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EVIDENCE-BASED DIAGNOSTICS

Predictors of Airspace Disease on Chest X-ray in Emergency Department Patients With Clinical Bronchiolitis: A Systematic Review and Meta-analysis

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Abstract

Background: An abnormal chest X-ray (CXR) inconsistent with simple bronchiolitis is found in 7%–23% of cases. Despite national guidelines stating "current evidence does not support routine radiography in children with bronchiolitis"; the use of CXR in these patients remains high. Inappropriate use of CXR not only exposes children to excess radiation, but also increases medical costs. The majority of the time, CXRs are obtained to diagnose or rule out pneumonia. We aim to provide an evidence-based approach defining the utility of CXR in bronchiolitis for the diagnosis and treatment of bacterial pneumonia.

Objectives: We performed a systematic review and meta-analysis to describe potential predictors of a CXR with airspace disease in patients with bronchiolitis.

Methods: We searched the medical literature from 1965 to June 2015 in PubMed/EMBASE using the following PICO formulation of our clinical question, "What characteristic(s) of history/physical examination (H&P) and vital signs (VS) in a child with bronchiolitis should prompt the physician to order a CXR?": Patients—pediatric emergency department (ED) patients (<2 years) with clinical bronchiolitis; Intervention—H&P and VS; Comparator—a CXR positive for airspace disease (+CXR), defined as atelectasis versus infiltrate or infiltrate/consolidation; and Outcome—operating characteristics of H&P and VS predicting an +CXR were calculated: sensitivity, specificity, and likelihood ratios (LR+ or LR−). The methodologic quality of the studies was assessed using the quality assessment of studies of diagnostic accuracy tool (QUADAS-2). We created a test–treatment threshold model based on the operating characteristics of the CXR to accurately identify a child with bronchiolitis and a superimposed bacterial pneumonia while accounting for the risks of a CXR and risks of treating patients with and without a bacterial infection.

Results: We found five studies including 1,139 patients meeting our inclusion/exclusion criteria. Prevalence of a +CXR ranged from 7% to 23%. An oxygen saturation < 95% was the predictor with highest LR+ of 2.3 (95% confidence interval = 1.3 to 3.07) to predict a +CXR. None of the H&P and VS variables were found to have sufficiently low LR− to significantly decrease the pretest probability of finding a +CXR. Our test–treatment threshold model showed that hypoxia (O_2 Sat < 95%) alone complicating bronchiolitis did not show a benefit to obtaining a CXR. Our model only suggested that a CXR maybe indicated for a child with hypoxia (O_2 Sat < 95%) and respiratory failure requiring ventilatory support.

Conclusion: No single predictor of a +CXR was of sufficient accuracy to either support or refute ordering a CXR in a child with clinical bronchiolitis. We provide a decision threshold model to estimate a test threshold for obtaining a CXR and a treatment threshold for administering antibiotics. Application of this model requires the clinician to approximate the empiric benefit of antibiotics based on the clinical situation, highlighting the importance of clinical assessment.

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Bronchiolitis is one of the top 10 emergency department (ED) diagnoses during the late fall and winter.[1] Despite the fact that national guidelines state that "When clinicians diagnose bronchiolitis on the basis of history and physical examination, radiographic studies should not be obtained routinely,"[2] the use of radiography in these patients remains high in the ED (65% before and 48.6% after guideline introduction)[3] and far from the benchmark of 17%. This benchmark was computed by Knapp et al.,[4] who looked at 27 hospitals and ranked them in descending order based on the acquisition of chest x-rays (CXR) and then taking the average of the best performing hospitals that comprised at least 10% of the total population.

Physicians evaluating a young child with lower respiratory symptoms in the ED are faced with a particularly daunting challenge. The patient is generally previously unknown to them and are often in the ED as opposed to the office setting because the parents perceive that the illness requires urgent care.[5] Furthermore, children younger than 5 years of age account for 70% of pneumonia hospitalizations in the United States, with the highest incidence among children younger than 2 years old at 62.2/10,000 patients.[6] The fear of missing a case of pneumonia, along with the ease of obtaining a CXR in the ED, are likely major knowledge translation barriers to decreasing the use of CXRs in bronchiolitis.

Excessive use of CXRs not only exposes children to unnecessary radiation, but also increases the financial and time cost of medical care.[7] Furthermore, a study by Schuh et al.[8] suggests that children with clinical bronchiolitis are more likely to receive antibiotics when radiography is performed. These concerns make the frequent use of CXRs in patients with bronchiolitis an ideal subject for a clinical decision rule.[9] In fact, a recent meta-analysis by Rambaud-Althaus et al.[10] failed to identify clinical features predictive of pneumonia in children under 5 years old. These authors suggested that a combination of clinical features with the best likelihood ratios (LRs) to create a decision tree may be helpful.

Evidence-based translational research to prevent the overdiagnosis and overtreatment resulting in increased medical costs, time spent, and complications from unnecessary medications has become a priority in medicine today.[11] Multiple quality improvement methodologies have been used to minimize x-ray use, with varying success.[12,13] Even with these publications, the practices have not yet been translated into clinical practice. We believe that an evidence-based, data-driven, meta-analysis combining clinical predictors of a positive CXR (+CXR), the probability of a CXR diagnosing a pneumonia, and the probably of the pneumonia being of bacterial origin susceptible to antibiotic therapy would provide a rational explanation to forgo a CXR in the majority of bronchiolitic children, despite peer and parental pressure.

METHODS

Search Strategy

The design and manuscript structure of this systematic review and meta-analysis conform to the recommendations from the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement.[14] In conjunction with a medical librarian, we searched the medical literature from January 1965 to June 2015 in PubMed and EMBASE for the search terms: diagnosis of bronchiolitis. Abstracts from Pediatric Academic Societies, American Academy of Pediatrics, Society of Academic Emergency Medicine, and the American College of Emergency Physicians meetings from 2011 to 2015 were also searched. Diagnosis was searched under MeSH headings, diagnosis-related groups, delayed diagnosis, computer-assisted diagnosis, early diagnosis, differential diagnosis, history/physical examination, and vital signs or radiography (see Data Supplement S1, available as supporting information in the online version of this paper)

Our study question was defined as, "What are the predictors of a CXR with airspace disease in pediatric patients presenting to an ED with bronchiolitis?" We chose airspace disease, which includes both infiltrate and atelectasis, since the two are often difficult to distinguish on CXR and as such are both likely to prompt antibiotic use.[15] We developed a search strategy for our clinical question using the following PICO formulation: Patients—pediatric ED patients with clinical bronchiolitis (<2 years old); Intervention—age, history, physical examination, and vital signs; Comparator—a CXR with airspace disease, including atelectasis versus infiltrate and infiltrate/consolidation; and Outcome—operating characteristics of history and physical and vital signs predicting an abnormal CXR were calculated and reported in terms of sensitivity, specificity, and LRs.

Studies were included if they examined patients less than 2 years old with clinical bronchiolitis and used age, historical variables, physical examination, or vital signs to predict the outcome of a CXR that demonstrated airspace disease. Studies were excluded if they did not present the numbers of patients with positive and negative CXR findings with the various predictors or did not provide sufficient data to construct a 2×2 table. The abstracts were hand searched, the full texts of relevant studies were reviewed by two investigators (SA and CL) independently, and discrepancies were resolved by a third author (JC). The searches were combined and limited by human subjects, pediatrics (age < 18 years). For the manuscript that did not provide data sufficient to make a 2×2 table, an attempt was made to contact the author to obtain original data.

Individual Evidence Quality Appraisal

The methodologic quality of the studies was assessed using the quality assessment of studies of diagnostic accuracy tool (QUADAS-2) by 2 investigators independently.[16] QUADAS-2 was piloted on two studies and, after resolving disagreements with discussion, was used on the other three studies. Four domains were assessed for biases. 1) Patient selection—Were the patients enrolled at random or consecutively? Were there inappropriate exclusions? Could the patients included not be representative of the all patients less than 2 years old presenting to the ED with a clinical picture of bronchiolitis? 2) Index test—was the history and physical

examination obtained without knowledge of the CXR results? Were thresholds for vital signs predetermined for the study? Is there concern that the way the history and physical were obtained would be different than done in clinical practice? 3) Reference standard—was a CXR obtained on every patient in the study? Were the radiologists blinded to the clinical findings? Was the way in which the CXR was read applicable to answer the question of if there is airspace disease? 4) Flow and timing—Could the order of how the history and physical and CXR were obtained and read have introduced bias? Studies would be considered low risk of bias if all four domains were rated no bias. An unweighted Cohen's kappa was calculated to measure agreement. To quantify the effect of heterogeneity between studies, the I^2 index, which describes the percentage of total variation across studies due to heterogeneity rather than chance, was calculated.[17]

Data Analysis

Two authors (SM, CL) independently abstracted data from the included studies, and a third author (RS) resolved any discrepancies. Information abstracted included study setting, study inclusion criteria, whether or not there was a finding of infiltrate/atelectasis/consolidation, and diagnostic test properties. Although all studies included cardiac findings as "abnormal," these cases were removed, as they did not fulfill our outcome of interest, which was airspace disease.

Two-by-two tables were constructed to calculate the sensitivity and specificity of various diagnostic variables based on history and physical examination. These include age, history of fever, temperature greater than 38°C, hypoxia (O_2 saturation < 95%), tachypnea (respiratory rate > 60), retractions, crackles, and asymmetric breath sounds. A sensitivity analysis was performed removing the article by Mahabee-Gittens et al. (1999),[18] since it was the only retrospective study. All authors independently checked data abstraction for accuracy. Data analysis was performed using Meta-DiSc (version 1.4, Unit of Biostatistics, Ramon y Cajal Hospital) with a random-effects model.[19]

Test–Treatment Threshold

The Pauker and Kassirer decision threshold model was used to develop a treatment algorithm.[20] This method is based on considering seven variables: false-negative and false-positive proportions, sensitivity, specificity, risk of a diagnostic test, risk of treatment, and anticipated benefit of treatment. Estimates of these variables were abstracted from our systematic review and meta-analysis to derive theoretical test and treatment thresholds for ED patients with bronchiolitis.

RESULTS

Description of Included Studies

A PubMed search identified 275 citations while an EMBASE search identified an additional 648 for a total of 923. There were 126 duplicates. Of the 797 abstracts that were screened, eight were reviewed in entirety,[8,18,21–23] three of which were excluded.[24–26] Five remaining studies comprising 1,139 subjects fulfilled criteria for inclusion in the review[8,18,21–23] (see Figure 1[27]).

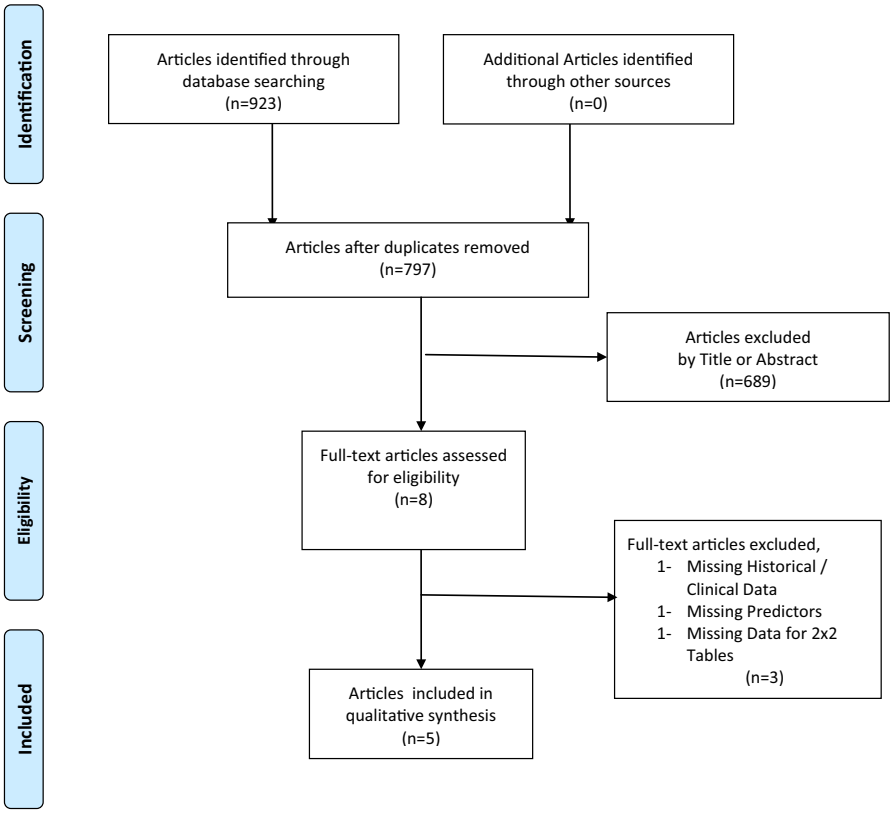

Figure 1. PRISMA flow diagram.[27] For more information, visit www.prisma-statement.org.

The study by Simpson et al.[24] was excluded due to the fact that the maximum age of the patients was unclear, as was the setting where the patients were seen. There was also inadequate historical and clinical data. The study by Dawson et al.[15] only included patients that were admitted to the hospital and also did not provide the necessary predictors. The study by Ecochard-Dugelay et al.[26] did not provide data sufficient to make a 2×2 table, and an attempt was made to contact the author to obtain original data, without success. Review of the bibliographies of pertinent articles did not identify additional studies that met our inclusion and exclusion criteria.

A description of the reviewed studies including study design, subject characteristics, potential predictors of airspace disease, criterion standard, and prevalence of a CXR with airspace disease is included in Table 1. In all studies, the criterion standard was airspace disease on CXR as interpreted by a radiologist. Four of the articles[8,21–23] were prospective, with Mahabee-Gittens et al. (1999)[18] being the one retrospective review.

All of the studies used similar exclusion criteria of complicated history (e.g., known congenital heart disease, chronic systemic disease, cystic fibrosis, sickle cell disease, neuromuscular disease, immunodeficiency). Schuh et al.[8] was the only study to also exclude subjects if they had acute otitis media or if they were "toxic." The five reviewed studies comprised a total of 1,139 subjects, which varied from 140 subjects in Farah et al.[21] to 270 for Mahbee-Gittens et al. (1999).[18]

The potential predictors of airspace disease included temperature of greater than 38°C in all studies. All studies used oxygen saturation as a potential predictor. Farah et al.[21] used less than 95% as the cutoff, whereas three studies[18,22,23] used a cutoff of less than 94% and Schuh et al.[8] used less than or equal to 93% as their outcome variable. Crackles on examination was used as a predictor in four[8,18,21,22] of the five studies. Other examination findings used as predictors were a respiratory rate greater than 60[18,21,22] retractions[18,23] and asymmetric breath sounds.[21,23] The historical predictors of a history of fever and age less than 6 months were examined in both studies by Mahabee-Gittens et al. (1999 and 2000).[18,22]

Individual Evidence Quality Appraisal

Two of the authors (SM and CL) independently rated the QUADAS-2 assessment with a kappa of 1. The methodologic quality of the included studies is summarized in Figure 2.

Despite the fact that both the 1990 and the 2000 studies by Mahabee-Gittens et al.[18,22] allowed patients with prior wheezing episodes to be enrolled, increasing the chance that the patients might have asthma as opposed to bronchiolitis, these studies had the highest prevalence of airspace disease. This is likely because both of the studies by Mahabee-Gittens et al.[18,22] obtained CXRs at physician discretion, which increases the risk of verification bias and elevates the sensitivity.[28] On the other hand, Schuh et al.[8] had the lowest prevalence (6.8%) of airspace disease, which is likely an underestimate since they excluded patients who were "toxic," which, for patients with respiratory illness, likely equates with airspace disease and produces spectrum bias and a decreased sensitivity of the test.[28] Similarly, enrollment into the studies in the studies by Farah et al.[21] and García García et al.[23] was by a practitioner involved in the medical care of the patient, making them at high risk for spectrum bias as well as verification bias.[28]

Additional questions were raised by the study by Mahabee-Gittens et al. (1999)[18] in the reliability of their retrospectively abstracted data. Gilbert et al.[29] has defined eight criteria for retrospective chart reviews to improve accuracy and minimize inconsistencies in data acquisition: 1) training, 2) case selection, 3) definition of variables, 4) abstraction forms, 5) meetings, 6) monitoring, 7) blinding, and 8) testing of interrater agreement. Mahabee-Gittens et al. (1999)[18] failed to document any of these methods to assure unbiased data collection from their medical records. Overall, we rate the quality of the evidence as poor.

Prevalence

We found a weighted prevalence of 15.5% for airspace disease which, varied between our studies with a low of 6.8% (95% confidence interval [CI] = 4.3 to 10.6)[8] to a high of 23.1% (95% CI = 17.9 to 29.3).[18] We conducted a sensitivity analysis by removing the one retrospective study by Mahabee-Gittens et al.[18] with the highest prevalence (23.1%) and Shuh et al.[8] with the lowest (6.8%) that revealed a 16.6% weighted prevalence of airspace disease for the other three reviewed studies, which were in a narrow range of 14.3% to 18.5%.

History and Physical

History and physical examination variables studied are listed in Table 2 with estimates of their operating characteristics. The physical examination finding that had the highest pooled positive likelihood ratio (LR+) was crackles on examination with a LR of 1.69 (95% CI = 1.13 to 2.51) with moderate statistical heterogeneity (I^2 = 51%, chi-square p = 0.12). When the retrospective study by Mahabee-Gittens et al.[18] is removed, the pooled LR+ for crackles on examination is 1.47 (95% CI = 1.1 to 2) with low statistical heterogeneity (I^2 = 0%, chi-square p = 0.5). The historical variable of absence of fever had the lowest pooled negative likelihood ratio (LR−), 0.69 (95% CI = 0.50 to 0.94) with low statistical heterogeneity (I^2 = 0%, chi-square p = 0.57).

Vital Signs

Vital sign variables studied are listed in Table 3 along with estimates of their diagnostic accuracy. The vital sign that had the highest LR+ was hypoxia as defined by an oxygen saturation < 95% but the heterogeneity was too great to pool, and the LR ranged was 1.11 to 3.91. By removing the only retrospective study by Mahabee-Gittens et al. (1999),[18] which also had the lowest specificity (55%), the pooled LR+ was 2.3 (95% CI = 1.73 to 3.16) with low statistical heterogeneity (I^2 = 0%, chi-square p = 0.5) and the pooled LR− was 0.79 (95% CI = 0.69 to 0.89) with moderate statistical heterogeneity (I^2 = 43%, chi-square p = 0.17). When looking for the vital sign with the lowest LR−, the absence of temperature greater than 38°C, the absence

Table 1
Description of Reviewed Studies

Study	Study Design	Subject Characteristics	Potential Predictors of Airspace Disease	Criterion Standard	Abnormal CXR Prevalence (95% CI)
Mahabee-Gittens et al., 1999[18] (United States)	Retrospective CXR at physician discretion	Inclusion: Age < 18 mo Wheezing Exclusion: Complicated history Sample size: 270 Mean age: 7.7 ± 4.9 mo Median age: 7.0 mo Sex: 59% (male)	Temp > 38°C O_2 sat < 93% Crackles RR > 60 Hx fever Age < 6 mo Retractions	CXR: Normal Consistent with asthma Focal infiltrate Other	18.5% (14.3%–23.6%)
Mahabee-Gittens et al., 2000[22] (United States)	Prospective CXR at physician discretion	Inclusion: Age < 18 mo Wheezing Exclusion: Complicated history Sample Size: 212 Mean age: 7.05 ± 5.05 mo Median age: 5.0 mo Sex: 61% (male)	Temp > 38°C O_2 sat < 93% Crackles RR > 60 Hx fever Age < 6 mo Retractions	CXR: Normal Focal infiltrate Pneumonia Consolidation Atelectasis vs. infiltrate	23.1% (17.9%–29.3%)
Farah et al., 2002[21] (United States)	Prospective CXR for all patients	Inclusion: Age < 12 mo First episode wheezing Exclusion: Complicated history Sample size: 140 Ages: 0–3 mo (49%) 3–12 mo (51%) Sex: 61% (male)	Temp > 38°C O_2 sat < 95% Crackles RR > 60 Rhinorrhea Cough Crackles Asymmetric BS	CXR: Normal Infiltrate vs. atelectasis Other	17.1% (11.7%–23.7%)
García et al., 2004[23] (Spain)	Prospective CXR for all patients	Inclusion: Age < 24 mo First episode wheezing Exclusion: Complicated history Sample size: 252 Mean age: 5.7 ± 4.6 mo Median age: 4.0 mo Sex: 61% (male)	Temp > 38°C O_2 sat < 94% Asymmetric BS	CXR: Normal Infiltrate vs. atelectasis Pneumonia Other	14.3% (10.1%–18.5%)
Schuh et al., 2007[8] (Canada)	Prospective CXR for all patients	Inclusion: Age 2–23 mo First episode wheezing Respiratory distress Exclusion: Complicated history Toxic Acute otitis media Sample size: 265 Mean age: 7.5 ± 5.5 mo Sex: 65% (male)	Temp > 38°C O_2 sat < 92% Crackles	CXR: Normal Simple Prominent bronchial markings Peribronchial infiltrates Hyperinflation Atelectasis Complex Simple + adjacent airway disease Inconsistent Lobar infiltrates Cardiomegaly Other	6.8% (4.3%–10.6%)

BS = breath sounds; CXR = chest x-ray; Hx = history; RR = relative risk.

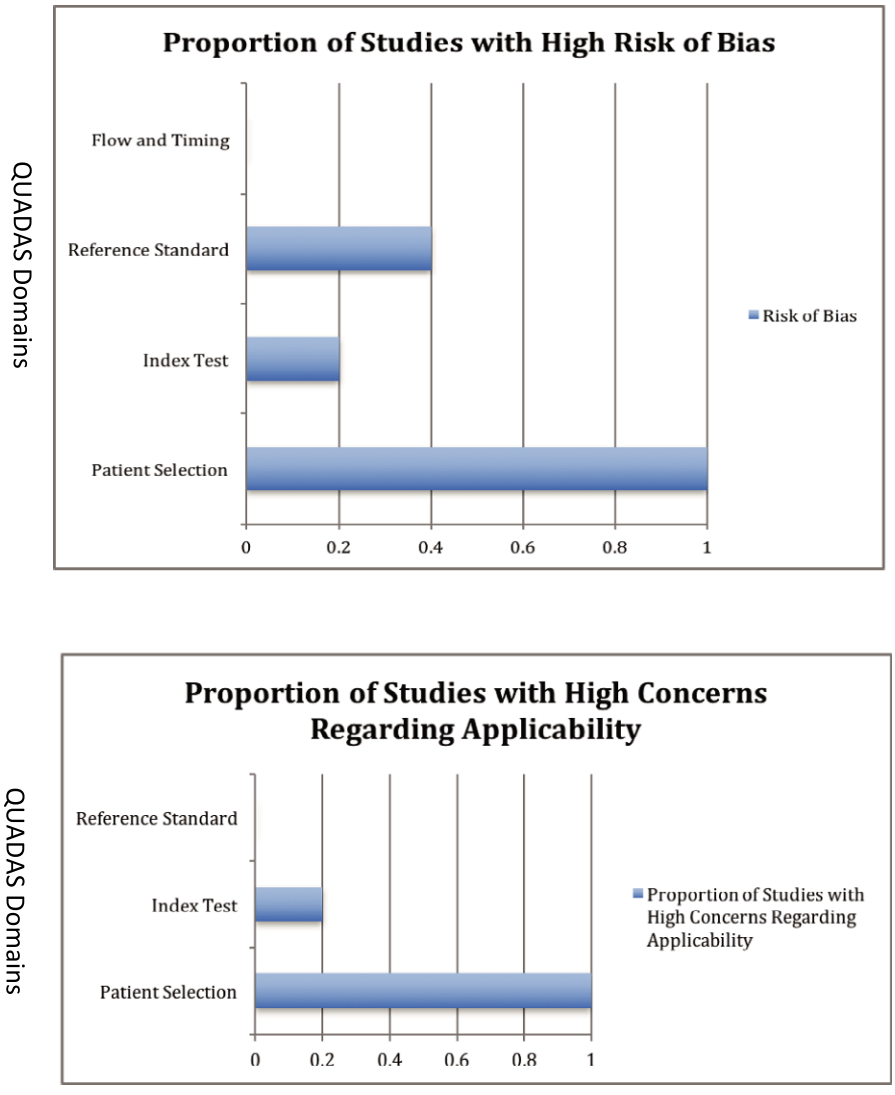

Figure 2. QUADAS-2 assessment of bias.

of oxygen saturation of less than 95%, and the absence of tachypnea of greater than 60 respirations/min were all very close with LR− of between 0.78 and 0.80.

Test–Treatment Threshold Estimates

The question we investigated in this systematic review and meta-analysis is, which characteristics of the history and physical examination would increase the probability of finding a +CXR in children with bronchiolitis. We presumed that the reason for physicians to obtain a CXR in children with a clinical picture of bronchiolitis is to search for bacterial pneumonia and to guide them if antibiotic use might be appropriate. This is why we limited our definition of a +CXR to those with airspace disease.

Figure 3 uses the Pauker and Kassirer decision threshold model[21] to estimate a test threshold for obtaining a CXR and a treatment threshold for administering antibiotics. This is based on the operating characteristics of the CXR to accurately identify a patient without bacterial pneumonia, the risk of treating patients without bacterial disease with antibiotics, the risk of obtaining a CXR, the operating characteristics of a CXR to accurately identify a bacterial pneumonia, and the benefit of antibiotic treatment of children with either a primary or a superimposed bacterial pneumonia. The following describes in detail how the numbers representing these risks were derived.

The operating characteristics of CXR findings for the prediction of bacterial pneumonia are derived from a study by Virkki et al.[30] This study utilized multiple bacteriologic and virologic methods to determine the likely cause of pneumonia in 251 children hospitalized with a +CXR. In a subset of 100 children less than 2 years old, only lobar infiltrates on CXR showed a statistically significant difference in the ability to predict a bacterial etiology. Lobar infiltrates had a sensitivity of 25% and a specificity of 96% in identifying a bacterial cause of pneumonia. These results are also consistent with the findings by Lynch et al.[31] in a systematic review that examined the operating characteristics of CXR for the diagnosis of pediatric bacterial pneumonia. The three studies[32–34] demonstrated relatively low sensitivities (15.8%–75%) and high specificities (50%–100%).

Table 2
Predictors of Airspace Disease: History and Physical Examinations

Predictors of Airspace Disease	Studies	Sample Size	Sensitivity (95% CI)	Specificity 95% CI)	LR+ (95% CI)	LR− (95% CI)
Age < 6 m	Mahabee-Gittens et al., 1999[18]	270	27% (15%–42%)	66% (59%–72%)	0.79 (0.48–1.30)	1.1 (0.91–1.35)
	Mahabee-Gittens et al., 2000[22]	196	60% (44%–74%)	43% (35%–51%)	1.05 (0.80–1.39)	0.93 (0.62–1.39)
Pooled data		*N* = 466	43% (33%–54%) I^2 = 90.4% χ^2 = 0.00	57% (51%–62%) I^2 = 94.7% χ^2 = 0.00	0.98 (0.76–1.27) I^2 = 6.8% χ^2 = 0.30	1.07 (0.90–1.28) I^2 = 0% χ^2 = 0.41
History of fever	Mahabee-Gittens et al., 1999[18]	262	63% (47%–77%)	55% (48%–62%)	1.40 (1.07–1.84)	0.67 (0.45–1.01)
	Mahabee-Gittens et al., 2000[22]	196	69% (54%–82%)	44% (36%–52%)	1.2 (0.96–1.56)	0.71 (0.54–1.40)
Pooled data		*N* = 458	66% (55%–76%) I^2 = 0% χ^2 = 0.55	51% (45%–56%) I^2 = 79% χ^2 = 0.29	1.30 (1.08–1.56) I^2 = 0% χ^2 = 0.46	0.69 (0.50–0.94)) I^2 = 0% χ^2 = 0.86
Retractions	Mahabee-Gittens et al., 1999[18]	270	56% (41%–71%)	32% (26%–39%)	0.83 (0.63–1.08)	1.37 (0.94–1.99)
	Mahabee-Gittens et al., 2000[22]	212	96% (86%–1.0%)	5% (2%–9%)	1.01 (0.94–1.08)	0.83 (1.8–3.79)
Pooled data		*N* = 482	76% (67%–84%) I^2 = 95.8% χ^2 = 0.00	20% (16%–25%) I^2 = 97.9% χ^2 = 0.00	0.93 (0.66–1.30) I^2 = 83.9% χ^2 = 0.01	1.33 (0.93–1.91) I^2 = 0% χ^2 = 0.52
Crackles	Mahabee-Gittens et al., 1999[18]	270	29% (17%–44%)	91% (86%–94%)	3.08 (1.69–5.62)	0.78 (0.65–0.94)
	Mahabee-Gittens et al., 2000[22]	212	45% (31%–60%)	72% (65%–79%)	1.63 (1.09–2.42)	0.76 (0.58–1.00)
	Farah et al., 2002	138	50% (28%–72%)	66% (56%–74%)	1.45 (0.89–2.36)	0.76 (0.49–1.18)
	Schuh et al., 2006[8]	265	21% (6%–46%)	77% (71%–82%)	0.91 (0.37–2.24)	1.03 (0.81–1.31)
Pooled data		*N* = 885	37% (29%–46%) I^2 = 53% χ^2 = 0.09	78% (75%–81%) I^2 = 91.9% χ^2 = 0.00	1.69 (1.13–2.51) I^2 = 50.8% χ^2 = 0.11	0.84 (0.72–0.97) I^2 = 26.9% χ^2 = 0.25
Asymmetric breath sounds	Farah et al., 2002[21]	138	23% (8%–45%)	84% (76%–90%)	1.34 (0.58–3.32)	0.92 (0.73–1.18)
	García García et al., 2004[23]	252	22% (10%–39%)	84% (79%–89%)	1.41 (0.71–7.80)	0.92 (0.77–1.11)
Pooled data		*N* = 390	22% (13%–35%) I^2 = 0% χ^2 = 0.96	84% (80%–88%) I^2 = 0% χ^2 = 0.88	1.40 (0.82–2.40) I^2 = 0% χ^2 = 0.98	0.92 (0.80–1.07) I^2 = 0% χ^2 = 0.99

LR+ = positive likelihood ratio; LR− = negative likelihood ratio.

The variable Rrx is the risk of using antibiotics in a child with purely viral disease. To define this, we looked for the complication rates for antibiotics. In a study by Kaushal et al.,[35] the incidence of adverse drug events, as defined by the Institute of Medicine as "an injury resulting from medical intervention related to a drug," in six outpatient pediatric practices was found to be 16%, most of which were due to antibiotics.

The risk of a CXR, Rt, is determined by the risk of cancer secondary to radiation exposure. Bartley et al.[36] in a case–control study of children aged 0–14 years found an association (odds ratio [OR] = 1.85; 95% CI = 1.12 to 2.79) of acute lymphocytic leukemia (ALL) with any x-ray. Since the OR was so low, we used a relative risk (RR) of 1.85 plus the known lifetime probability of ALL of all children in the United States, which is 0.0141%.[37] Taking these factors into account, this means that the probability of ALL from x-ray exposure = Rt = RR(exposed) × probability of (unexposed) = 0.026%.

Brx is the benefit of treatment. This is defined as the cure rate of antibiotics in a child with clinical bronchiolitis, a +CXR, and bacterial disease. A 2013, Cochrane Review by Lodha et al.[38] of the utility of antibiotics for community acquired pediatric pneumonia failed to find any placebo-controlled randomized controlled trials. Without a placebo to define the spontaneous cure rate without antibiotics, the true benefit of antibiotics for children with bacterial pneumonia cannot be experimentally derived.

In lieu of an experimentally derived number for Brx, and based on a review of the literature, we presume that it is reasonable to estimate that the benefit of antibiotics correlates with the child's clinical condition. Just being admitted for bronchiolitis does not seem to be of sufficient severity to derive a benefit from antibiotics since the majority of the patients in the systematic review of antibiotics for bronchiolitis by Farley et al.[39] were admitted and antibiotics compared to placebo showed no benefit. This is consistent with the findings of Jain et al.,[6] who reviewed 2,638 hospital admissions of children with a diagnosis of pneumonia and a +CXR. They found only 15% of pneumonias to be of bacterial origin, and in children < 2 years, only 7% were bacterial. To support the notion that increased clinical severity corresponds with an increased likelihood of bacterial

Table 3
Predictors of Airspace Disease: Vital Signs

Predictors of Airspace Disease	Studies	Sample Size	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR− (95% CI)
Temperature > 38°C	Mahabee-Gittens et al., 1999[18]	242	31% (18%–47%)	85% (79%–90%)	2.06 (1.18–3.61)	0.81(0.66–1.00)
	Mahabee-Gittens et al., 2000[22]	196	65% (58%–78%)	49% (40%–56%)	1.25 (0.97–1.62)	0.73 (0.42–1.11)
	Farah et al., 2002[21]	133	38% (18%–62%)	78% (69%–85%)	1.71 (0.90–3.25)	0.80 (0.59–1.30)
	Garcia et al., 2004	252	69% (52%–84%)	57% (50%–63%)	1.6 (1.23–2.08)	0.54 (0.33–0.90)
	Schuh et al., 2006[8]	265	42% (20%–67%)	66% (60%–72%)	1.23 (0.71–2.15)	0.88 (0.59–1.30)
Pooled data		*N* = 1,088	51% (43%–59%) I^2 = 77.2% χ^2 p = 0.00	66% (63%–69%) I^2 = 94.6% χ^2 p = 0.00	1.46 (1.24–1.71) I^2 = 0% χ^2 p = 0.43	0.78 (0.68–0.90) I^2 = 0% χ^2 p = 0.57
Oxygen saturation < 95%	Mahabee-Gittens et al., 1999[18]	237	50% (34%–66%)	55% (48%–62%)	1.11 (0.78–1.56)	0.91 (0.65–1.27)
	Mahabee-Gittens et al., 2000[22]	211	31% (19%–46%)	84% (78%–89%)	1.96 (1.13–3.39)	0.82 (0.67–1.00)
	Farah et al., 2002[21]	128	48% (26%–70%)	81% (73%–88%)	2.55 (1.40–4.63)	0.64 (0.42–0.98)
	García García et al., 2004[23]	252	36% (21%–54%)	83% (78%–88%)	2.17 (1.28–3.67)	0.77 (0.60–0.99)
	Schuh et al., 2006[8]	265	26% (9%–51%)	94% (90%–96%)	4.05 (1.66–9.84)	0.79 (0.60–1.03)
Pooled data		*N* = 1,093	38% (31%–47%) I^2 = 34.5% χ^2 p = 0.19	80% (77%–83%) I^2 = 96.2% χ^2 p = 0.00	1.98 (1.30–3.03) I^2 = 66.6% χ^2 p = 0.02	0.80 (0.71–0.90) I^2 = 0% χ^2 p = 0.77
Tachypnea > 60 rpm	Mahabee-Gittens et al., 1999[18]	247	47% (31%–62%)	50% (43%–57%)	0.93 (0.66–1.32)	1.07 (0.78–1.46)
	Mahabee-Gittens et al., 2000[22]	211	31% (19%–46%)	71% (63%–77%)	1.06 (0.66–1.72)	0.97 (0.79–1.21)
	Farah et al., 2002[21]	138	77% (50%–89%)	84% (76%–90%)	4.44 (2.84–7.21)	0.33 (0.16–0.65)
Pooled data		*N* = 596	45% (36%–55%) I^2 = 81.4 χ^2 p = 0.01	65% (61%–69%) I^2 = 95.2% χ^2 p = 0.00	1.62 (0.63–4.22) I^2 = 93.1% χ^2 p = 0.00	0.78 (0.48–1.28) I^2 = 82.8% χ^2 p = 0.00

LR+ = positive likelihood ratio; LR− = negative likelihood ratio.

disease, Bloomfield et al.[40] found bacteremia in only 0.6% of respiratory syncytial virus (RSV)-positive children, but that 2.9% were bacteremic if admitted to the PICU and 6.5% were bacteremic if they had cyanotic heart disease. Furthermore, Levin et al.[41] using blood cultures and tracheal aspirates in intubated children with bronchiolitis, found a 20% prevalence of concomitant bacterial pneumonia and concluded that empiric antibiotics are recommended for children with bronchiolitis and respiratory failure.

Based on the above, we produced three models of test–treatment estimates; the difference in each model is the varying estimate of the benefit of treatment (Brx) with empiric antibiotics. These estimates of Brx must be considered guess-timates based upon the authors' best guesses from our clinical experience. The test–treatment calculator will be available online, so the readers can substitute their own estimates of Brx. We chose a low of Brx = 5%, representative of children with bronchiolitis clinically appropriate for discharge from the ED. A Brx = 20% estimates the clinical severity of a patient appropriate for admission to an inpatient floor. And Brx = 75% represents the patient with respiratory failure, requiring respiratory support in the PICU. As you can see from Figure 2, the estimates of the test and treatment thresholds shift to the left (lower probabilities for testing and treating) as the benefit for empiric antibiotic testing is increased. This means that children with mild or even moderate bronchiolitis who are eventually discharged from the ED are the least likely to have a concomitant bacterial lung infection resulting in a +CXR and have the smallest benefit from antibiotics.

On each model (Brx 5%, Brx 20%, and Brx 75%), the left-most edge of the heavy line defines the lower threshold at which it would be reasonable to obtain a CXR in search of a bacterial pneumonia. The right-most edge of the heavy line is the lower threshold at which it would be reasonable to empirically start treatment for a bacterial pneumonia. The dotted line across the three models reflects the posttest probability of +CXR with an oxygen saturation of <95%. The significance of this will be detailed in the discussion.

DISCUSSION

This systematic review and meta-analysis to answer the question if there are historical or physical examination findings that predict a CXR with airspace disease in the patient with a clinical presentation of bronchiolitis found that the majority of studies were prone to multiple biases. The study by Mahabee-Gittens et al. (1999)[18] was particularly prone to multiple biases related to the study's retrospective study design; it was without adequate safeguards to prevent data entry bias and failed to blind the CXR reviewers to the clinical parameters, which likely lead to a bias in their final reading of the CXRs. The study by Mahabee-Gittens et al. (2000)[22] similarly did not blind the CXR reviewers. Spectrum bias

$T_{testing\ threshold}$ =[(Ppos/nd) × (Rrx) + Rt] ÷ [(Ppos/nd × Rrx) + (Ppos/d × Brx)] = 1) 36%, 2) 12%, 3) 4%
$T_{treatment\ threshold}$ =[(Pneg/nd) × (Rrx) - Rt] ÷ [(Pneg/nd × Rrx) + (Pneg/d x Brx)] =1) 81%, 2) 52%, 3) 22%

Where assumptions are based upon the summary estimates for probability of bacterial superinfection in bronchiolitis with +CXR (lobar infiltrates) *

Ppos/nd = probability of a positive result in patients without disease = 1-specificity = 1-0.96= 0.04*

Pneg/nd = probability of a negative result in patients without disease = specificity = 0.96*

Rrx = risk of treatment in patients without disease = 0.16

Rt = risk of diagnostic test = 0.00026

Ppos/d = probability of a positive result in patients with disease = sensitivity = 0.25*

Pneg/d = probability of a negative result in patients with disease = 1 – sensitivity = 1-0.25= 0.75*

Brx = benefit of treatment in patients with disease = 1) 0.05, 2) 0.20, 3) 0.75

* Virkki et al using Lobar infiltrates ages < 2 years.

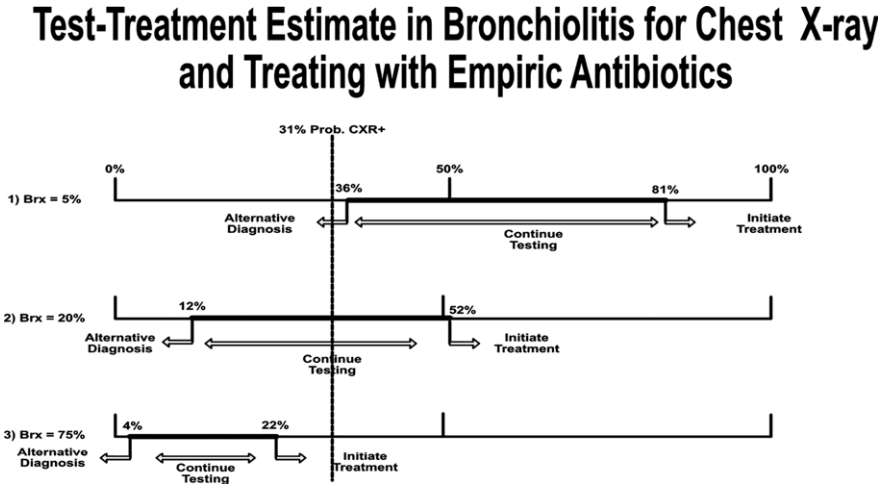

Figure 3. Test–treatment threshold formulas.

was also evident in Mahabee-Gittens et al. (1999),[18] which only enrolled patients who had a CXR performed, in other words, patients in whom the practitioner suspected a finding; this study recorded the highest prevalence (23.1%) of abnormal CXR. The study by Schuh et al.[8] with the lowest prevalence of abnormal CXR (6.8%) may also be subject to spectrum bias by excluding toxic patients, who likely had a higher prevalence of abnormal CXR, but only including patients that were felt to need treatment for their respiratory status. The studies by Farah et al.[21] and the García et al.[23] were also potentially biased by the fact that enrollment was carried out by persons who were both investigator and treating physician.

To minimize the impact of bias, we removed the high +CXR prevalence study by Mahabee-Gittens et al. (1999)[18] as well as the low +CXR prevalence study by Schuh et al.[8] and found a weighted prevalence of a +CXR across the remaining three studies to be 16.8%. We found that history and physical examination findings do not significantly increase or decrease the posttest probability of airspace disease on CXR, with the one exception being an oxygen saturation < 95%. Oxygen saturation < 95% had a LR+ of 2.3, suggesting that children with hypoxia would have the highest probability of having a +CXR. This means that if you have a child with an oxygen saturation of <95% on room air, the posttest probability of a +CXR is increased from 16.8% to ~31%. We found no single variable yielded a posttest probability of +CXR below 16.8%.

A recent systematic review by Farley et al.[39] reviewed seven randomized placebo-controlled studies of antibiotics for bronchiolitis (824 patients) and found no evidence to support antibiotics for bronchiolitis. Unfortunately, these studies failed to consistently control for radiologic findings of patients with airspace disease, and none of the individual studies were sufficiently powered to distinguish if there would be benefit of antibiotic use in those children with a clinical picture of bronchiolitis and a CXR consistent with airspace disease.

In an effort to discern who might benefit from testing with a CXR and/or treatment with antibiotics, the test–treatment threshold diagram provides a visual guide based on the clinical impression of disease severity to provide the pretest probability. For the patient that is clinically appropriate for discharge and unlikely to benefit from antibiotics (Brx = 5%), the testing threshold

estimate is 35%. This means that if the probability of a +CXR is less than 35%, then the risks outweigh the benefits of obtaining a CXR. For this same clinically well group, the treatment threshold is 80%. This means that unless the probability of the patient having a bacterial pneumonia that would benefit from antibiotics is greater than 80%, empiric antibiotics should not be given since the risks outweigh the benefits. To add our clinical predictor of oxygen saturation < 95% into the equation, if a patient has bronchiolitis with hypoxia, the posttest probability of a +CXR is 31%, which is still below the 35% testing threshold. Thus, in the well-appearing child with bronchiolitis and hypoxia, we see no benefit in ordering a CXR or starting antibiotics.

In our second model, Brx = 20%, the testing threshold estimate is 12%, below our 31% probability of a +CXR in the patient with hypoxia, and further testing would be required to get to the treatment threshold of 52%. Put into clinical context, for a patient with bronchiolitis that is appropriate for admission to the floor with hypoxia, it is reasonable to obtain a CXR, but simply having a +CXR does not justify treatment with antibiotics, and it would be desirable to perform further testing with C-reactive protein or procalcitonin[42] to help define whether there is a bacterial source that would benefit from antibiotics.

Based on the third model, where Brx = 75% and the benefit for empiric antibiotics is very high, treatment is appropriate if the estimated probability of a bacterial pneumonia is just 21%, and testing with a CXR should be performed if there is over a 4% estimated probability of bacterial pneumonia. In other words, in children with severe bronchiolitis as defined by respiratory failure, a CXR for the sole purpose of looking for a bacterial pneumonia is superfluous and we agree with Levin et al.[41] that many of these children will have a bacterial super infection and should be treated empirically with antibiotics.

The aim of this systematic review and meta-analysis is not to expect physicians to predict a concomitant bacterial infection in a child with bronchiolitis in their settings and make bedside estimates of posttest probability for each history and physical examination finding. The data are presented to the thoughtful physician as we found it, and while an interactive diagnostic calculator at bedside would be helpful to put treatment decisions in context, it should not be the final determinant of treatment decisions.

When using this calculator, it is important to keep in mind that a CXR is a composite of shadows. The interpretation of CXR by different providers can be highly variable. A study by Johnson and Kline[43] demonstrated that although the intra-rater reliability of CXR interpretation for pneumonia is good for pediatric radiologists (mean $\kappa = 0.87$; 95% CI = 0.60 to 0.99), it is moderate to poor for both junior pediatric EM physicians (mean $\kappa = 0.62$; 95% CI = 0.35 to 0.98) and senior EM physicians (mean $\kappa = 0.68$; 95% CI = 0.40 to 0.95). Interobserver agreement was fair to moderate overall: between pediatric radiologists, $\kappa = 0.51$ (95% CI = 0.39–0.64); between senior EM physicians, $\kappa = 0.55$ (95% CI = 0.41 to 69); and between junior pediatric EM physicians, $\kappa = 0.37$ (95% CI = 0.25 to 0.51). This uncertainty is compounded by the fact that a +CXR in patients with bronchiolitis often influences the physician to inappropriately prescribe antibiotics.[3,8,15]

Taking in all the aforementioned issues, we have provided what we hope is a helpful framework within which one can apply the recommendations that were derived review of the literature and expert consensus by the American Association of Pediatrics[2] that state: "When clinicians diagnose bronchiolitis on the basis of history and physical examination, radiographic or laboratory studies should not be obtained routinely" and "Clinicians should not administer antibacterial medications to infants and children with a diagnosis of bronchiolitis unless there is a concomitant bacterial infection, or a strong suspicion of one."

Implications for Future Research

The ideal future study to clarify the question of which patients with a +CXR and bronchiolitis would benefit from antibiotics should focus on the "intermediate-risk" group of patients, i.e., those admitted to a general floor, for bronchiolitis. These patients require further testing to reach the treatment threshold; thus, examination of a combination of further tests like rapid antigen panels, procalcitonin, and/or C-reactive protein to see if we can improve the "test" to identify those that actually benefit from antibiotics would be helpful. A combination of laboratory and clinical variables is needed since it is known that coinfection with some viruses, specifically RSV, actually increases the virulence of pneumococcus,[44] making a positive test for RSV in itself insufficient testing to decrease the risk to a "safe" threshold. The ideal study design would require bronchiolitis patients with a +CXR and admitted to a general floor (not ICU) to be randomized to antibiotics verses placebo.

Lung ultrasound may be the ultimate tool to distinguish if a patient with clinical bronchiolitis would benefit from antibiotics as it does not involve ionizing radiation and can be performed repeatedly at the bedside. There has been great interest in using lung ultrasound to distinguish bacterial pneumonia from viral processes.[45,46] Again, the ideal study design would be to randomize bronchiolitis patients with a lung ultrasound positive for pneumonia to antibiotic versus placebo. If randomizing patients prospectively is not feasible, then we would propose a large national or international database of patients with bronchiolitis be established so natural clusters of different diagnostic modalities and treatments could be tested retrospectively.

To minimize the spectrum bias and verification bias that we found in our study, we propose that future studies include clinical gestalt as another variable in the prediction of a +CXR. In addition, clinical gestalt, and all the variables in the history and physical should be tested for inter- and intra-relater reliability by kappa statistics. Another tactic to improve the quality of studies about the diagnosis of bronchiolitis is to adhere to the Standards for Reporting of Diagnostic Accuracy Studies 2015 (STARD2015) statement. This statement contains 30 items that have been identified as essential to be reported in a diagnostic accuracy study.[47]

The clinical applicability of future studies could also be improved by focusing on narrower subsets of bronchiolitics: by age and by using rapid antigen testing to

subgroup patients by specific viral agents. This would be helpful due to the fact there is an incredible amount of growth and development that occurs in the first 2 years of life, which mandates subdividing of normal vital signs by age and since bronchiolitis is a constellation of symptoms caused by a variety of viruses as opposed to a single virus.

Once more specific data are gathered, they can be used to create clinical decision rules. The derivation and validation of clinical decision rules should be normalized by racial, ethnic, and even genetic variability. We would also like to see future clinical decision rules to incorporate shared decision-making with families cognizant of the risks and benefits of obtaining CXR and starting empiric antibiotics.

LIMITATIONS

This study has several limitations including that only two databases, PubMed and EMBASE were used to identify studies that met our specific criteria. The results of this review are based on a paucity of studies meeting our criteria, one of which was retrospective in design. Unfortunately, the paucity of rigorous data is not uncommon in pediatric emergency medicine as not only is it a relatively young field, but research involving pediatric patients generally lags that in adults.[48]

Finally, our test–treatment threshold paradigm was based on hypothetical values of the clinical benefits conferred by antibiotics rather than clinical evidence. It is also limited by the quality of the studies used to provide the variables in the equation.

CONCLUSIONS

We found that no single history or physical examination finding had a likelihood ratio high enough to predict a chest x-ray with airspace disease in the patient with a clinical presentation of bronchiolitis. This is not to say that these findings are not of value, since they are necessary to define the at risk population.

We provide a decision threshold model to estimate a test threshold for obtaining a chest x-ray and a treatment threshold for administering antibiotics. Application of this model requires the clinician to approximate the benefit of empiric benefit of antibiotics based on the clinical situation, highlighting the importance of the overall clinical assessment.

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Supporting Information

The following supporting information is available in the online version of this paper:

Data Supplement S1. EMBASE search terms.