BMJ Global Health

An analysis of clinical predictive values for radiographic pneumonia in children

Chris A Rees ![ORCID],[1] Sudha Basnet,[2] Angela Gentile,[3] Bradford D Gessner,[4] Cissy B Kartasasmita,[5] Marilla Lucero,[6] Luis Martinez,[7] Kerry-Ann F O'Grady,[8] Raul O Ruvinsky,[9] Claudia Turner,[10] Harry Campbell,[11] Harish Nair,[11] Jennifer Falconer,[12] Linda J Williams,[11] Margaret Horne,[11] Tor Strand,[13] Yasir B Nisar,[14] Shamim A Qazi,[15] Mark I Neuman,[1] on behalf of the World Health Organization PREPARE study group[16]

For numbered affiliations see end of article.

Correspondence to
Dr Mark I Neuman;
mark.neuman@childrens.harvard.edu

ABSTRACT

Introduction Healthcare providers in resource-limited settings rely on the presence of tachypnoea and chest indrawing to establish a diagnosis of pneumonia in children. We aimed to determine the test characteristics of commonly assessed signs and symptoms for the radiographic diagnosis of pneumonia in children 0–59 months of age.

Methods We conducted an analysis using patient-level pooled data from 41 shared datasets of paediatric pneumonia. We included hospital-based studies in which >80% of children had chest radiography performed. Primary endpoint pneumonia (presence of dense opacity occupying a portion or entire lobe of the lung or presence of pleural effusion on chest radiograph) was used as the reference criterion radiographic standard. We assessed the sensitivity, specificity, and likelihood ratios for clinical findings, and combinations of findings, for the diagnosis of primary endpoint pneumonia among children 0–59 months of age.

Results Ten studies met inclusion criteria comprising 15 029 children; 24.9% (n=3743) had radiographic pneumonia. The presence of age-based tachypnoea demonstrated a sensitivity of 0.92 and a specificity of 0.22 while lower chest indrawing revealed a sensitivity of 0.74 and specificity of 0.15 for the diagnosis of radiographic pneumonia. The sensitivity and specificity for oxygen saturation <90% was 0.40 and 0.67, respectively, and was 0.17 and 0.88 for oxygen saturation <85%. Specificity was improved when individual clinical factors such as tachypnoea, fever and hypoxaemia were combined, however, the sensitivity was lower.

Conclusions No single sign or symptom was strongly associated with radiographic primary end point pneumonia in children. Performance characteristics were improved by combining individual signs and symptoms.

Key questions

What is already known?

► Pneumonia is the leading cause of morbidity and mortality among children 1–59 months of age worldwide.

► The diagnosis of childhood pneumonia is often established based on clinical findings, as the definitive aetiological diagnosis can only be made using invasive testing.

► Antibiotic treatment decisions for children with suspected pneumonia in low-income and middle-income countries rely largely on clinical findings, including tachypnoea and chest indrawing.

What are the new findings?

► Our study of over 15 000 children from geographically diverse parts of the world is the largest to date to assess the test characteristics of clinical signs and symptoms for radiographic pneumonia among children 0–59 months of age.

► Individual findings commonly used to identify pneumonia in resource-limited settings, including tachypnoea and lower chest indrawing, had low specificity for the diagnosis of radiographic pneumonia.

► The combination of tachypnoea and fever, tachypnoea and hypoxaemia, and fever and hypoxaemia led to improved specificity with only a modest decrement in sensitivity for radiographic pneumonia.

What do the new findings imply?

► Individual symptoms and physical examination findings are not highly predictive of primary endpoint pneumonia on chest radiograph.

► Combining temperature, respiratory rate, and oxygen saturation improves specificity in the identification of radiographic pneumonia.

► The diagnostic performance of a combination of signs and symptoms should be explored in a prospective fashion to allow for a judicious approach to antibiotic treatment in children with suspected pneumonia.

INTRODUCTION

Pneumonia is the leading cause of morbidity and mortality among children 1–59 months of age worldwide.[1 2] Annually, there are over 800 000 deaths from pneumonia among children worldwide.[2] Such morbidity and mortality from childhood pneumonia disproportionately affects children in low-income and middle-income countries, with nearly 90%

of pneumonia-related deaths occurring in sub-Saharan Africa and South and Southeastern Asia alone.[2 3] Despite the large global burden of disease of childhood pneumonia, a commonly agreed upon standardised approach to the diagnosis of pneumonia is lacking.[4]

The diagnosis of childhood pneumonia is often established based on clinical findings, as the definitive diagnosis can only be made using invasive testing such as lung biopsies, which are reserved for patients in whom traditional therapeutics have failed.[5] As such, chest radiography is often used in clinical practice for the diagnosis of childhood pneumonia and has been used as a reference standard in previous investigations.[6–10] In a large, multicountry study in Asia and sub-Saharan Africa, chest radiography correlated with clinically diagnosed pneumonia in over half of patients included.[11] Nevertheless, the routine use of chest radiography for the diagnosis of childhood pneumonia in the outpatient setting is not recommended by the Infectious Disease Society of America.[5] Similarly, the World Health Organization's (WHO) integrated management of childhood illness (IMCI) chart booklet used in many low-income and middle-income countries, recommends the diagnosis of pneumonia be made clinically, with reliance on tachypnoea or lower chest indrawing in a child with cough or difficulty breathing.[12 13] However, recent analyses suggest that the sensitivity (54%–62%) and specificity (59%–64%) of tachypnoea and sensitivity (38%–48%) and specificity (72%–80%) of lower chest indrawing is lower than originally estimated.[9 10 14] Concerns around the low specificity of the WHO pneumonia signs, and potential excess antibiotic prescribing, prompted further evaluation of these clinical criteria for the diagnosis of pneumonia in children.

The development of sensitive and specific diagnostic clinical criteria for childhood pneumonia is imperative as chest radiography is not routinely available in many low- and middle-income countries. Previous systematic reviews evaluating the utility of symptoms and physical examination findings for the diagnosis of childhood pneumonia have relied on data reported in published articles, without access to individual patient-level data.[9 10] Additionally, the overwhelming majority of these investigations were conducted in high-income countries. The reliance on predetermined cut-points from published articles for clinical criteria such as respiratory rate (RR) and oxygen saturation (SpO_2) may lead to imprecision in the analysis of diagnostic clinical criteria for childhood pneumonia.

With the aim of better understanding the clinical diagnostic criteria for childhood pneumonia, the WHO established the Pneumonia REsearch Partnership to Assess WHO Recommendations (PREPARE) study group. The PREPARE study group obtained patient-level data from 30 study groups, comprising 41 separate datasets on childhood pneumonia from across the world. Using the large, representative PREPARE dataset, our objective was to determine the sensitivity and specificity of key clinical features and combination of clinical features in the diagnosis of childhood pneumonia against a radiological reference standard. Accurate identification of children with pneumonia using clinical factors could potentially allow providers to more accurately diagnose childhood pneumonia and, subsequently, more appropriately target antibiotic therapy.

METHODS
Study design
We conducted an analysis using datasets from the WHO's PREPARE study group. The WHO PREPARE study group assembled datasets through retrospective identification of primary data on childhood pneumonia from over 20 low- and middle-income countries in Asia, Africa and Latin America as well as two high-income countries (ie, the USA and Australia). Study sites were considered for inclusion in WHO PREPARE study group if they included data from control arms of vaccine trials, community-based cohorts, and hospital-based studies with clinical and epidemiological data collected. Potential study sites were identified from a list of contributors to a systematic review of global burden of hospital admissions for severe acute lower respiratory infections in children.[15] Based on a review of the paediatric pneumonia literature, we identified 50 groups who were involved in pneumonia research who had published articles between 2005 and 2018. These groups had conducted pneumonia research with and without interventions, randomised controlled trials, epidemiological studies, and vaccine trials. We invited all 50 study groups to participate by attending an inception meeting in Ferny-Voltaire, France. Representatives from 38 groups attended that meeting where each investigator presented their site data. As a result of that meeting, 30 study groups agreed to participate and provided 41 unique databases for the WHO PREPARE study group. Datasets were limited to include only data on children 0–59 months of age, despite potentially containing data from older children.

For this study, to include datasets in which chest radiography was performed in a generalisable fashion, we limited our analysis to datasets of hospital-based studies that included data on chest radiography and had a chest radiography performed in ≥80% of cases. Studies in which chest radiography was performed in <80% of cases may have suffered from selection bias as chest radiography may have been performed only in children with severe illness and at higher risk of pneumonia and were excluded. Community-based studies were not included as chest radiography was rarely performed.

Patient and public involvement statement
The development of the research question was informed by the large disease burden of pneumonia among children worldwide. Patients were not involved in the design, recruitment, or conduct of the study. Results of this study will be made publicly available through publication

where study participants may access them. Patients were not advisers in this study.

Pneumonia case definition

Datasets were included in this analysis if they included data on children presenting acutely with cough or difficulty breathing and included pneumonia as defined by the WHO radiological criteria for primary endpoint pneumonia[6] (n=8) or if they used lobar consolidation on chest radiography as diagnostic criteria for pneumonia (n=2). Though originally created for use in vaccine trials, primary endpoint pneumonia has been applied to large cohorts of children with pneumonia in several low- and middle-income countries with good inter-rater reliability.[16] A majority of the datasets (n=6) included in this analysis enrolled children with tachypnoea, as this is the primary determinant of pneumonia based on the WHO IMCI chart booklet. Primary endpoint pneumonia was selected as the radiographic reference standard as it is clearly defined, is reliable across studies, is independent of predictor clinical variables that are often studied in work evaluating childhood pneumonia, is a clear indication of pneumonia and not viral acute lower respiratory tract infection, and highlights bacterial pneumonia that requires antibiotic treatment. Lobar consolidation was used as a reference standard in two included datasets and has shown high inter-rater reliability among paediatric radiologists in prospective studies.[17] All radiographs in the included studies were interpreted by a radiologist; many of the studies required review by two or more radiologists.

Data analysis

Using radiographic pneumonia as the reference standard, we evaluated the sensitivity, specificity, and likelihood ratios (LRs) for individual clinical findings. We calculated 95% CIs for all +LR and −LRs. Candidate variables from patients' histories that were used to calculate test characteristics included history of cough, fever, difficulty breathing, vomiting, and poor feeding. We evaluated the test characteristics of tachypnoea as defined by the WHO IMCI age-specific cutoffs (ie, RR of ≥60 breaths per minutes in children <2 months old, >50 breaths per minute in children 2–11 months old, and ≥40 breaths per minute in children 12–59 months old)[18] as well as the addition of five and 10 respirations per minute to the age-specific WHO classification of tachypnoea.

Using radiographic pneumonia as the reference standard, we also evaluated the test characteristics of lower chest indrawing, nasal flaring, grunting, wheezing, body temperature, SpO_2, presence of rales or crepitations, inability to drink, presence of convulsions, cyanosis, head nodding/bobbing, presence of irritability, lethargy and presence of any danger sign (ie, inability to drink, convulsions, cyanosis, head nodding/bobbing, irritability, abnormally sleepy, lethargy, nasal flaring, grunting, and SpO_2 <90%). We stratified analyses by age (<2 months, 2–11 months, and 12–59 months) and by the presence

or absence of wheezing. We assessed the test characteristics of varying age-specific RR and SpO_2 in patients both with and without wheezing to eliminate children who may have asthma who are sometimes included in studies evaluating pneumonia. We also assessed the sensitivity, specificity, and LRs of combinations of clinical signs and symptoms compared with the reference standard of radiographic pneumonia. We had a study power of >95% to detect a difference in radiographic pneumonia of at least 7% between children who had some clinical features of pneumonia (eg, presence of chest indrawing, any danger sign, temperature ≥38°C, or SpO_2 <90%) and those who did not have these clinical features. All analyses were conducted using Stata V.14 (StataCorp, College Station, TX, USA).

RESULTS

Of the 41 separate datasets, 26 were hospital based, of which 10 met inclusion criteria, containing a total of 15 029 patients (figure 1). The mean age of patients was
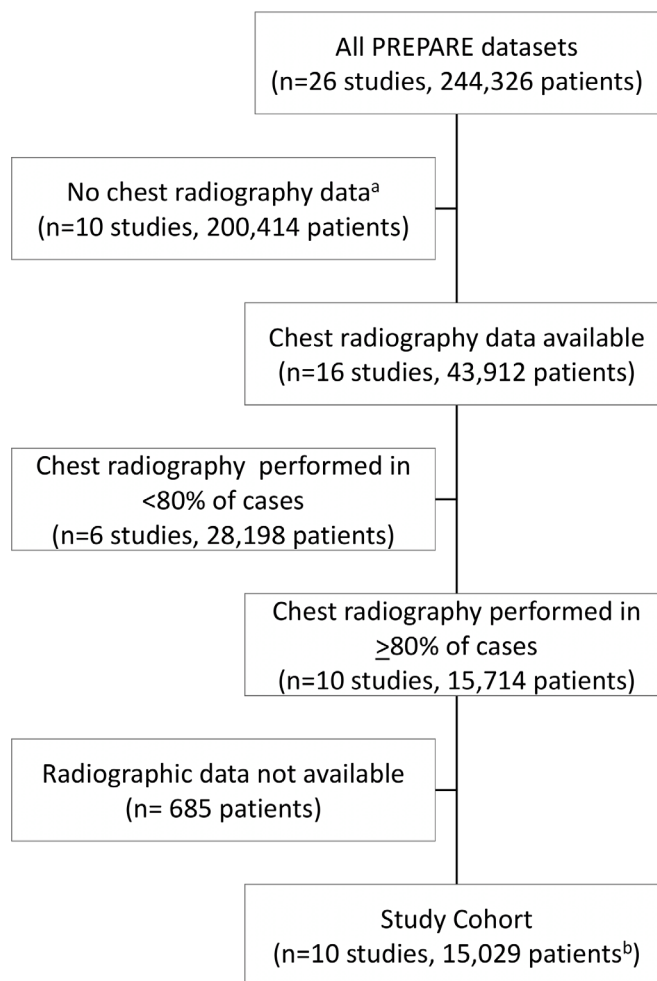
Figure 1 Hospital-based studies including children 0 to ≤59 months of age. [a]Chest radiography not performed or data regarding presence of pneumonia/infiltrate not recorded. [b]Radiographic pneumonia in 3743 patients (24.9%). PREPARE, Pneumonia REsearch Partnership to Assess WHO Recommendations.

Table 1 Study characteristics

Study	Location	Age range	Inclusion and exclusion criteria	Sample size	Radiographic pneumonia, N (%)	Definition of pneumonia by chest radiograph
Puumalainen et al and Arcay, et al. (ARIVAC)[48 49]	Philippines	6 weeks to 59 months	Tachypnoea*, lower chest indrawing (severe pneumonia)† or cyanosis and/or inability to drink (very severe pneumonia)‡	1153	187 (16.2)	Primary end point pneumonia (PEP)§
Basnet et al[50]	Nepal	2–35 months	Cough <14 days and/or difficulty breathing ≤72 hours with presence of lower chest indrawing, provided lower chest indrawing persisted after 3 doses of bronchodilators.	551	135 (24.5)	Lobar pneumonia/consolidation¶
Gentile et al[51]	Argentina	0–59 months	Children hospitalised with pneumonia.	401	201 (50.1)	PEP§
Gessner et al[52]	Indonesia	0–24 months	WHO defined non-severe** and severe pneumonia†.	5814	1025 (17.6)	PEP§
Hortal et al[53]	Uruguay	0–59 months	Children hospitalised with acute lower respiratory tract infection with chest X-ray performed.	811	412 (50.8)	PEP§
Tan et al[54]	Indonesia	<5 years	All children with diagnosis of pneumonia and having ≥1 of the following: fever, cough, dyspnoea, or tachypnoea*.	1251	128 (10.2)	Lobar pneumonia/consolidation¶
Neuman, et al[24]	USA	0–59 months	Children with chest X-ray performed for suspicion of pneumonia. Excluded children with chronic conditions.	1796	161 (9.0)	PEP§
O'Grady et al[55]	Central Australia	0–59 months	Child with cough with tachypnoea* and/or chest indrawing†. Excluded children with wheezing and chronic conditions.	147	40 (27.2)	PEP§
Ferrero et al[56]	Argentina	1–59 months	WHO defined non-severe** and severe pneumonia†. Excluded hospital-acquired pneumonia.	2085	1123 (53.9)	PEP§
Turner et al[57]	Thailand	0–2 years	WHO defined non-severe** and severe pneumonia†.	1020	331 (32.5)	PEP§

*Tachypnoea: respiratory rate ≥60 per minute in infants <2 months old, ≥50 per minute in infants 2–11 months old, or ≥40 per minute in children 12–59 months of age.
†Severe pneumonia (old WHO pneumonia classification): cough and/or fast breathing with lower chest indrawing.
‡Very severe pneumonia (old WHO pneumonia classification): one or more danger sign including abnormally sleepy, lethargy, central cyanosis, inability to drink, convulsions, head nodding/bobbing, nasal flaring or grunting.
§PEP: a dense opacity that may be a fluffy consolidation of a portion or whole of a lobe or of the entire lung, often containing air bronchograms and sometimes associated with pleural effusion.
¶Lobar pneumonia or consolidation: Chest X-ray findings showing lobar pneumonia or consolidation.
**Non-severe pneumonia: cough and fast breathing, defined as respiratory rate of ≥50 per minute in children 2–11 months old or ≥40 per minute in children 12–59 months old.

13.0 months (standard deviation ±12.3) with median of 9.0 months (4.4–16.9). Details regarding the setting and patient population for the 10 included datasets are shown in table 1. Of the 15 029 patients included, 24.9% (n=3743) had radiographic pneumonia.

The sensitivity and specificity of individual symptoms and physical examination findings for the diagnosis of radiographic pneumonia are shown in table 2. No single sign or symptom was strongly associated with radiographic pneumonia. The presence of poor feeding (+LR 1.67 (95%CI 1.29 to 2.16)), axillary/body temperature ≥38°C (+LR 1.36 (95%CI 1.31 to 1.41)), head nodding/bobbing (+LR 1.84 (95%CI 1.38 to 2.45)), grunting (+LR

1.72 (95%CI 1.27 to 2.33)), and hypoxaemia at SpO_2 <85% (+LR 1.42 [95%CI 1.27 to 1.59)) were weakly associated with the presence of radiographic pneumonia, while the absence of the following features was associated with a lower likelihood of radiographic pneumonia: axillary/body temperature ≥38°C (−LR 0.77 (95%CI 0.74 to 0.80)), rales/crepitations (−LR 0.73 (95%CI 0.66 to 0.80)), and SpO_2 <95% (−LR 0.83 (95%CI 0.78 to 0.88)).

Age-specific RR thresholds were neither highly sensitive nor specific for the radiographic diagnosis of pneumonia in the overall cohort and among the subset of children without wheezing (table 3). Among children 2–11 months of age, those with RR ≥60 breaths per minute

Table 2 Test characteristics of signs and symptoms of radiographic pneumonia

Symptom or sign*	Sample size, n	Sign or symptom present, n	Radiographic pneumonia, n	Sensitivity	Specificity	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
Cough[48-51 53-55 57]	4961	4405	1060	0.77	0.08	**0.83 (0.81 to 0.86)**	**3.1 (2.65 to 3.57)**
Fever[19 50 51 53 54 57]	5472	4531	1076	0.82	0.17	0.98 (0.95 to 1.01)	1.10 (0.96 to 1.25)
Difficulty breathing[48-51 53-55]	4061	3566	772	0.70	0.08	**0.76 (0.73 to 0.79)**	**3.98 (3.41 to 4.65)**
Vomiting[50 51 53 54]	2688	349	101	0.12	0.87	0.94 (0.76 to 1.17)	1.01 (0.98 to 1.04)
Poor feeding[48-50 54]	2905	265	65	0.14	0.91	**1.67 (1.29 to 2.16)**	**0.94 (0.90 to 0.98)**
Respiratory rate (RR) WHO cut off†[19 48 49 51-55 57]	12478	9754	2006	0.79	0.22	1.01 (0.99 to 1.04)	0.96 (0.88 to 1.04)
RR WHO cut-off+5‡[19 48 49 51-55 57]	12478	8012	1648	0.65	0.36	1.02 (0.99 to 1.06)	0.96 (0.91 to 1.02)
RR WHO cut-off +10§[19 48-55 57]	12478	6140	1301	0.51	0.51	**1.05 (1.004 to 1.09)**	**0.95 (0.91 to 0.997)**
Lower chest indrawing[48-50 52-57]	12546	10388	2509	0.74	0.15	**0.87 (0.85 to 0.89)**	**1.74 (1.61 to 1.88)**
Temperature ≥38°C[19 48-50 52-57]	14188	5940	1894	0.54	0.60	**1.36 (1.31 to 1.41)**	**0.77 (0.74 to 0.80)**
Rales/crepitations[19 48-50 52 54 55 57]	11416	8584	1596	0.82	0.26	**1.09 (1.07 to 1.12)**	**0.73 (0.66 to 0.80)**
Unable to drink[50 54]	1769	429	75	0.29	0.76	1.17 (0.95 to 1.45)	0.95 (0.87 to 1.03)
Convulsions[52 54]	1324	160	22	0.14	0.88	1.24 (0.82 to 1.88)	0.97 (0.90 to 1.04)
Cyanosis[48-50 52-54 56]	5618	228	112	0.06	0.96	**1.52 (1.19 to 1.94)**	**0.98 (0.97 to 0.99)**
Head nodding/bobbing[50 54 57]	2757	169	63	0.11	0.94	**1.84 (1.38 to 2.45)**	**0.95 (0.92 to 0.98)**
Irritable[48 49 54]	2298	115	21	0.05	0.95	1.34 (0.88 to 2.19)	0.98 (0.95 to 1.01)
Abnormally sleepy/lethargy[48-50 52 54 56]	4999	349	76	0.05	0.93	**0.72 (0.56 to 0.92)**	**1.02 (1.01 to 1.04)**
Nasal flaring[50 54 55 57]	2898	439	117	0.18	0.85	**1.24 (1.03 to 1.50)**	0.96 (0.92 to 1.00)
Grunting[19 50 54 57]	4554	183	53	0.06	0.96	**1.72 (1.27 to 2.33)**	**0.97 (0.95 to 0.99)**
Wheeze[19 50-52 54 55 57]	10801	2928	571	0.29	0.73	1.05 (0.97 to 1.13)	0.98 (0.95 to 1.01)
Oxygen saturation (SpO₂) <95%[19 48-55 57]	11967	7298	1687	0.67	0.40	**1.11 (1.08 to 1.15)**	**0.83 (0.78 to 0.88)**
SpO₂ <90%[19 48-55 57]	11967	3048	810	0.32	0.75	**1.30 (1.22 to 1.39)**	**0.90 (0.87 to 0.93)**
SpO₂ <85%[19 48-55 57]	11967	1216	373	0.15	0.90	**1.42 (1.27 to 1.59)**	**0.95 (0.93 to 0.97)**
Any danger signs¶[19 48-57]	14732	4399	1049	0.28	0.70	**0.67 (0.60 to 0.75)**	1.06 (1.04 to 1.07)

Bold values are statistically significant.

*Following missing values were excluded from the analysis: 373 (7%) for cough, 358 (6%) for fever, 218 (5%) for difficult breathing, 326 (11%) for vomiting, 50 (2%) for poor feeding, 286 (2%) for lower chest indrawing, 440 (4%) for temperature readings, 316 (3%) for rales/crepitations, 33 (2%) for convulsions, 243 (4%) for cyanosis, 65 (2%) for head nodding/bobbing, 106 (4%) for irritability, 63 (1%) for abnormally sleepy/lethargy, 71 (2%) for nasal flaring, 64 (1%) for grunting, 179 (2%) for wheeze, 977 (8%) for SpO₂ readings, 297 (2%) for any danger sign.

†RR of ≥60 per minute in infants <2 months old, >50 per minute in infants 2–11 months old or ≥40 per minute in children 12–59 months old.

‡RR of ≥65 per minute in infants <2 months old, >55 per minute in infants 2–11 months old or ≥45 per minute in children 12–59 months old.

§RR of ≥70 per minute in infants <2 months old, >60 per minute in infants 2–11 months old, >50 per minute in children 12–59 months old.

¶Any danger sign included: unable to drink, convulsions, cyanosis, head nodding/bobbing, irritability, abnormally sleepy, lethargy, nasal flaring, grunting, and SpO₂ <90%.

Table 3 Test characteristics of varying respiratory rates (RRs) by age group among all children and those without wheezing*

RR	Patients with RR above threshold, n	Patients with radiographic pneumonia, n	Sensitivity	Specificity	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
All children						
Age <2 months (n=1073)						
RR ≥60	650	104	0.60	0.39	0.98 (0.86 to 1.12)	1.03 (0.84 to 1.25)
RR ≥65	357	63	0.36	0.67	1.11 (0.89 to 1.38)	0.95 (0.84 to 1.07)
RR ≥70	182	30	0.17	0.83	1.02 (0.71 to 1.46)	1.00 (0.93 to 1.07)
Age 2–11 months (n=7145)						
RR ≥50	5986	1187	0.85	0.17	1.02 (1.00 to 1.05)	0.89 (0.77 to 1.02)
RR ≥55	4926	982	0.71	0.31	1.03 (0.99 to 1.07)	0.94 (0.86 to 1.03)
RR ≥60	3717	772	0.55	0.49	**1.08 (1.03 to 1.14)**	**0.91 (0.86 to 0.97)**
Age 12–59 months (n=4260)						
RR ≥40	3140	715	0.74	0.26	1.00 (0.96 to 1.04)	1.00 (0.89 to 1.13)
RR ≥45	2685	603	0.62	0.37	0.98 (0.93 to 1.04)	1.03 (0.94 to 1.13)
RR ≥50	2268	499	0.51	0.46	0.96 (0.89 to 1.02)	1.05 (0.98 to 1.13)
Children without wheezing						
Age <2 months (n=937)						
RR ≥60	570	85	0.60	0.39	0.99 (0.86 to 1.14)	1.02 (0.81 to 1.27)
RR ≥65	318	54	0.38	0.67	1.15 (0.92 to 1.46)	0.92 (0.80 to 1.06)
RR ≥70	162	26	0.18	0.83	1.08 (0.74 to 1.58)	0.98 (0.90 to 1.07)
Age 2–11 months (n=5340)						
RR ≥50	4449	886	0.84	0.17	1.01 (0.99 to 1.04)	0.93 (0.79 to 1.08)
RR ≥55	3650	730	0.69	0.32	1.02 (0.97 to 1.07)	0.96 (0.86 to 1.06)
RR ≥60	2731	571	0.54	0.50	**1.08 (1.01 to 1.15)**	**0.92 (0.86 to 0.99)**
Age 12–59 months (n=3225)						
RR ≥40	2270	540	0.70	0.29	0.98 (0.93 to 1.04)	1.04 (0.92 to 1.17)
RR ≥45	1937	449	0.58	0.39	0.95 (0.89 to 1.02)	1.07 (0.98 to 1.18)
RR ≥50	1612	368	0.47	0.49	0.93 (0.86 to 1.02)	1.07 (0.99 to 1.16)

Bold values are statistically significant.
*182 missing values for RR were excluded from the analysis.

were more likely to have radiographic pneumonia (+LR 1.08 (95%CI 1.03 to 1.14)), while those with RR <60 were less likely to have radiographic pneumonia (−LR 0.91 (95%CI 0.86 to 0.97)).

The test characteristics of SpO$_2$ for radiographic pneumonia for all children and those without wheezing are shown in online supplementary table 1. Sensitivity decreased and specificity increased with increasing levels of hypoxaemia, although no single threshold had optimal test characteristics for the identification of radiographic pneumonia.

The combinations of varying degrees of hypoxaemia, fever and tachypnoea are shown in tables 4–6. At each SpO$_2$ category, specificity increased with increasing RR. Among children with SpO$_2$ <90%, children with RRs ≥10 breaths per minute above the WHO threshold for age-defined tachypnoea were slightly more likely to have radiographic pneumonia (+LR 1.40 (95%CI 1.28 to 1.53)), while those without this degree of tachypnoea

were less likely to have radiographic pneumonia (−LR 0.92 (95%CI 0.90 to 0.94)) (table 4). Among the subset of children with temperature ≥38°C, those with an RR ≥10 breaths per minute above the WHO threshold for age-defined tachypnoea were slightly more likely to have radiographic pneumonia (+LR 1.24 (95%CI 1.14 to 1.35)) (table 5). The combination of temperature ≥38°C and SpO$_2$ <85% was highly specific for radiographic pneumonia (specificity 0.96, (95% CI 0.96 to 0.97)) while the sensitivity was quite low (sensitivity 0.07, (95% CI 0.06 to 0.08)) (table 6).

DISCUSSION

Our study of over 15 000 children from geographically diverse parts of the world is the largest to date assessing the test characteristics of clinical signs and symptoms for radiographic pneumonia among children 0–59 months of age. We observed that individual findings commonly

Table 4 Test characteristics of varying respiratory rates (RRs) with SpO₂ levels in children

RR and SpO$_2$	Patients with RR above threshold, n (n=9360)	Radiographic pneumonia, n (n=2444)	Sensitivity	Specificity	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
SpO$_2$ <95%						
RR ≥age specific cut-off*	6519	1460	0.60	0.46	**1.11 (1.07 to 1.15)**	**0.87 (0.83 to 0.92)**
RR ≥5 above age-specific cut-off†	5529	1242	0.51	0.54	**1.11 (1.06 to 1.16)**	**0.90 (0.87 to 0.95)**
RR ≥10 above age-specific cut-off‡	4400	1016	0.42	0.64	**1.15 (1.09 to 1.22)**	**0.91 (0.88 to 0.95)**
SpO$_2$ <90%						
RR ≥age-specific cut-off*	2835	731	0.30	0.78	**1.33 (1.24 to 1.43)**	**0.90 (0.88 to 0.93)**
RR ≥5 above age-specific cut-off†	2465	641	0.26	0.81	**1.35 (1.25 to 1.46)**	**0.92 (0.89 to 0.94)**
RR ≥10 above age-specific cut-off‡	2064	551	0.23	0.84	**1.40 (1.28 to 1.53)**	**0.92 (0.90 to 0.94)**
SpO$_2$ <85%						
RR ≥age-specific cut-off*	1204	342	0.14	0.91	**1.52 (1.36 to 1.71)**	**0.95 (0.93 to 0.96)**
RR ≥5 above age-specific cut-off†	1049	305	0.12	0.92	**1.57 (1.39 to 1.79)**	**0.95 (0.94 to 0.97)**
RR ≥10 above age-specific cut-off‡	887	263	0.11	0.93	**1.62 (1.41 to 1.86)**	**0.96 (0.94 to 0.97)**

Bold values are statistically significant.

*RR of ≥60 per minute in infants <2 months old, >50 per minute in infants 2–11 months old, or ≥40 per minute in children 12–59 months old.

†RR of ≥65 per minute in infants <2 months old, >55 per minute in infants 2–11 months old, or ≥45 per minute in children 12–59 months old.

‡RR of ≥70 per minute in infants <2 months old, >60 per minute in infants 2–11 months old, >50 per minute in children 12–59 months old.

SPO$_2$, oxygen saturation.

used to identify pneumonia in resource-limited settings, including tachypnoea and chest indrawing, had poor specificity for the diagnosis of radiographic pneumonia. The test characteristics of all signs and symptoms did not materially differ based on the presence or absence of wheeze. Our study demonstrates that no individual symptom or physical examination finding was strongly associated with radiographic pneumonia in children. Extreme levels of hypoxaemia were highly specific for radiographic pneumonia, although sensitivity was low. Lower thresholds of hypoxaemia commonly used in clinical settings (ie, <95% and <90%)[19] demonstrated moderate sensitivity and specificity for the identification of radiographic pneumonia.

The WHO guideline recommends oral amoxicillin treatment in children 2–59 months of age with chest indrawing.[12 20] In our analysis, chest indrawing alone was not specific for the radiographic diagnosis of pneumonia. It has been suggested that children with chest indrawing and signs of severe respiratory distress, oxygen desaturations, moderate malnutrition, and unknown HIV-status in HIV-endemic areas be monitored daily or referred for inpatient management given their risk for

decompensation.[21] In a large prospective pneumonia aetiology study in low- and middle-income countries, tachypnoea, hypoxaemia, crackles, and fever were all independently associated with an abnormal chest radiograph.[11] Oxygen desaturation was the most specific single sign for radiographic pneumonia in our study. In a small, retrospective study of 147 children in Rwanda, oxygen desaturation was significantly associated with radiographic pneumonia.[22] In a larger prospective study of nearly 400 children in Norway, hypoxaemia (defined as SpO₂ <92%) independently predicted radiographic pneumonia and was the only clinical feature that predicted radiographic pneumonia.[23] If available, SpO₂ should be measured in children evaluated for pneumonia as the presence of extreme levels of hypoxaemia is highly specific for the diagnosis of radiographic pneumonia.

Although tachypnoea is used to assess for pneumonia in many resource-limited settings, our data showed that commonly used, age-specific RR thresholds were neither sensitive nor specific for the identification of radiographic pneumonia in children. This finding adds further support to the body of evidence suggesting that tachypnoea should not be used as an isolated finding

Table 5 Test characteristics of varying respiratory rates (RRs) with fever (temperature ≥38°C) in children

RR and fever	Patients with RR above threshold, n (n=9410)	Radiographic pneumonia, n (n=2335)	Sensitivity	Specificity	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
Afebrile (temperature <38°C)						
RR ≥age-specific cut-off*	5809	1073	0.46	0.51	**0.94 (0.89 to 0.99)**	**1.06 (1.01 to 1.10**)
RR ≥5 above age-specific cut-off†	4619	856	0.37	0.61	0.94 (0.89 to 1.00)	1.04 (1.00 to 1.07)
RR ≥10 above age-specific cut-off‡	3479	649	0.28	0.71	0.95 (0.88 to 1.02)	1.02 (0.99 to 1.05)
Febrile (temperature ≥38°C)						
RR ≥age-specific cut-off*	3601	787	0.34	0.71	**1.16 (1.09 to 1.24)**	**0.93 (0.91 to 0.96)**
RR ≥5 above age-specific cut-off†	3045	678	0.29	0.76	**1.19 (1.10 to 1.28)**	**0.94 (0.91 to 0.97)**
RR ≥10 above age-specific cut-off‡	2446	564	0.24	0.81	**1.24 (1.14 to 1.35)**	**0.94 (0.92 to 0.97)**

Bold values are statistically significant.
*RR of ≥60 per minute in infants <2 months old, >50 per minute in infants 2–11 months old or ≥40 per minute in children 12–59 months old.
†RR of ≥65 per minute in infants <2 months old, >55 per minute in infants 2–11 months old, or ≥45 per minute in children 12–59 months old.
‡RR of ≥70 per minute in infants <2 months old, >60 per minute in infants 2–11 months old, >50 per minute in children 12–59 months old.

to diagnose pneumonia and subsequently determine which children would benefit from antibiotic treatment.[9] [10] [24] [25] Radiographic pneumonia, though often used as the reference standard for the diagnosis of pneumonia, should be interpreted in the context of its limitations including the potential delayed manifestations of radiographic findings, inability to reliably distinguish bacterial and viral infections, and variable inter-rater reliability among radiologists for certain findings suggestive of pneumonia.[17] Our investigation used primary end point radiographic pneumonia, which was developed for vaccine trials to identify pneumonia that could be prevented by *Streptococcus pneumoniae* and *Haemophilus*

influenzae B vaccines and it became a useful and a sensitive tool to evaluate vaccine outcomes.[26] [27] Primary end point radiographic pneumonia is a subset of all cases of clinical pneumonia.[11] Our finding that tachypnoea is not strongly associated with radiographic pneumonia might partially explain the variable results from randomised trials comparing amoxicillin and placebo among children with fast breathing pneumonia.[28–30] Furthermore, many children receiving a diagnosis of pneumonia in resource-limited settings may harbour other respiratory illnesses such as asthma or other viral infections as demonstrated by the Pneumonia Etiology Research for Child Health study group.[31]

Table 6 Test characteristics of varying oxygen saturations (SpO$_2$) without and with fever (temperature ≥38°C) in children

Fever and SpO$_2$	Patients with symptoms, n (n=11 547)	Radiographic pneumonia, n (n=2323)	Sensitivity	Specificity	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
Afebrile (temperature <38°C)						
SpO$_2$ <95%	4421	870	0.37	0.62	0.97 (0.92 to 1.03)	**1.02 (0.98 to 1.05)**
SpO$_2$ <90%	1827	407	0.18	0.85	**1.14 (1.03 to 1.26)**	**0.97 (0.95 to 0.99)**
SpO$_2$ <85%	810	192	0.08	0.93	**1.23 (1.06 to 1.44)**	0.98 (0.97 to 1.00)
Febrile (temperature ≥38°C)						
SpO$_2$ <95%	2636	666	0.29	0.79	**1.34 (1.24 to 1.45)**	**0.91 (0.88 to 0.93)**
SpO$_2$ <90%	1178	340	0.15	0.91	**1.61 (1.43 to 1.81)**	**0.94 (0.92 to 0.96)**
SpO$_2$ <85%	520	170	0.07	0.96	**1.93 (1.61 to 2.30)**	**0.96 (0.95 to 0.97)**

Bold values are statistically significant.

Treatment decisions for children with suspected pneumonia in low-income and middle-income countries rely largely on clinical findings, including tachypnoea and chest indrawing.[12 13] This allows community health workers and healthcare providers at primary level health facilities to make decisions around antibiotic administration and the need for referral in areas with scarce resources. However, other signs, such as hypoxaemia, are critical to identify as it has been shown to be associated with radiographic pneumonia,[9 24] and carries up to a fivefold increased risk of mortality when compared with children without hypoxaemia in low- and middle-income countries.[32–36] Our study identified extreme levels of hypoxaemia as highly specific for radiographic pneumonia. Though the WHO IMCI chart booklet recommends use of pulse oximetry when available,[12] many low-resource settings lack this tool.[37 38] However, the recent development of low-cost technologies for pulse oximetry,[39] including hardware attached to mobile phones,[40–42] may expand its use in resource-limited settings.

The major strength of our aggregated database containing individual patient-level data is our ability to evaluate the test characteristics of combinations of signs, symptoms, and physical examination findings for the radiographic diagnosis of pneumonia. Prior single-centre studies have not been powered to identify which combinations of clinical findings could be used to identify radiographic pneumonia.[24 43–47] Additionally, prior meta-analyses investigating the test characteristics of clinical signs and symptoms for the prediction of radiographic pneumonia observed that no single sign or symptom was highly accurate for the identification of radiographic pneumonia,[9 10] and discussed the impetus for future studies to allow for the assessment of a combination of signs and symptoms to improve the care of children with suspected pneumonia. In this study, by aggregating patient-level data from ten investigations, we observed that by combining certain signs and symptoms, including tachypnoea, oxygen desaturation, and fever, we were able to improve the discriminator ability to identify radiographic pneumonia. The diagnostic performance of a combination of signs and symptoms should be explored in a prospective fashion to allow for a judicious approach to antibiotic treatment in children with suspected pneumonia.

Limitations

The results of this analysis should be interpreted in the context of their limitations. First, as many studies used in this analysis used the WHO IMCI definition of tachypnoea and lower chest indrawing as an inclusion criterion, there may be overestimation of the true sensitivity and specificity of tachypnoea in the radiographic diagnosis of childhood pneumonia. Also, the inclusion criterion of tachypnoea as defined by WHO thresholds limited our ability to assess the test characteristics of RRs below the WHO thresholds in the radiographic diagnosis of pneumonia. Second, there was no common standardised approach to define radiographic pneumonia across all 10 studies, though most studies included in this analysis used primary endpoint pneumonia or lobar consolidation, which is part of end point pneumonia definition.[16] The inclusion of both primary end point pneumonia and lobar consolidation as the reference standard may have introduced some heterogeneity to our findings but improves the generalisability of our findings to more practical clinical settings. Third, lack of uniformity of recording some signs and symptoms across included studies may have led to overestimation or underestimation of the test characteristics for the signs and symptoms evaluated in this analysis. Fourth, we did not conduct formal statistical analyses to account for heterogeneity in the included studies' inclusion and exclusion criteria. Fifth, there was a high degree of heterogeneity with respect to study types, settings, type of clinician performing the evaluation, and patient population. Lastly, our findings may not be as applicable to extremely resource-limited settings in which chest radiography is not routinely available.

CONCLUSIONS

In this study, including >15 000 children 0–59 months of age, we observed that no individual symptom or physical examination finding was predictive of end point radiographic pneumonia. The presence of tachypnoea as an isolated finding was neither sensitive nor specific, while extreme levels of hypoxaemia was a specific finding among children with radiographic pneumonia. Combinations of commonly used vital signs including temperature, RR and SpO_2 improved the specificity for the identification of radiographic pneumonia.

Author affiliations
[1]Division of Emergency Medicine, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA
[2]Center for Intervention Science in Maternal and Child Health, University of Bergen, Bergen, Norway
[3]Department of Epidemiology, "R. Gutiérrez" Children's Hospital, Buenos Aires, Argentina
[4]Pfizer Vaccines, Collegeville, Pennsylvania, USA
[5]Department of Child Health, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia
[6]Research Institute for Tropical Medicine, Manila, Philippines
[7]PNUD/National University, Montevideo, Uruguay
[8]Institute of Health & Biomedical Innovation @ Centre for Children's Health Research, Queensland University of Technology, South Brisbane, Queensland, Australia
[9]Dirección de Control de Enfermedades Inmunoprevenibles, Ministerio de Salud de la Nación, Buenos Aires, Argentina
[10]Shoklo Malaria Research Unit, Mae Sot, Thailand
[11]Centre for Global Health, Usher Institute, The University of Edinburgh, Edinburgh, Scotland
[12]Institute for Global Health and Development, Queen Margaret University, Edinburgh, Scotland
[13]Research Department, Innlandet Hospital Trust, Lillehammer, Norway
[14]Department of Maternal, Newborn, Child and Adolescent Health and Ageing, World Health Organization, Geneva, Switzerland
[15]Department of Maternal, Newborn, Child and Adolescent Health (Retired), World Health Organization, Geneva, Switzerland
[16]Pneumonia Research Partnership to Assess WHO Recommendations

Twitter Luis Martinez @lmartinezarroyo

ORCID iD
Chris A Rees http://orcid.org/0000-0001-6449-0377

REFERENCES

1 Liu L, Oza S, Hogan D, *et al*. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. *Lancet* 2015;385:430–40.
2 GBD 2017 Lower Respiratory Infections Collaborators. Quantifying risks and interventions that have affected the burden of lower respiratory infections among children younger than 5 years: an analysis for the global burden of disease study 2017. *Lancet Infect Dis* 2020;20:60–79.
3 UNICEF. *Pneumonia and Diarrhoea: Tackling the Deadliest Diseases for the World's Poorest Children*. New York: UNICEF, 2012.
4 Lynch T, Bialy L, Kellner JD, *et al*. A systematic review on the diagnosis of pediatric bacterial pneumonia: when gold is bronze. *PLoS One* 2010;5:e11989.
5 Bradley JS, Byington CL, Shah SS, *et al*. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the pediatric infectious diseases Society and the infectious diseases Society of America. *Clin Infect Dis* 2011;53:e25–76.
6 Cherian T, Mulholland EK, Carlin JB, *et al*. Standardized interpretation of paediatric chest radiographs for the diagnosis of pneumonia in epidemiological studies. *Bull World Health Organ* 2005;83:353–9.
7 Ben Shimol S, Dagan R, Givon-Lavi N, *et al*. Evaluation of the world Health organization criteria for chest radiographs for pneumonia diagnosis in children. *Eur J Pediatr* 2012;171:369–74.
8 Kelly MS, Crotty EJ, Rattan MS, *et al*. Chest radiographic findings and outcomes of pneumonia among children in Botswana. *Pediatr Infect Dis J* 2016;35:257–62.
9 Shah SN, Bachur RG, Simel DL, *et al*. Does this child have pneumonia?: the rational clinical examination systematic review. *JAMA* 2017;318:462–71.
10 Rambaud-Althaus C, Althaus F, Genton B, *et al*. Clinical features for diagnosis of pneumonia in children younger than 5 years: a systematic review and meta-analysis. *Lancet Infect Dis* 2015;15:439–50.
11 Fancourt N, Deloria Knoll M, Baggett HC, *et al*. Chest radiograph findings in childhood pneumonia cases from the multisite PERCH study. *Clin Infect Dis* 2017;64:S262–70.
12 World Health Organization. Integrated management of childhood illness (IMCI): chart booklet, 2014. Available: https://apps.who.int/iris/bitstream/handle/10665/104772/9789241506823_Chartbook_eng.pdf;jsessionid=BE494386E475C23748C604BA2CD963B4?sequence=16 [Accessed 6 Nov 2019].
13 World Health Organization. *Recommendations for management of common childhood conditions: evidence for technical update of pocket book recommendations*. Geneva: WHO, 2012.
14 World Health Organization. Programme for the control of acute respiratory infections. technical bases for the who recommendations on the management of pneumonia in children at first-level health facilities, 1991. Available: https://apps.who.int/iris/bitstream/handle/10665/61199/WHO_ARI_91.20.pdf;jsessionid=8AB3354797C019D582E86BBD09C84A69?sequence=1 [Accessed 6 Nov 2019].
15 Nair H, Simões EA, Rudan I, *et al*. Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis. *Lancet* 2013;381:1380–90.
16 Fancourt N, Deloria Knoll M, Barger-Kamate B, *et al*. Standardized interpretation of chest radiographs in cases of pediatric pneumonia from the PERCH study. *Clin Infect Dis* 2017;64:S253–61.
17 Neuman MI, Lee EY, Bixby S, *et al*. Variability in the interpretation of chest radiographs for the diagnosis of pneumonia in children. *J Hosp Med* 2012;7:294–8.
18 WHO. Integrated management of childhood illness: conclusions. who division of child health and development. *Bull World Health Organ* 1997;75 Suppl 1:119–28.
19 World Health Organization. Oxygen therapy for children: a manual for health workers, 2016. Available: https://apps.who.int/iris/bitstream/handle/10665/204584/9789241549554_eng.pdf;jsessionid=7E6665B4A7D61A95AC8C23FB6E205DD8?sequence=1 [Accessed 15 Oct 2019].
20 World Health Organization. Revised who classification and treatment of childhood pneumonia at health facilities, 2014. Available: https://apps.who.int/iris/bitstream/handle/10665/137319/9789241507813_eng.pdf?sequence=1 [Accessed 15 Nov 2019].
21 McCollum ED, Ginsburg AS. Outpatient management of children with World Health organization chest Indrawing pneumonia: implementation risks and proposed solutions. *Clin Infect Dis* 2017;65:1560–4.
22 Modi P, Munyaneza RBM, Goldberg E, *et al*. Oxygen saturation can predict pediatric pneumonia in a resource-limited setting. *J Emerg Med* 2013;45:752–60.
23 Berg AS, Inchley CS, Fjaerli HO, *et al*. Clinical features and inflammatory markers in pediatric pneumonia: a prospective study. *Eur J Pediatr* 2017;176:629–38.
24 Neuman MI, Monuteaux MC, Scully KJ, *et al*. Prediction of pneumonia in a pediatric emergency department. *Pediatrics* 2011;128:246–53.
25 Shah S, Bachur R, Kim D, *et al*. Lack of predictive value of tachypnea in the diagnosis of pneumonia in children. *Pediatr Infect Dis J* 2010;29:406–9.
26 Mahomed N, Fancourt N, de Campo J, *et al*. Preliminary report from the world health organisation chest radiography in epidemiological studies project. *Pediatr Radiol* 2017;47:1399–404.
27 World Health Organization Pneumonia Vaccine Trial Investigators' Group. Standardization of interpretation of chest radiographs for the diagnosis of pneumonia in children, 2001. Available: https://apps.who.int/iris/bitstream/handle/10665/66956/WHO_V_and_B_01.35.pdf?sequence=1 [Accessed 15 Nov 2019].
28 Ginsburg AS, Mvalo T, Nkwopara E, *et al*. Placebo vs amoxicillin for nonsevere Fast-Breathing pneumonia in Malawian children aged 2 to 59 months: a double-blind, randomized clinical Noninferiority trial. *JAMA Pediatr* 2019;173:21–8.
29 Hazir T, Nisar YB, Abbasi S, *et al*. Comparison of oral amoxicillin with placebo for the treatment of World health organization-defined nonsevere pneumonia in children aged 2-59 months: a multicenter, double-blind, randomized, placebo-controlled trial in Pakistan. *Clin Infect Dis* 2011;52:293–300.
30 Tikmani SS, Muhammad AA, Shafiq Y, *et al*. Ambulatory treatment of fast breathing in young infants aged. *Clin Infect Dis* 2017;64:184–9.
31 Pneumonia Etiology Research for Child Health (PERCH) Study Group. Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study. *Lancet* 2019;394:757–79.
32 Hooli S, Colbourn T, Lufesi N, *et al*. Predicting hospitalised paediatric pneumonia mortality risk: an external validation of RISC and mRISC,

and local tool development (RISC-Malawi) from Malawi. *PLoS One* 2016;11:e0168126.

33 Junge S, Palmer A, Greenwood BM, *et al*. The spectrum of hypoxaemia in children admitted to hospital in the Gambia, West Africa. *Trop Med Int Health* 2006;11:367–72.

34 Usen S, Weber M, Mulholland K, *et al*. Clinical predictors of hypoxaemia in Gambian children with acute lower respiratory tract infection: prospective cohort study. *BMJ* 1999;318:86–91.

35 Onyango FE, Steinhoff MC, Wafula EM, *et al*. Hypoxaemia in young Kenyan children with acute lower respiratory infection. *BMJ* 1993;306:612–5.

36 Lazzerini M, Sonego M, Pellegrin MC. Hypoxaemia as a mortality risk factor in acute lower respiratory infections in children in low and middle-income countries: systematic review and meta-analysis. *PLoS One* 2015;10:e0136166.

37 McCollum ED, Bjornstad E, Preidis GA, *et al*. Multicenter study of hypoxemia prevalence and quality of oxygen treatment for hospitalized Malawian children. *Trans R Soc Trop Med Hyg* 2013;107:285–92.

38 Graham H, Tosif S, Gray A, *et al*. Providing oxygen to children in hospitals: a realist review. *Bull World Health Organ* 2017;95:288–302.

39 Shokouhian M, Morling RCS, Kale I. Low cost MATLAB-based pulse oximeter for deployment in research and development applications. *Conf Proc IEEE Eng Med Biol Soc* 2013;2013:1740–3.

40 Tomlinson S, Behrmann S, Cranford J, *et al*. Accuracy of smartphone-based pulse oximetry compared with Hospital-Grade pulse oximetry in healthy children. *Telemed J E Health* 2018;24:527–35.

41 Petersen CL, Gan H, MacInnis MJ, *et al*. Ultra-low-cost clinical pulse oximetry. *Conf Proc IEEE Eng Med Biol Soc* 2013;2013:2874–7.

42 Jordan TB, Meyers CL, Schrading WA, *et al*. The utility of iPhone oximetry apps: a comparison with standard pulse oximetry measurement in the emergency department. *Am J Emerg Med* 2020;38:925–8.

43 Leventhal JM. Clinical predictors of pneumonia as a guide to ordering chest roentgenograms. *Clin Pediatr* 1982;21:730–4.

44 Lynch T, Platt R, Gouin S, *et al*. Can we predict which children with clinically suspected pneumonia will have the presence of focal infiltrates on chest radiographs? *Pediatrics* 2004;113:e186–9.

45 Mahabee-Gittens EM, Bachman DT, Shapiro ED, *et al*. Chest radiographs in the pediatric emergency department for children. *Clin Pediatr* 1999;38:395–9.

46 Mahabee-Gittens EM, Dowd MD, Beck JA, *et al*. Clinical factors associated with focal infiltrates in wheezing infants and toddlers. *Clin Pediatr* 2000;39:387–93.

47 Mahabee-Gittens EM, Grupp-Phelan J, Brody AS, *et al*. Identifying children with pneumonia in the emergency department. *Clin Pediatr* 2005;44:427–35.

48 Puumalainen T, Quiambao B, Abucejo-Ladesma E, *et al*. Clinical case review: a method to improve identification of true clinical and radiographic pneumonia in children meeting the world Health organization definition for pneumonia. *BMC Infect Dis* 2008;8:95.

49 Arcay JD, Ocampo AF, Solis RK, *et al*. Radiology quality assurance in a developing country setting: the 11-valent pneumococcal conjugate vaccine trial, Bohol, Philippines. *Vaccine* 2007;25:2528–32.

50 Basnet S, Shrestha PS, Sharma A, *et al*. A randomized controlled trial of zinc as adjuvant therapy for severe pneumonia in young children. *Pediatrics* 2012;129:701–8.

51 Gentile Ángela, Juarez MdelV, Luciön MF, *et al*. Influence of respiratory viruses on the evaluation of the 13-valent pneumococcal conjugate vaccine effectiveness in children under 5 years old: a time-series study for the 2001-2013 period. *Arch Argent Pediatr* 2015;113:310–6.

52 Gessner BD, Sutanto A, Linehan M, *et al*. Incidences of vaccine-preventable Haemophilus influenzae type B pneumonia and meningitis in Indonesian children: hamlet-randomised vaccine-probe trial. *Lancet* 2005;365:43–52.

53 Hortal M, Estevan M, Iraola I, *et al*. A population-based assessment of the disease burden of consolidated pneumonia in hospitalized children under five years of age. *Int J Infect Dis* 2007;11:273–7.

54 Tan KK, Dang DA, Kim KH, *et al*. Burden of hospitalized childhood community-acquired pneumonia: a retrospective cross-sectional study in Vietnam, Malaysia, Indonesia and the Republic of Korea. *Hum Vaccin Immunother* 2018;14:95–105.

55 O'Grady K-AF, Torzillo PJ, Ruben AR, *et al*. Identification of radiological alveolar pneumonia in children with high rates of hospitalized respiratory infections: comparison of WHO-defined and pediatric pulmonologist diagnosis in the clinical context. *Pediatr Pulmonol* 2012;47:386–92.

56 Ferrero F, Nascimento-Carvalho CM, Cardoso M-R, *et al*. Radiographic findings among children hospitalized with severe community-acquired pneumonia. *Pediatr Pulmonol* 2010;45:1009–13.

57 Turner C, Turner P, Carrara V, *et al*. High rates of pneumonia in children under two years of age in a South East Asian refugee population. *PLoS One* 2013;8:e54026.