generally considered more indicative of pneumonia (Table 1), including crackles (62%), nasal flaring (54%), hypoxemia (26%), grunting (17%), and head nodding (14%). CXR-normal cases had a mean of 1.7 of these signs, with 858/1652

**Figure 1.** Flow diagram of case enrollment, chest radiograph (CXR) conclusions, and CXR status stratified by 30-day follow-up findings.
We assessed the relationship between CXR findings and mortality (Figure 1 and Table 3). Those who died and had an interpretable CXR were twice as likely to have findings of consolidation (50% vs 24%) and less likely to have other infiltrates only (18% vs 28%) compared to those who survived. Of 3208 cases with an interpretable CXR and documented 30-day survival status, 837 (26%) had a CXR finding of any consolidation of which 113 died (case fatality ratio [CFR], 13.5%) compared to 874 cases with other infiltrate only among whom there were 41 deaths (CFR, 4.7%) and 1497 cases that were CXR-normal among whom there were 73 deaths (CFR, 4.9%; Table 3). These trends were similar when stratified by age (<12 months and ≥12 months; data not shown).

**DISCUSSION**

The PERCH study allows for a comprehensive assessment of the association between clinical characteristics and CXR findings in childhood pneumonia cases under highly standardized clinical and radiographic interpretation conditions. We found that at the time of admission, those with WHO-defined severe or very severe pneumonia who had tachypnea, hypoxemia, crackles, or fever were more likely to have an abnormal CXR than those who did not have these findings, irrespective of other clinical signs. In contrast, those with convulsions or wheeze were less likely than those without these findings to have an abnormal CXR. These findings provide evidence that PERCH analyses restricted to cases with abnormal CXRs largely represent true pneumonia cases. CXR-normal cases likely include some children who have true pneumonia, as suggested by the 52% of these cases who had 2 or more findings of hypoxemia, crackles, head nodding, nasal flaring, or grunting; however, it is difficult to distinguish with certainty which of these cases have pneumonia and which do not. Thus, as expected, standardized CXR definitions for epidemiological studies have limited predictive value for clinical care because a substantial proportion of children with a normal CXR finding also have clinical signs or risk factors indicative of pneumonia.

The categorization of CXRs in this study followed an established methodology developed by the WHO for use in bacterial vaccine trials [7]. Previous evidence on correlations between clinical signs and radiological findings is mixed and comparisons are difficult because of varied definitions of “radiological pneumonia.” Some studies showed that tachypnea [12], hypoxemia [13], and crackles [14] on admission may be predictive of radiological pneumonia, while others found clinical signs to be poor predictors of radiographic findings [15, 16]. A recent metaanalysis indicated that no single clinical feature is sufficient to predict radiological pneumonia [17], although that analysis involved unstandardized CXR interpretation methods and CXR definitions. In contrast, our findings suggest that hypoxemia, tachypnea, crackles, and fever may predict the WHO standardized definition of CXR consolidation in a study where case enrollment used a standardized clinical definition known to have high sensitivity but low specificity (Table 2).

We identified substantial differences between sites in the distribution of CXR findings (Table 1 and Figure 2). Between 4% and 20% of CXRs from each site were uninterpretable, and...
Table 1. Distribution of Signs and Pneumonia Risk Factors by Chest Radiograph Findings Among Children Aged 1–59 Months Hospitalized With World Health Organization Defined Severe or Very Severe Pneumonia

<table>
<thead>
<tr>
<th>Age category, mo</th>
<th>Total (row %)</th>
<th>All CXRs</th>
<th>Abnormal CXRs</th>
<th>Any Consolidation</th>
<th>Other Infiltrate Only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Normal</td>
<td>Abnormal</td>
<td>PValue</td>
<td></td>
</tr>
<tr>
<td>1–5</td>
<td>1414</td>
<td>653 (39.5)</td>
<td>761 (39.3)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>6–11</td>
<td>818</td>
<td>350 (21.2)</td>
<td>468 (24.2)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>24–59</td>
<td>513</td>
<td>274 (16.6)</td>
<td>239 (14.2)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Pneumonia severity</td>
<td>10</td>
<td>60 (2.3)</td>
<td>60 (2.3)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>2483</td>
<td>1121 (45.3)</td>
<td>1362 (70.4)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Very severe</td>
<td>1104</td>
<td>531 (32.1)</td>
<td>573 (29.6)</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

Danger signs\%:
- Head nodding (n = 1103): 570 (23.8%)
- Central cyanosis (n = 1103): 71 (3.6%)
- Convulsions (n = 1103): 203 (14.5%)
- Leathargy (n = 1104): 357 (32.3%)
- Difficult breathing (n = 1101): 243 (21.9%)
- Vomiting (n = 1102): 104 (9.5%)

Other clinical signs and history:
- Temperature ≥38.5°C: 3564
- Tachycardia = heart rate >160 beats per minute (bpm) if age 1–11 months, >150 bpm if 12–35 months, and >140 bpm if 36–59 months.
- Central cyanosis (n = 1103): 71 (3.6%)
- Convulsions (n = 1103): 203 (14.5%)
- Leathargy (n = 1104): 357 (32.3%)
- Difficult breathing (n = 1101): 243 (21.9%)
- Vomiting (n = 1102): 104 (9.5%)

Restricted to cases with an interpretable chest radiograph finding (n = 3587); for variables missing observations, a total n for that variable is shown in parentheses.

Abbreviations: CXR, chest radiograph; Hib, Haemophilus influenzae type b conjugate vaccine; HIV, human immunodeficiency virus; PCV, Pneumococcal conjugate vaccine.

χ² test for all categorical variables. Two-sample t test with equal variances for comparison of means of duration of illness.

Very severe cases only.

South Africa and Zambia sites only.

\%Hypoxemia = room air pulse oximetry reading of <90% if at elevation (Zambia and South Africa) or <92% if at all other sites. If a room air oxygen saturation reading was not available and the child was on supplemental oxygen, they were considered hypoxic.

\%Tachypnea = respiratory rate >60 breaths per minute if age <2 months, >50 if 2–11 months, and >40 if 12–59 months.

\%Weight-for-age = severe if less than −3 standard deviations (SDs) from the median weight-for-age; moderate if less than −2 and ≥−3 SDs; and normal if >−2 SDs.

\%Unvaccinated = children too young (<4 months) to have completed a full biologic course of Hib and/or PCV vaccines, as these children by definition are considered to be "unvaccinated" but are not an appropriate comparison group for those who have been vaccinated. Complete vaccination for PCV was defined as 3 or more doses, or 2 doses if there was at least 8 weeks between doses and the child was aged <9 months at enrollment or ≥12 months at the time of the first dose, or 1 or more doses if the age at any of the doses, or age at introduction, was ≥24 months. Complete vaccination for Hib conjugate vaccine was defined as 3 or more doses, or 1 or more doses for a child aged ≥12 months at first dose.

\%Antibiotic pretreatment was defined by having either a positive serum bioassay or documented administration of antibiotics on the day of admission at the referral or study hospital prior to blood culture collection.

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## Table 2. Independent Associations Between Chest Radiograph Findings and Clinical Signs, Risk Factors, and Admission Diagnoses Among Children 1–59 Months of age Hospitalized with WHO Severe and Very Severe Pneumonia

<table>
<thead>
<tr>
<th>Abnormal vs Normal (ref)</th>
<th>Any consolidation vs Other infiltrate only (ref)</th>
<th>Any consolidation vs Normal (ref)</th>
<th>Other infiltrate only vs Normal (ref)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted OR*</td>
<td>P Value</td>
<td>Adjusted OR*</td>
<td>P Value</td>
</tr>
<tr>
<td>Hypoxemia#</td>
<td>1.94 &lt;.001</td>
<td>1.13 .30</td>
<td>2.05 &lt;.001</td>
</tr>
<tr>
<td>Nasal flaring</td>
<td>1.10 .24</td>
<td>1.29 .03</td>
<td>1.29 .02</td>
</tr>
<tr>
<td>Tachypnea#</td>
<td>1.40 .001</td>
<td>1.39 .02</td>
<td>1.67 &lt;.001</td>
</tr>
<tr>
<td>Crackles</td>
<td>1.41 &lt;.001</td>
<td>1.01 .90</td>
<td>1.38 .001</td>
</tr>
<tr>
<td>Wheeze</td>
<td>0.69 &lt;.001</td>
<td>0.61 &lt;.001</td>
<td>0.52 &lt;.001</td>
</tr>
<tr>
<td>Temperature &gt;38.5°C</td>
<td>1.41 &lt;.001</td>
<td>1.24 .10</td>
<td>1.60 &lt;.001</td>
</tr>
<tr>
<td>Grunting</td>
<td>1.07 0.55</td>
<td>1.25 .15</td>
<td>1.14 .34</td>
</tr>
<tr>
<td>Tachycardia#</td>
<td>1.00 0.99</td>
<td>1.09 .40</td>
<td>1.02 .85</td>
</tr>
<tr>
<td>Admission diagnoses</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Paraffin ingestion</td>
<td>1.34 .69</td>
<td></td>
<td>2.62 .20</td>
</tr>
<tr>
<td>Meningitis#</td>
<td>0.30 &lt;.001</td>
<td>0.67 .21</td>
<td>0.25 &lt;.001</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1.09 .72</td>
<td>1.03 .93</td>
<td>1.12 .70</td>
</tr>
<tr>
<td>Shock#</td>
<td>1.10 .32</td>
<td>1.29 .04</td>
<td>1.29 .03</td>
</tr>
<tr>
<td>Bronchiolitis</td>
<td>0.67 &lt;.001</td>
<td>0.72 .04</td>
<td>0.59 &lt;.001</td>
</tr>
<tr>
<td>Asthma</td>
<td>0.71 .04</td>
<td>0.82 .45</td>
<td>0.73 .05</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>0.59 .003</td>
<td>0.99 .96</td>
<td>0.61 .02</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>4.32 &lt;.001</td>
<td>0.86 .71</td>
<td>4.49 .002</td>
</tr>
<tr>
<td>Very severe cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical and danger signs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head nodding</td>
<td>0.75 .17</td>
<td>1.68 .06</td>
<td>0.93 .75</td>
</tr>
<tr>
<td>Central cyanosis</td>
<td>1.55 .16</td>
<td>0.86 .65</td>
<td>1.34 .43</td>
</tr>
<tr>
<td>Inability to feed/drink</td>
<td>1.00 1.00</td>
<td>1.67 .03</td>
<td>1.25 .27</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.66 .12</td>
<td>0.63 .25</td>
<td>0.47 .04</td>
</tr>
<tr>
<td>Lethargy or unconsciousness</td>
<td>0.98 .93</td>
<td>1.69 .04</td>
<td>1.25 .28</td>
</tr>
<tr>
<td>Convulsions</td>
<td>0.49 .002</td>
<td>0.86 .67</td>
<td>0.46 .007</td>
</tr>
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<td>Hypoxemia#</td>
<td>1.63 .002</td>
<td>1.34 .16</td>
<td>1.79 .002</td>
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<tr>
<td>Nasal flaring</td>
<td>1.61 .006</td>
<td>0.98 .95</td>
<td>1.68 .02</td>
</tr>
<tr>
<td>Tachypnea#</td>
<td>1.59 .009</td>
<td>1.45 .17</td>
<td>2.04 .002</td>
</tr>
<tr>
<td>Crackles</td>
<td>1.95 &lt;.001</td>
<td>1.26 .26</td>
<td>1.96 &lt;.001</td>
</tr>
<tr>
<td>Wheeze</td>
<td>0.67 .03</td>
<td>0.63 .06</td>
<td>0.56 .008</td>
</tr>
<tr>
<td>Temperature &gt;38.5°C</td>
<td>1.24 .23</td>
<td>0.98 .93</td>
<td>1.30 .22</td>
</tr>
<tr>
<td>Grunting</td>
<td>0.82 .31</td>
<td>1.01 .97</td>
<td>0.82 .40</td>
</tr>
<tr>
<td>Tachycardia#</td>
<td>1.33 .05</td>
<td>1.38 .10</td>
<td>1.46 .03</td>
</tr>
</tbody>
</table>

**Adjusted OR**: Odds ratio adjusted for age (in months), site, and HIV status. **P Value**: Probability value for the adjusted odds ratio. **Value**: Value of the adjusted odds ratio.

### Abbreviations:
- OR: Odds ratio
- WHO: World Health Organization
- HIV: Human Immunodeficiency Virus

### Clinical Signs
- Hypoxemia:
  - Definition: Oxygen saturation <93% when breathing room air.
  - Including: Central cyanosis (observed by medical personnel), and central cyanosis (self-reported).

### Admission Diagnoses
- Paraffin ingestion:
  - Definition: Ingestion of paraffin wax or similar substances.

### Very Severe Cases
- Head nodding:
  - Definition: Lack of head movement upon stimulation.
- Central cyanosis:
  - Definition: Bluish discoloration of the skin and mucous membranes.
- Inability to feed/drink:
  - Definition: Difficulty in swallowing or inadequate intake of fluids.
- Vomiting:
  - Definition: Forceful expulsion of stomach contents through the mouth.
- Lethargy or unconsciousness:
  - Definition: Reduced level of consciousness or unresponsiveness.
- Convulsions:
  - Definition: Sudden, rapid, and repeated muscle contractions.
- Hypoxemia:
  - Definition: Oxygen saturation <93% when breathing room air.
- Nasal flaring:
  - Definition: Elevation of the nares.
- Tachypnea:
  - Definition: Respiratory rate >60 breaths per minute.
- Crackles:
  - Definition: Crackling sounds heard upon auscultation.
- Wheeze:
  - Definition: Whistling sounds heard upon auscultation.
- Temperature >38.5°C:
  - Definition: Body temperature above 38.5°C.
- Grunting:
  - Definition: Forceful expulsion of air through the mouth.
- Tachycardia:
  - Definition: Heart rate >160 beats per minute.

### Epidemiology of CXRs in Pneumonia
- Although we used a more stringent definition of "uninterpretable for other infiltrate and/or consolidation" compared to the "uninterpretable for consolidation only" definition in most applications of the WHO methodology, high proportions of uninterpretable images highlight the challenges of achieving adequate radiographic images in resource-poor settings.
- The proportion of PERCH cases with a finding of consolidation ranged from 11% to 37% in HIV-negative cases. Such differences are consistent with findings of consolidation in previous studies of pneumonia.

The Gambian pneumococcal conjugate vaccine trial, 17% of hospitalized pneumonia cases in the control arm had consolidation in the presence of Hib vaccine [19], while in the Bangladesh Hib vaccine case-control study, 26% of all hospitalized pneumonia cases, vaccinated and nonvaccinated combined, had consolidation [20]. The proportion of abnormal CXRs (consolidation or other infiltrate) among HIV-negative cases also varied by site from 35% to 64% (and thus a range of normal CXRs from 36% to 65%), while 88% of HIV-positive cases had an abnormal CXR in both South Africa and Zambia.
understanding is that etiology, severity, duration of infection, and host immune reaction are major predictors of CXR findings [21–23]. If this is true, observed differences in the distributions of CXR findings between sites likely reflect determinants of those CXR predictors, such as healthcare-seeking behaviors, availability of antibiotics, and environmental and living conditions. Epidemiologic studies that use CXR case definitions should recognize that differences between studies could reflect not only differences in pneumonia etiology but also variables that alter the timing of care seeking or host response to infection.

Age has an important interaction with CXR results and severity, as expected (Supplemental Table 1). Danger signs, which are not specific for respiratory disease, were more indicative of an abnormal CXR in younger children; we observed that among very severe cases, the youngest children (aged 1–5 months) were more likely to have an abnormal CXR than older children. However, more specific pneumonia findings (such as lower chest wall indrawing) are less associated with pneumonia in younger children because the physiologic compliance of the lower chest makes this finding more common in a variety of illnesses. Thus, among severe cases, we observed that an abnormal CXR was less likely among the youngest children compared to those in other age groups. These findings suggest that danger signs may not be useful criteria for diagnosing pneumonia in children aged >6 months, particularly in pneumonia studies where a low proportion of false positives is important. However, danger signs remain useful for bacterial treatment algorithms, since they will identify nonpneumonia cases that nevertheless require treatment.

We observed significant differences in case fatality ratios among HIV-negative cases depending on their CXR findings; those with consolidation on CXR were at significantly higher risk of death than those with a normal CXR or with other infiltrates only. The presence of other infiltrates did not alter the risk of death compared to a normal CXR appearance in children with severe or very severe pneumonia. This likely reflects the association between consolidation and bacterial pneumonia and the tendency for bacterial pneumonia to be more severe than viral pneumonia. An association between a CXR finding of "dense infiltrates" and mortality has also been documented in the Philippines [24]; in Fiji, CXR consolidation had a case fatality ratio of 6.8% using the WHO methodology [25]. Our findings are limited in that 100 cases who died were missing a CXR, the majority (92%) because death occurred before this could be obtained. If the distribution of CXR findings in these cases differed from the other cases who died, the difference in case fatality ratios may either be underestimated or overestimated. Nonetheless, these findings suggest that in order to further reduce the mortality burden of pneumonia, a focus on groups with a high prevalence of consolidation should be a priority.

Our findings have important methodological limitations. First, without a gold standard for pneumonia diagnosis, clinical signs and radiological findings may be correlated to each other without being correlated to true pneumonia. Second, if observers recording clinical signs were aware of a case's CXR appearance, the independence of these measurements may be violated. Third, our definition of hypoxemia included those on supplemental oxygen,
which may not reliably indicate true hypoxemia on admission. Finally, our study was not designed to assess the relationship between duration of illness and abnormal CXR findings, yet this is likely to have a strong influence on CXR positivity.

In summary, the WHO clinical pneumonia definitions were designed as a sensitive tool for the management of pneumonia cases. Our experience suggests that almost half of these cases do not have radiological evidence of pneumonia. Chest radiography continues to be a valuable method for case identification that is correlated to clinical signs of pneumonia and can be applied to a variety of pneumonia studies, including etiology studies. Yet, radiologic findings in cases of clinical pneumonia likely reflect a complex mix of etiology, healthcare-seeking patterns, antibiotic use, age, and underlying health conditions such as HIV and malnutrition.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. N. F. performed the analysis, interpreted results, and drafted the manuscript. M. D. K. and K. L. O. assisted with analysis and interpretation. O. S. L., K. L. O., D. R. F., D. R. M., M. D. K., L. L. H. C. B., W. A. B., S. R. C. H., K. K. L., S. A. M., J. A. G. S., and D. M. T. conceived and designed the study and supervised study conduct. J. I. O. A., B. B. K. J. C., A. N. D., M. D., A. J. D., B. E. E., M. M. H., Y. J., N. M., D. P. M., K. N., S. N., D. E. P., C. P. M., S. W. S., S. T., and S. M. A. Z. were involved in study conduct. B. B. K., M. D., B. E. E., N., M. D. P., K., and M. S. O. were part of the PERCH Chest Radiograph Reading Panel. S. Z. provided statistical expertise and led the integrated etiology analysis. R. A. K. provided technical guidance. All authors reviewed and approved the manuscript. N. F. had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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References