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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 air space 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 Exam (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 vs infiltrate or infiltrate/consolidation. Outcome: Operating characteristics of H&P and VS predicting an + CXR were calculated: Sensitivity, Specificity, and Likelihood Ratios (LR+ or LR-). The methodological 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 5 studies including 1,139 patients meeting our inclusion/exclusion criteria. Prevalence of a +CXR ranged from 7%-23%. An oxygen saturation < 95% was the predictor with highest LR+ = 2.3 (95% CI, 1.3-3.07) to predict a +CXR. None of the H&P and VS variables were found to have sufficiently low LR- to significantly decrease the pre-test probability of finding a +CXR. Our test-treatment threshold model showed that hypoxia (O2 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 (O2 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.

INTRODUCTION:

Bronchiolitis is one of the top 10 emergency department (ED) diagnoses during the late fall and winter. Despite the fact that national guidelines state “When clinicians diagnose bronchiolitis on the basis of history and physical examination, radiographic studies should not be obtained routinely”, the use of radiography in these patients remains high in the ED (65% before and 48.6% after guideline introduction) and far from the benchmark of 17%. This benchmark was computed by Knapp et al. who looked at 27 hospitals and ranked them in descending order based on the acquisition of chest x-rays (CXR), 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. Furthermore, children younger than 5 years of age account for 70 percent of pneumonia hospitalizations in the United States, with the highest incidence among children younger than 2 years old at 62.2/10,000 patients. The fear of missing a case of pneumonia, along with the ease of obtaining a chest x-ray 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. Furthermore, a study by Schuh et al 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. In fact, a recent meta-analysis by Rambaud-Althaus et al 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 to create a decision tree may be helpful.

Evidence based translational research to prevent the over diagnosis and overtreatment resulting in increased medical costs, time spent and complications from unnecessary medications has become a priority in medicine today. Multiple quality improvement methodologies have been used to minimize x-ray use, with varying success. Even with these publications, the practices have not yet been translated into clinical practice. We believe an evidence based, data driven, meta-
analysis combining clinical predictors of a positive 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. 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 2011-2015 were also searched. Diagnosis was searched under MeSH headings, diagnosis-related groups, delayed diagnosis, computer-assisted diagnosis, early diagnosis, differential diagnosis, History/Physical exam, Vital Signs or Radiography. (See Appendix A)

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. We developed a search strategy for our clinical question using the following PICO formulation: Patients: Pediatric Emergency Department (ED) patients with clinical bronchiolitis (< 2 years old). Intervention: Age, History, Physical Exam and Vital Signs. Comparator: A CXR with airspace disease, including atelectasis vs infiltrate and infiltrate/consolidation. Outcome: Operating characteristics of History and Physical and Vital Signs predicting an abnormal CXR were calculated and reported in terms of Sensitivity, Specificity, and Likelihood Ratios (LR).

Studies were included if they examined patients less than 2 years old with clinical bronchiolitis and used age, historical variables, physical exam 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 and 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 2x2 table, an attempt was made to contact the author to obtain original data.

Individual evidence quality appraisal:
The methodological quality of the studies was assessed using the quality assessment of studies of diagnostic accuracy tool (QUADAS-2) by 2 investigators independently. QUADAS-2 was piloted on 2 studies and, after resolving disagreements with discussion, was used on the other 3 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 vitals 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 4 domains were rated no bias. An un-weighted 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 Exam. These include age, history of fever, temperature greater than 38°C, hypoxia (O2 saturation less than 95%), tachypnea (respiratory rate greater than 60), retractions, crackles and asymmetric breath sounds. A sensitivity analysis was performed removing the paper by 1999 Mahabee-Gittens et al^{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, Spain) 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, 8 were reviewed in entirety,^{8,18,21-23} 3 of which were excluded^{24-26}. Five
remaining studies comprising 1,139 subjects fulfilled criteria for inclusion in the review.\textsuperscript{8,18,21-23} (See PRISMA Flow Diagram - Figure 1) The study by Simpson W. et al\textsuperscript{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\textsuperscript{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\textsuperscript{26} did not provide data sufficient to make a 2x2 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, gold standard and prevalence of a CXR with airspace disease is included in Table 1. In all studies, the gold standard was airspace disease on CXR as interpreted by a radiologist. Four of the manuscripts\textsuperscript{8,21-23} were prospective, with Mahabee-Gittens et al 1999\textsuperscript{18} being the one retrospective review.

All of the studies used similar exclusion criteria of complicated history (eg. known congenital heart disease, chronic systemic disease, cystic fibrosis, sickle cell disease, neuromuscular disease, immunodeficiency etc). Schuh et al\textsuperscript{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\textsuperscript{21} to 270 for Mahbee-Gittens, 1999.\textsuperscript{18}

The potential predictors of airspace disease included temperature of greater than 38 degrees centigrade in all studies. All studies used oxygen saturation as a potential predictor. Farah et al\textsuperscript{21} used less than 95% as the cut off, whereas three studies\textsuperscript{18,22,23} used a cut off of less than 94% and Schuh et al\textsuperscript{8} used less than or equal to 93% as their outcome variable. Crackles on exam was used as a predictor in four\textsuperscript{8,18,21,22} of the five studies. Other exam findings used as predictors were a respiratory rate greater than 60\textsuperscript{18,21,22}, retractions\textsuperscript{18,23} and asymmetric breath sounds.\textsuperscript{21,23} The historical predictors of a history of fever and age less than 6 months were examined in both the Mahabee-Gittens et al 1999 & 2000 studies.\textsuperscript{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 methodological quality of the included studies is summarized in Figure 2.

Despite the fact that, both the 1990 and 2000 Mahabee-Gittens et al\textsuperscript{18,22} studies 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 air-space disease. This is likely because both of the Mahabee-Gittens et al\textsuperscript{18,22} studies obtained CXRs at physician discretion, which increases the risk of verification bias and elevates the sensitivity.\textsuperscript{27} On the other hand, Schuh et al.\textsuperscript{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.\textsuperscript{27} Similarly, enrollment into the studies in the Farah et al and
Garcia et al studies\textsuperscript{21,23} 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.\textsuperscript{27}

Additional questions were raised by the study by Mahabee-Gittens et al 1999\textsuperscript{18} in the reliability of their retrospectively abstracted data. Gilbert et al\textsuperscript{28} has defined 8 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\textsuperscript{18} fails 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\% CI 4.3-10.6)\textsuperscript{8} to a high of 23.1\% (95\% CI 17.9-29.3)\textsuperscript{18}. We conducted a sensitivity analysis by removing the one retrospective study by Mahabee-Gittens et al\textsuperscript{18} with the highest prevalence (23.1\%) and Shuh et al\textsuperscript{8} with the lowest (6.8\%) that revealed a 16.6\% weighted prevalence of airspace disease for the other 3 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 exam finding that had the highest pooled positive likelihood ratio (LR+) was crackles on examination with a LR of 1.69 (95\% CI 1.13-2.51) with moderate statistical heterogeneity ($I^2=51\%$, $\chi^2$ p=0.12). When the retrospective study by Mahabee-Gittens et al\textsuperscript{18} is removed, the pooled LR+ for crackles on examination is 1.47 (95\% CI 1.1-2) with low statistical heterogeneity ($I^2=0\%$, $\chi^2$ p=0.5). The historical variable of absence of fever had the lowest pooled negative likelihood ratio (LR-), 0.69 (95\% CI 0.50-0.94) with low statistical heterogeneity ($I^2=0\%$, $\chi^2$ 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\textsuperscript{18} which also had the lowest specificity (55\%), the pooled LR+ is 2.3 (95\% CI 1.73-3.16) with low statistical heterogeneity ($I^2=0\%$, $\chi^2$ p=0.5) and the pooled LR- 0.79 (95\% CI 0.69-0.89) with moderate statistical heterogeneity ($I^2=43\%$, $\chi^2$ p=0.17). When looking for the vital sign with the lowest LR-, absence of temperature greater than 38C, absence of oxygen saturation of less than 95\% and absence of tachypnea of greater than 60 respirations per minute 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 H&P would increase the probability of finding a positive CXR in children with bronchiolitis. We presumed that the reason for physicians to obtain a chest x-ray 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 positive chest x-ray (+CXR) to those with air-space disease.

Figure 3 uses the Pauker and Kassirer decision threshold model\textsuperscript{20} 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.\textsuperscript{29} This study utilized multiple bacteriological and virological 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.\textsuperscript{30} in a systematic review which examined the operating characteristics of CXR for the diagnosis of pediatric bacterial pneumonia. The three studies\textsuperscript{31-33} demonstrated relatively low sensitivities (15.8% - 75%) and high specificities (50% - 100%).

The variable $R_{rx}$ 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 R et al.\textsuperscript{34}, 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 6 outpatient pediatric practices was found to be 16%, most of which were due to antibiotics.

The risk of a CXR, $R_t$, is determined by the risk of cancer secondary to radiation exposure. Bartley et al.\textsuperscript{35} in a case-control study of children aged 0-14 years found an association (odds ratio = 1.85 (95% CI, 1.12-2.79)) of Acute Lymphocytic Leukemia (ALL) with any x-ray. Since the odds ratio 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%.\textsuperscript{36} Taking these factors into account, this means that the probability of ALL from x-ray exposure = $R_t = RR(\text{exposed}) \times \text{probability of (unexposed)} = 0.026\%$.

$B_{rx}$ is the benefit of treatment. This is defined as the cure rate of antibiotics in a child with clinical bronchiolitis, a positive CXR and bacterial disease. A 2013, Cochrane Review by Lodha et al.\textsuperscript{37} 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 $B_{rx}$, 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

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majority of the patients in the systematic review of antibiotics for bronchiolitis by Farely et al\textsuperscript{38} were admitted and antibiotics compared to placebo showed no benefit. This is consistent with the findings of Jain et al\textsuperscript{6}, who reviewed 2,638 hospital admissions of children with a diagnosis of pneumonia and a positive CXR. They found only 15\% of pneumonias to be of bacterial origin, and in children < 2yrs, only 7\% were bacterial. To support the notion that increased clinical severity corresponds with an increased likelihood of bacterial disease, Bloomfield et al\textsuperscript{39} found bacteremia in only 0.6\% of 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\textsuperscript{40} 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 estimates based upon the authors’ best guesses from our clinical experience. The test-treatment calculator will be available online, so the reader 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 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 positive 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 post-test probability of positive 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 exam 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\textsuperscript{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 Mahabee-Gittens et al 2000\textsuperscript{22} study similarly did not blind the CXR reviewers.

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Spectrum bias was also evident in Mahabee-Gittens et al 1999, 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 chest x-rays. The study by Schuh et al with the lowest prevalence of abnormal chest x-rays (6.8%) may also be subject to spectrum bias by excluding toxic patients, who likely had a higher prevalence of abnormal chest x-rays, but only including patients that were felt to need treatment for their respiratory status. The Farah et al and the Garcia et al studies were also potentially biased by the fact that enrollment was carried out by persons who were both investigator and treating physician.

In order to minimize the impact of bias, we removed the high +CXR prevalence study by Mahabee-Gittens et al 1999 as well as the low +CXR prevalence study by Schuh et al and found a weighted prevalence of a +CXR across the remaining three studies to be 16.8%. We found that history and physical exam findings do not significantly increase or decrease the post-test 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 post-test probability of a +CXR is increased from 16.8% to ~31%. We found no single variable yielded a post-test probability of +CXR below 16.8%.

A recent systematic review by Farley et al 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 radiological 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 pre-test 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 post-test 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 do further testing with C reactive protein or procalcitonin \(^{41}\) 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\(^{40}\) 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 post-test probability for each history and physical exam finding. The data is 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 chest x-rays by different providers can be highly variable. A study by Johnson et al\(^{42}\) demonstrated that although the intra-rater reliability of CXR interpretation for pneumonia is good for pediatric radiologists (mean kappa = 0.87; 95\% CI 0.60-0.99), it is moderate to poor for both junior pediatric EM physicians (mean kappa = 0.62; 95\% CI 0.35-0.98) and senior EM physicians (mean kappa = 0.68; 95\% CI 0.40-0.95). Inter observer agreement was fair to moderate overall; between pediatric radiologists, kappa = 0.51 (0.39-0.64); between senior EM physicians, kappa = 0.55 (0.41-69), and between junior pediatric EM physicians, kappa = 0.37 (0.25-0.51). 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, ie, 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

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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 co-infection with some viruses, specifically Respiratory Syncytial Virus (RSV), actually increases the virulence of pneumococcus, 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. Again, the ideal study design would be to randomize bronchiolitis patients with a lung ultrasound positive for pneumonia to antibiotic verses 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.

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 two 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 is 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.

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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 exam 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 CXR 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.

REFERENCES:


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<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Subject Characteristics</th>
<th>Potential Predictors of Airspace Disease</th>
<th>Gold standard</th>
<th>Abnormal CXR Prevalence (95% CI)</th>
</tr>
</thead>
</table>
| Mahabee-Gittens et al., 1999 (USA) | • Retrospective CXR at physician discretion | Inclusion:  
  - Age <18 M  
  - Wheezing  
Exclusion:  
  - Complicated History  
  **Sample Size:** 270  
  **Mean Age:** 7.7 +/- 4.9 M  
  **Median Age:** 7.0 M  
  **Gender:** 59% (m) | • Temp > 38C  
  • O2 sat < 93%  
  • Crackles  
  • RR > 60  
  • Hx fever  
  • Age < 6m  
  • Retractions | CXR:  
  - Normal  
  - Consistent with asthma  
  - Focal infiltrate  
  - Other | 18.5% (14.3%-23.6%) |
| Mahabee-Gittens et al., 2000 (USA) | • Prospective CXR at physician discretion | Inclusion:  
  - Age <18 M  
  - Wheezing  
Exclusion:  
  - Complicated History  
  **Sample Size:** 212  
  **Mean Age:** 7.05 +/- 5.05 M  
  **Median Age:** 5.0 M  
  **Gender:** 61% (m) | • Temp > 38C  
  • O2 sat < 93%  
  • Crackles  
  • RR > 60  
  • Hx fever  
  • Age < 6m  
  • Retractions | CXR:  
  - Normal  
  - Focal infiltrate  
  - Pneumonia  
  - Consolidation  
  - Atelectasis vs Infiltrate | 23.1% (17.9%-29.3%) |
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Inclusion</th>
<th>Exclusion</th>
<th>Sample Size</th>
<th>Ages</th>
<th>Gender (%)</th>
<th>CXR</th>
<th>Findings</th>
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</thead>
<tbody>
<tr>
<td>Farah et al., 2002 (USA)</td>
<td>Prospective</td>
<td>Age &lt;12 M, First episode wheezing</td>
<td>Complicated History</td>
<td>140</td>
<td>0-3 M (49%)</td>
<td>3-12 M (51%)</td>
<td>Normal, Infiltrate vs Atelectasis, Other</td>
<td>17.1% (11.7%-23.7%)</td>
</tr>
<tr>
<td></td>
<td>CXR for all patients</td>
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<tr>
<td>Garcia et al., 2004 (Spain)</td>
<td>Prospective</td>
<td>Age &lt;24 M, First episode wheezing</td>
<td>Complicated History</td>
<td>252</td>
<td>Mean Age: 5.7 +/- 4.6 M</td>
<td>Median Age: 4.0 M</td>
<td>Normal, Infiltrate vs Atelectasis, Pneumonia, Other</td>
<td>14.3% (10.1%-18.5%)</td>
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<tr>
<td></td>
<td>CXR for all patients</td>
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<td></td>
<td>Gender: 61% (m)</td>
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<tr>
<td>Schuh et al., 2007 (Canada)</td>
<td>Prospective</td>
<td>Age 2-23 M, First episode wheezing</td>
<td>Complicated History</td>
<td>265</td>
<td></td>
<td></td>
<td>Normal, Simple, Prominent Bronchial Markings, Peribronchial infiltrates, Hyperinflation, Atelectasis, Complex, Simple + Adjacent airway disease, Inconsistent, Lobar Infiltrates</td>
<td>6.8% (4.3%-10.6%)</td>
</tr>
</tbody>
</table>
### Predictors of Airspace Disease

<table>
<thead>
<tr>
<th>Predictors of Airspace Disease</th>
<th>Studies</th>
<th>Sample Size</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>LR+ (95% CI)</th>
<th>LR- (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 6 m</td>
<td>Mahabee-Gittens et al, 1999</td>
<td>270</td>
<td>27% (15-42)</td>
<td>66% (59-72)</td>
<td>0.79 (0.48-1.30)</td>
<td>1.1 (0.91-1.35)</td>
</tr>
<tr>
<td></td>
<td>Mahabee-Gittens et al, 2000</td>
<td>196</td>
<td>60% (44-74)</td>
<td>43% (35-51)</td>
<td>1.05 (0.80-1.39)</td>
<td>0.93 (0.62-1.39)</td>
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<td>43% (33-54)</td>
<td>57% (51-62)</td>
<td>0.98 (0.76-1.27)</td>
<td>1.07 (0.90-1.28)</td>
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<td>$I^2=94.7%$</td>
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<td>$\chi^2=0.30$</td>
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<tr>
<td>History of Fever</td>
<td>Mahabee-Gittens et al, 1999</td>
<td></td>
<td>63% (47-77)</td>
<td>55% (48-62)</td>
<td>1.40 (1.07-1.84)</td>
<td>0.67 (0.45-1.01)</td>
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<td></td>
<td>N=458</td>
<td>66% (55-76)</td>
<td>51% (45-56)</td>
<td>1.30 (1.08-1.56)</td>
<td>0.69 (0.50-0.94)</td>
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<td>69% (54-82)</td>
<td>44% (36-52)</td>
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<tr>
<td><strong>Mahabee-Gittens et al, 1999</strong></td>
<td>270</td>
<td>56% (41-71)</td>
<td>32% (26-39)</td>
<td>0.83 (0.63-1.08)</td>
<td>1.37 (0.94-1.99)</td>
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<td><strong>N=270</strong></td>
<td></td>
<td>32% (26-39)</td>
<td>0.83 (0.63-1.08)</td>
<td>1.37 (0.94-1.99)</td>
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<tr>
<td><strong>Retractions</strong></td>
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<tr>
<td><strong>Mahabee-Gittens et al, 1999</strong></td>
<td>212</td>
<td>96% (86-1.0)</td>
<td>5% (2-9)</td>
<td>1.01 (0.94-1.08)</td>
<td>0.83 (1.8-3.79)</td>
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<td><strong>N=212</strong></td>
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<tr>
<td><strong>Crackles</strong></td>
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<tr>
<td><strong>Mahabee-Gittens et al, 1999</strong></td>
<td>270</td>
<td>29% (17-44)</td>
<td>91% (86-94)</td>
<td>3.08 (1.69-5.62)</td>
<td>0.78 (0.65-0.94)</td>
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<td><strong>N=270</strong></td>
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<tr>
<td><strong>Mahabee-Gittens et al, 2000</strong></td>
<td>212</td>
<td>45% (31-60)</td>
<td>72% (65-79)</td>
<td>1.63 (1.09-2.42)</td>
<td>0.76 (0.58-1.00)</td>
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<tr>
<td><strong>N=212</strong></td>
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<tr>
<td><strong>Farah et al, 2002</strong></td>
<td>138</td>
<td>50% (28-72)</td>
<td>66% (56-74)</td>
<td>1.45 (0.89-2.36)</td>
<td>0.76 (0.49-1.18)</td>
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<tr>
<td>Study</td>
<td>N</td>
<td>Asymmetry (Range)</td>
<td>Reference Range</td>
<td>Odd Ratio (95% CI)</td>
<td>Chi-Squared (df=1)</td>
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<tr>
<td><strong>Asymmetric Breath Sounds</strong></td>
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<tr>
<td>Farah et al, 2002</td>
<td>138</td>
<td>23% (8-45)</td>
<td>84% (76-90)</td>
<td>1.34 (0.58-3.32)</td>
<td>0.92 (0.73-1.18)</td>
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<tr>
<td>Garcia et al, 2004</td>
<td>252</td>
<td>22% (10-39)</td>
<td>84% (79-89)</td>
<td>1.41 (0.71-7.80)</td>
<td>0.92 (0.77-1.11)</td>
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<tr>
<td></td>
<td>N=390</td>
<td>22% (13-35)</td>
<td>84% (80-88)</td>
<td>1.40 (0.82-2.40)</td>
<td>0.92 (0.80-1.07)</td>
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<td></td>
<td>I^2=0%</td>
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<td>(\chi^2=0.96)</td>
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<td>(\chi^2=0.98)</td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Asymmetry (Range)</th>
<th>Reference Range</th>
<th>Odd Ratio (95% CI)</th>
<th>Chi-Squared (df=1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schuh et al, 2006</td>
<td>265</td>
<td>21% (6-46)</td>
<td>77% (71-82)</td>
<td>0.91 (0.37-2.24)</td>
<td>1.03 (0.81-1.31)</td>
</tr>
<tr>
<td><strong>Pooled Data</strong></td>
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<tr>
<td></td>
<td>N=885</td>
<td>37% (29-46)</td>
<td>78% (75-81)</td>
<td>1.69 (1.13-2.51)</td>
<td>0.84 (0.72-0.97)</td>
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<td></td>
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<td>I^2=53%</td>
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<td>I^2=50.8%</td>
<td>(\chi^2=0.11)</td>
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<td>(\chi^2=0.09)</td>
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### Predictors of Airspace Disease

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample Size</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>LR+ (95% CI)</th>
<th>LR- (95% CI)</th>
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<tbody>
<tr>
<td><strong>Temperature &gt;38 C</strong></td>
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<tr>
<td>Mahabee-Gittens et al, 1999</td>
<td>242</td>
<td>31% (18-47)</td>
<td>85% (79-90)</td>
<td>2.06 (1.18-3.61)</td>
<td>0.81 (0.66-1.00)</td>
</tr>
<tr>
<td>Mahabee-Gittens et al, 2000</td>
<td>196</td>
<td>65% (58-78)</td>
<td>49% (40-56)</td>
<td>1.25 (0.97-1.62)</td>
<td>0.73 (0.42-1.11)</td>
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<tr>
<td>Farah et al, 2002</td>
<td>133</td>
<td>38% (18-62)</td>
<td>78% (69-85)</td>
<td>1.71 (0.90-3.25)</td>
<td>0.80 (0.59-1.30)</td>
</tr>
<tr>
<td>Garcia et al, 2004</td>
<td>252</td>
<td>69% (52-84)</td>
<td>57% (50-63)</td>
<td>1.6 (1.23-2.08)</td>
<td>0.54 (0.33-0.90)</td>
</tr>
<tr>
<td>Schuh et al, 2006</td>
<td>265</td>
<td>42% (20-67)</td>
<td>66% (60-72)</td>
<td>1.23 (0.71-2.15)</td>
<td>0.88 (0.59-1.30)</td>
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<td><strong>Pooled Data</strong></td>
<td>N=1,088</td>
<td>51% (43-59)</td>
<td>66% (63-69)</td>
<td>1.46 (1.24-1.71)</td>
<td>0.78 (0.68-0.90)</td>
</tr>
</tbody>
</table>

\[I^2 = 0\%\]

\[\chi^2 = 0\%\]

\[p = 0.57\]

### Oxygen Saturation <95%

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sample Size</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>LR+ (95% CI)</th>
<th>LR- (95% CI)</th>
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<tbody>
<tr>
<td>Mahabee-Gittens et al, 1999</td>
<td>237</td>
<td>50% (34-66)</td>
<td>55% (48-62)</td>
<td>1.11 (0.78-1.56)</td>
<td>0.91 (0.65-1.27)</td>
</tr>
<tr>
<td>Mahabee-Gittens et al, 2000</td>
<td>211</td>
<td>31% (19-46)</td>
<td>84% (78-89)</td>
<td>1.96 (1.13-3.39)</td>
<td>0.82 (0.67-1.00)</td>
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<tr>
<td>Farah et al, 2002</td>
<td>128</td>
<td>48% (26-70)</td>
<td>81% (73-88)</td>
<td>2.55 (1.40-4.63)</td>
<td>0.64 (0.42-0.98)</td>
</tr>
<tr>
<td>Garcia et al, 2004</td>
<td>252</td>
<td>36% (21-54)</td>
<td>83% (78-88)</td>
<td>2.17 (1.28-3.67)</td>
<td>0.77 (0.60-0.99)</td>
</tr>
<tr>
<td>Schuh et al, 2006</td>
<td>265</td>
<td>26% (9-51)</td>
<td>94% (90-96)</td>
<td>4.05 (1.66-9.84)</td>
<td>0.79 (0.60-1.03)</td>
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<table>
<thead>
<tr>
<th>Pooled Data</th>
<th>N=1,093</th>
<th>38% (31-47)</th>
<th>( I^2=34.5% )</th>
<th>( \chi^2 ) p=0.19</th>
<th>80% (77-83)</th>
<th>( I^2=96.2% )</th>
<th>( \chi^2 ) p=0.00</th>
<th>1.98 (1.30-3.03)</th>
<th>( I^2=66.6% )</th>
<th>( \chi^2 ) p=0.02</th>
<th>0.80 (0.71-0.90)</th>
<th>( I^2=0% )</th>
<th>( \chi^2 ) p=0.77</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachypnea &gt;60 rpm</td>
<td>Mahabee-Gittens et al, 1999</td>
<td>247</td>
<td>47% (31-62)</td>
<td>( I^2=34.5% )</td>
<td>( \chi^2 ) p=0.19</td>
<td>50% (43-57)</td>
<td>( I^2=96.2% )</td>
<td>( \chi^2 ) p=0.00</td>
<td>0.93 (0.66-1.32)</td>
<td>( I^2=66.6% )</td>
<td>( \chi^2 ) p=0.02</td>
<td>1.07 (0.78-1.46)</td>
<td>( I^2=0% )</td>
</tr>
<tr>
<td>Mahabee-Gittens et al, 2000</td>
<td>211</td>
<td>31% (19-46)</td>
<td>( I^2=0% )</td>
<td>( \chi^2 ) p=0.77</td>
<td>71% (63-77)</td>
<td>( I^2=96.2% )</td>
<td>( \chi^2 ) p=0.00</td>
<td>1.06 (0.66-1.72)</td>
<td>( I^2=66.6% )</td>
<td>( \chi^2 ) p=0.02</td>
<td>0.97 (0.79-1.21)</td>
<td>( I^2=0% )</td>
<td>( \chi^2 ) p=0.77</td>
</tr>
<tr>
<td>Farah et al, 2002</td>
<td>138</td>
<td>77% (50-89)</td>
<td>( I^2=81.4% )</td>
<td>( \chi^2 ) p=0.01</td>
<td>84% (76-90)</td>
<td>( I^2=95.2% )</td>
<td>( \chi^2 ) p=0.00</td>
<td>4.44 (2.84-7.21)</td>
<td>( I^2=93.1% )</td>
<td>( \chi^2 ) p=0.00</td>
<td>0.33 (0.16-0.65)</td>
<td>( I^2=82.8% )</td>
<td>( \chi^2 ) p=0.00</td>
</tr>
</tbody>
</table>

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PRISMA Flow Diagram

Articles identified through database searching (n=923)

Articles identified through other sources (n=0)

Articles after duplicates removed (n=797)

Articles excluded by Title or Abstract (n=689)

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Articles included in qualitative synthesis (n=5)


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Figure 2. QUADAS-2 Assessment of Bias

Proportion of Studies with High Risk of Bias

- Flow and Timing
- Reference Standard
- Index Test
- Patient Selection

Proportion of Studies with High Concerns Regarding Applicability

- Reference Standard
- Index Test
- Patient Selection

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Figure 3 Test-Treatment Threshold Formulas

\[ T_{testing\ threshold} = \left( \frac{(P_{pos}/nd)}{(R_{x})} + R_{t} \right) = \left( \frac{(P_{pos}/nd \times R_{x})}{(P_{pos}/d \times R_{x})} + (P_{pos}/d \times B_{x}) \right) = 1) \ 36\%, \ 2) \ 12\%, \ 3) \ 4\% \]

\[ T_{treatment\ threshold} = \left( \frac{(P_{neg}/nd)}{(R_{x})} - R_{t} \right) = \left( \frac{(P_{neg}/nd \times R_{x}) - (P_{neg}/nd \times B_{x})}{(P_{neg}/d \times R_{x})} + (P_{neg}/d \times B_{x}) \right) = 1) \ 81\%, \ 2) \ 52\%, \ 3) \ 22\% \]

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

\[ P_{pos}/nd = \text{probability of a positive result in patients without disease} = 1 - \text{specificity} = 1 - 0.96 = 0.04 \]

\[ P_{neg}/nd = \text{probability of a negative result in patients without disease} = \text{specificity} = 0.96 \]

\[ R_{x} = \text{risk of treatment in patients without disease} = 0.16 \]

\[ R_{t} = \text{risk of diagnostic test} = 0.00026 \]

\[ P_{pos}/d = \text{probability of a positive result in patients with disease} = \text{sensitivity} = 0.25^* \]

\[ P_{neg}/d = \text{probability of a negative result in patients with disease} = 1 - \text{sensitivity} = 1 - 0.25 = 0.75^* \]

\[ B_{x} = \text{benefit of treatment in patients with disease} = 1) \ 0.05, \ 2) \ 0.20, \ 3) \ 0.75 \]

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

Test-Treatment Estimate in Bronchiolitis for Chest X-ray and Treating with Empiric Antibiotics

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EMBASE search terms:

('bronchiolitis'/exp OR bronchiolitis OR 'wheezing'/exp OR wheezing) AND ('infant'/exp OR infant OR 'newborn'/exp OR newborn OR 'child'/exp OR child OR pediatric OR paediatric) AND (clinical OR finding OR exam* OR 'history'/exp OR history OR 'fever'/exp OR fever OR 'hypoxia'/exp OR hypoxia OR retraction OR tachypn* OR predict*) AND (cxr OR ('chest'/exp OR chest) AND ('x ray'/exp OR 'x ray')) OR radiograph* OR roentgenogra*) AND ('pneumonia'/exp OR pneumonia OR consolidation OR infiltrate OR ('air'/exp OR air) AND ('space'/exp OR space) AND ('disease'/exp OR disease)) OR 'air space disease' OR abnormal*)

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(((bronchiolitis) OR (wheezing)) AND ((infant) OR (newborn) OR (child) OR (pediatric) OR (paediatric)) AND ((clinical) OR (finding) OR (exam*) OR (history) OR (fever) OR (hypoxia) OR (retraction) OR (tachypn*) OR (predict*)) AND ((cxr) OR (chest x ray) OR (radiograph*) OR (X ray) OR (roentgenogra*)) AND ((pneumonia) OR (consolidation) OR (infiltrate) OR (air space disease) OR (abnormal*)))