abstract

BACKGROUND AND OBJECTIVE: Current guidelines strongly recommend collection of blood cultures (BCs) in children requiring hospitalization for presumed moderate to severe bacterial community-acquired pneumonia (CAP). Our objective was to systematically review the international pediatric literature to evaluate how often BCs are positive in hospitalized children with CAP, identify the most commonly isolated pathogens, and determine the impact of positive BCs on clinical management.

METHODS: We identified articles in PubMed and Scopus published from January 1970 through December 2013 that addressed BCs in children with CAP. We extracted total number of BCs collected and prevalence of positive BCs and used meta-regression to evaluate whether subgroups had any impact on prevalence.

RESULTS: Meta-analysis showed that the overall prevalence of positive BCs was 5.14% (95% confidence interval 3.61–7.28). Studies focusing on severe CAP had a significant effect on prevalence (P = .008), at 9.89% (95% CI 6.79–14.19) compared with 4.17% (95% confidence interval 2.79–6.18) for studies not focusing on severe CAP. The most commonly isolated organisms were Streptococcus pneumoniae (76.7%) followed by Haemophilus influenzae (3.1%) and Staphylococcus aureus (2.1%). Contaminants accounted for 14.7%. Only 3 studies reported on BC-driven change in management, with contrasting findings.

CONCLUSIONS: BCs in pediatric CAP identified organisms in only a small percentage of patients, predominantly S. pneumoniae. False-positive BC rates can be substantial. The 3 studies that examined BC-driven changes in management had conflicting results. This systematic review was limited by heterogeneous case definitions, which may overestimate the true prevalence of positive BCs in hospitalized children.

Guidelines from the Infectious Diseases Society of America on management of community-acquired pneumonia (CAP) in children strongly recommend collection of blood cultures (BCs) in those requiring hospitalization for presumed moderate to severe bacterial CAP. The support for these recommendations, however, is based on low- or moderate-quality evidence. Although management guidelines have demonstrated a decrease in morbidity and mortality in adults with presumed pneumonia, BCs are generally considered to be of limited utility because they infrequently identify organisms and rarely alter antimicrobial management even when positive. Other considerations complicating BC collection in children...
are the high prevalence of viral and mixed bacterial and viral respiratory infections in children,8 the concern for potential discomfort and distress to the child, and the possibility of false-positive BCs leading to unnecessary antimicrobial use and hospitalization.

We performed a systematic review of the literature with 2 objectives: to identify how often BCs were positive and which pathogens were most commonly isolated in hospitalized children with CAP and to determine the impact of positive BCs on antimicrobial management in hospitalized patients.

**METHODS**

**Data Sources**

Pertinent articles were identified using the stepwise approach specified in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement.9 We searched PubMed and Scopus databases to identify articles published in English from January 1970 through December 2013 that addressed BCs in children with CAP. We conducted keyword searches to identify articles with at least 1 of the following Medical Subject Headings terms in the title or abstract: community-acquired infections, community-acquired pneumonia, blood culture, blood/microbiology, infant, child, or adolescent (Table 1). At least 1 of the terms from each category was needed for inclusion. Additional references were identified by hand-searching the reference lists of included articles and snowballing.

**Study Selection**

Two reviewers (PI and EB) independently scored abstracts for relevance to the clinical questions using a validated methodology.10,11 If at least 1 reviewer judged the full text of an article to be clinically relevant, then 2 independent reviewers critically appraised the article using a structured data collection form based on published guidelines.12,13 These 2 reviewers determined by consensus whether the article should be cited in the systematic review. The senior author (PF) assessed the identified articles for completeness.

Criteria for inclusion were studies involving patients up to 18 years of age with a diagnosis of CAP who were evaluated in the emergency department (ED) or hospitalized. CAP was defined as a case with clinical, radiographic, and/or microbiologic diagnosis of pneumonia at time of or within 48 hours of admission to hospital. Studies using an International Statistical Classification of Diseases and Related Health Problems, Ninth Revision (ICD-9) code of pneumonia in any position were also accepted. A positive BC was defined as a BC with growth of an organism. A false-positive BC was defined following the National Healthcare Safety Network definition of skin contaminants.14 To be included in the review, BCs were included only from participants in the study who also met their study's definition of CAP. We included peer-reviewed studies but excluded case reports, guidelines, and reviews if no new data were provided. We excluded studies that were based in the ambulatory setting and those that predominantly included patients with comorbidities (underlying chronic heart and lung conditions, malnutrition, immunodeficiency, or immunosuppression). We also excluded studies evaluating known positive isolates, such as studies evaluating diagnostic methods for detection of Streptococcus pneumoniae in children with pneumonia or studies focusing on pneumonia or invasive disease caused by particular pathogens.

**Quality Assessment**

The methodologic quality of the included studies was evaluated using a modified version of the Downs and Black critical appraisal tool.15 This validated tool comprises 27 questions, each with a maximum score of 1 or 2 points, that address reporting, external validity, internal validity (bias and confounding), and power.15,16 Because the majority of studies were not designed to detect a clinically important effect, we removed power in our modified version. On the basis of the score (assigned by PI), study quality was determined to be excellent (25–27), good (19–24), fair (14–18), or poor (≤13).

**Data Extraction**

Data on total number of BCs collected and prevalence of positive BCs in patients with a diagnosis of pneumonia were extracted. Studies with insufficient data or data that did not
sufficiently differentiate total number of BCs from positive BCs were excluded. Communications were sent to authors if clarifications from a study were needed. The primary outcome was the rate of positive BCs. The secondary outcome was whether there was a change in the antimicrobial prescribed. Data extraction was recorded in Microsoft Excel (version 14.4.4).

**Statistical Analysis**

Statistical modeling was performed using the “metafor” package in R statistical software (version 2.14.1). Logistic transformations were used to calculate the 95% confidence interval (CI) for study-specific prevalence estimates to avoid exceeding the 0–1 limits. Meta-analysis of the prevalence of the positive BCs in patients with CAP was conducted using random effects models to incorporate heterogeneity across studies. Studies were also grouped by study-level characteristics and pooled proportions were calculated within these subgroups using random effects models. We used meta-regression to test differences in the prevalence of positive BCs between particular subgroups, and subgroup meta-analysis was conducted for subgroups with significant impact on prevalence. Publication bias was examined and adjusted by the trim and fill method. The significant level for all tests was set at 5%.

**RESULTS**

The search identified 220 articles of which 199 were systematically excluded, and 21 were included in this review (Fig 1). The studies included 15 prospective and 6 retrospective studies, comprising a total of 8621 patients (Table 2). The majority of studies were from Europe (7), followed by Asia (5), United States (5), the Middle East (2), and South America and Africa (1 each). Studies ranged from publication dates in 1989 to 2013. Ten studies focused on the etiology of CAP. One study was focused on influenza A–related CAP. Two studies examined radiographic features in CAP. Four studies evaluated bacteremia in children with CAP. One study examined management of CAP, and another focused on severe CAP admissions to the ICU. The majority of studies used observational cohort design, except for 1 study that used a nested case-control design.

**Quality Assessment**

The included studies ranged in methodologic quality (Table 3). Six studies were assessed as good, 11 were fair, and 4 were poor. Poorly rated studies suffered from outcomes that were not clearly described, omission of follow-up of participants, and lack of adequate adjustment of confounding in the analyses.

**Diagnostic Criteria**

The diagnostic criteria for CAP were diverse. Only 2 studies had clinical, laboratory, and radiographic criteria for CAP. One study based the diagnosis on clinical features alone, whereas 1 study based the diagnosis on microbiologic data alone and 1 on radiographic findings alone. Four studies identified pneumonia cases using ICD-9 billing codes for pneumonia. Five studies did not document any exclusion criteria.
<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Study Design and Setting</th>
<th>Age (Range)</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Definition of CAP</th>
<th>BCs, n, TP BCs, n (%)</th>
<th>Bacteria Isolated in TP BCs, n (%)</th>
<th>BC-Directed Change in Management</th>
</tr>
</thead>
</table>
| United States                | USA      | Retro, ED                | Median 27 mo (0–21 y) | CXR diagnosis of pneumonia, infiltrate, consolidation                                | Not documented                                                                      | 409; 11 (2.7%); 33 (8.1%)  
  *S. pneumoniae* 10 (23%),  
  *H. parainfluenza* 1 (2%), contaminants 33 (75%)  
  No change in therapy in all cases                                                                                              |  
  | Hickey et al 1996           |          |                          |                                                                                      |                                                                                      |                                                                                                                                  |                                                                                               |                                                                                  |                                                                                   |
| Sandora et al 2009           | USA      | Retro cohort, inpatient  | 18 mo–18 y; 56% <5 y | 18 mo–18 y, *ICD-9* code of pneumonia                                                | CXR findings plus clinical features in a patient not hospitalized or long-term care resident within previous 14 d  
  *ICD-9* code                                                                                                                  | 219; 3 (1.4%); 3 (0.7%)  
  *S. pneumoniae* 4 (14%),  
  *S. aureus* 1 (11%),  
  *H. influenzae* 1 (11%), coagulase-negative  
  *Staphylococcus* 3 (33%)  
  Not documented                                                                                                                |  
  | Shah et al 2017             | USA      | Nested case-control retro, ED | Median 2 y (0–18 y) | ≤18 y, evaluated in ED and *ICD-9* code with CAP                                     | Required hospitalization ≤14 d before diagnosis of pneumonia; immunocompromising/chronic medical condition |                                                                                                                                  |                                                                                               |                                                                                  | 17% had appropriate broadening, 67% had appropriate narrowing; 17% had pathogen not sensitive to empirical therapy |
| Heine et al 2013             | USA      | Retro, inpatient         | Mean 4.9 y (0–18 y) | *ICD-9* code of pneumonia                                                            | Not documented                                                                      | 155; 5 (3.2%); 5 (3.2%)  
  *S. pneumoniae* 3 (30%),  
  *E. coli* 1 (10%),  
  *S. pyogenes* 1 (10%), contaminants 5 (50%)  
  Not documented                                                                                                              |  
  | Myers et al 2013            | USA      | Multicenter retro, inpatient | Median 3.1 y (1.3–6.7 y) | 60 d–18 y, *ICD-9* code of pneumonia/effusion, positive CXR and/or clinical features and laboratory results | Hospitalized since birth, chronic comorbid condition or primary diagnosis of trauma | 369; 26 (70%); 8 (2.2%)  
  *S. pneumoniae* 19 (56%),  
  *H. influenzae* 1 (3%),  
  *S. aureus* 6 (18%), contaminants 8 (24%)  
  39% had therapy broadened, 27% were narrowed, 39% had no change                                                                 |  
  | Western Europe              | UK       | Pro, inpatient            | Median 53 mo, (1 mo–12 y) | 1 mo–14 y with clinical features and positive CXR                                      | Hospital-acquired pneumonia and those with underlying pulmonary or immunologic disease | 57; 2 (3.5%)  
  *S. pneumoniae* 2 (100%)  
  Not documented                                                                                                                  |  
  | Isaacs 1989                 |          |                          |                                                                                      |                                                                                      |                                                                                                                                  |                                                                                               |                                                                                  |  
  | Juven et al 2000            | Finland  | Pro, inpatient            | Mean 3.8 y (0.1–16.7 y) | Children with CAP                                                                      | Fever >37.5°C and/or respiratory symptoms and positive CXR                                                                    | 125; 1 (0.8%)  
  *S. pneumoniae* 1 (100%)  
  Not documented                                                                                                                  |  
<p>| | | | | | | | | |
|                                |          |                          |                                                                                      |                                                                                      |                                                                                                                                  |                                                                                               |                                                                                  |                                                                                   |</p>
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<th>Age (Range)</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Definition of CAP</th>
<th>BCGs, n (%)</th>
<th>TP BCGs, n (%)</th>
<th>FP BCGs, n (%)</th>
<th>Bacteria Isolated in TP BCGs, n (%)</th>
<th>BC-Directed Change in Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moulin et al 2001</td>
<td>France</td>
<td>Pro, inpatient</td>
<td>Mean 1.9 y  (0.4–5 y)</td>
<td>Severe febrile CAP and immunocompetent</td>
<td>Chronic disease, antimicrobial 10 d before admission, not admitted to hospital, or no BC</td>
<td>T &gt;38°C and a positive CXR</td>
<td>88; 10 (11.4%)</td>
<td>-</td>
<td>-</td>
<td>S pneumoniae 10 (100%)</td>
<td>Not documented</td>
</tr>
<tr>
<td>Laundy et al 2003</td>
<td>UK</td>
<td>Pro, ED, out-patient</td>
<td>Median 1.3 y (2 wk–4.8 y)</td>
<td>Children ≤5 y regardless of risk factors</td>
<td>Young children with obvious bronchiolitis</td>
<td>Fever ≥38.5°C and tachypnea per WHO criteria ± cough, with positive clinical exam/CXR</td>
<td>51; 4 (8%)</td>
<td>-</td>
<td>-</td>
<td>S pneumoniae 3 (75%), N meningitidis 1 documented (25%)</td>
<td>Not documented</td>
</tr>
<tr>
<td>Kurz et al 2013</td>
<td>Austria</td>
<td>Pro, inpatient</td>
<td>Median 36 mo (2 mo–17 y)</td>
<td>2 mo–18 y hospitalized with diagnosis of CAP</td>
<td>Preexisting lung disease, immunodeficiency, immunosuppressive therapy</td>
<td>Clinical features, positive CXR</td>
<td>173; 5 (2.9%); 2 (1.2%)</td>
<td>-</td>
<td>-</td>
<td>S pneumoniae 2 (29%), S aureus 1 (14%), M catarrhalis 1 (14%), Rothia 1 (14%), coagulase-negative Staphylococcus 2 (29%)</td>
<td>Narrowing of treatment based on test results</td>
</tr>
<tr>
<td>International</td>
<td></td>
<td></td>
<td>Average 3 y, 7 mo (5 mo–14.5 y)</td>
<td>2 mo–16 y with diagnosis of severe bacterial pneumonia &lt;12 y with CA-LRTI</td>
<td>Not documented</td>
<td>Clinical features, laboratory findings and positive CXR</td>
<td>147; 16 (10.9%); 1 (0.7%)</td>
<td>-</td>
<td>-</td>
<td>S pneumoniae 13 (76%), H influenzae 3 (18%), S viridans 1 (6%)</td>
<td>Not documented</td>
</tr>
<tr>
<td>Leibovitz et al 1990</td>
<td>Israel</td>
<td>Pro, inpatient, out-patient</td>
<td>Mean 0.6 y (1 d–11.8 y)</td>
<td>Nosocomial pneumonia, immuno-compromised host</td>
<td>Cough/fever &lt;2 wk duration, clinical features or positive CXR</td>
<td>Cough/fever &lt;2 wk duration, clinical features or positive CXR</td>
<td>121; 4 (3.3%)</td>
<td>-</td>
<td>-</td>
<td>S pneumoniae 1 (25%), H influenzae 1 (25%), Enterobacter 1 (25%), S pneumoniae, H influenzae 1 (25%)</td>
<td>Not documented</td>
</tr>
<tr>
<td>Chong et al 1997</td>
<td>Singapore</td>
<td>Pro, inpatient</td>
<td>Median 14 m (10 d–12 y)</td>
<td>CA-LRTI, not previously admitted or visited hospital in previous 8 wk</td>
<td>Symptoms &gt;1 wk, chronic disease, bronchial asthma, malnutrition</td>
<td>Symptoms &gt;1 wk, chronic disease, bronchial asthma, malnutrition</td>
<td>390; 38 (9.7%)</td>
<td>-</td>
<td>-</td>
<td>Not documented</td>
<td>Not documented</td>
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<tr>
<td>Hijazi et al 1997</td>
<td>Kuwait</td>
<td>Pro, inpatient</td>
<td>Median 10 wk (2 wk–5 y)</td>
<td>Admitted to PICU; intubated in ER; RR &gt;80–90/min with anticipated apnea; positive CXR</td>
<td>Not documented</td>
<td>Not documented</td>
<td>23; 4 (174%)</td>
<td>-</td>
<td>-</td>
<td>K pneumoniae 2 (50%) not specified 2</td>
<td>Not documented</td>
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<tr>
<td>Delport et al 2002</td>
<td>South Africa</td>
<td>Pro, inpatient</td>
<td>Median 10 wk (2 wk–5 y)</td>
<td>Not documented</td>
<td>Not documented</td>
<td>Not documented</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>K pneumoniae 2 (50%) not specified 2</td>
<td>Not documented</td>
</tr>
</tbody>
</table>
**TABLE 2 Continued**

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Study Design and Setting</th>
<th>Age (Range)</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Definition of CAP</th>
<th>Bacteria Isolated in TP BCs, n (%); FP BCs, n (%)</th>
<th>BC-Directed Change in Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tajima et al 2006</td>
<td>Japan</td>
<td>Pro, inpatient</td>
<td>1 mo–13 y</td>
<td>Initial diagnosis of pneumonia</td>
<td>Not documented</td>
<td>Clinical course before admission, CXR, laboratory tests</td>
<td>157; H influenzae 1 (50%), S pneumoniae 1 (50%)</td>
<td>Not documented</td>
</tr>
<tr>
<td>Secmeer et al 2008</td>
<td>Turkey</td>
<td>Retro, inpatient</td>
<td>Mean 6.5 ± 3.5 y (2–16 y)</td>
<td>2–16 y hospitalized with CAP and parapneumonic effusion</td>
<td>Nosocomial infection</td>
<td>Not documented</td>
<td>98; S pneumoniae 1 (25%), Stenotrophomonas maltophilia 1 (25%), coagulase-negative Staphylococcus 2 (50%)</td>
<td>Not documented</td>
</tr>
<tr>
<td>Ferrero et al 2010</td>
<td>Argentina, Brazil, Dominican Republic</td>
<td>Pro multicenter observational, inpatient</td>
<td>3–59 mo; majority (372%) were 12–23 mo</td>
<td>3–59 mo hospitalized with severe CAP</td>
<td>No evidence of CAP on CXR</td>
<td>Presence of cough/clinical features</td>
<td>2536; S pneumoniae 181 (7.1%); Not documented</td>
<td></td>
</tr>
<tr>
<td>Zhang et al 2011</td>
<td>China</td>
<td>Pro, inpatient</td>
<td>Mean 2.3 y (2–14 y)</td>
<td>2 mo–14 y, admitted directly from community with CAP</td>
<td>Tuberculosis diagnosis, sent to pulmonary hospital for care</td>
<td>Fever ≥37.5°C or respiratory symptoms and positive CXR</td>
<td>821; S pneumoniae 7 (100%); Not documented</td>
<td></td>
</tr>
<tr>
<td>Chen et al 2012</td>
<td>Taiwan</td>
<td>Pro, inpatient</td>
<td>Median 4 y 3 mo (7 mo–16 y, 7 mo)</td>
<td>3 mo–18 y, clinical features, positive CXR</td>
<td>Chronic comorbid disease, malignancy immunodeficiency, or immunosuppression</td>
<td>One clinical feature and positive CXR</td>
<td>209; S pneumoniae 2 (100%); Not documented</td>
<td></td>
</tr>
<tr>
<td>Sur et al 2012</td>
<td>Romania</td>
<td>Pro, inpatient</td>
<td>1–18 y</td>
<td>Clinical features, positive CXR</td>
<td>Underlying lung disease/malformation, nonacute/recurrent pneumonia</td>
<td>Clinical features</td>
<td>560; S pneumoniae 31 (82%), K pneumoniae 4 (11%), H influenzae 3 (8%); Not documented</td>
<td>Not documented</td>
</tr>
<tr>
<td>Lakhani et al 2013</td>
<td>India</td>
<td>Pro, inpatient, rural population</td>
<td>1 mo–5 y; majority (48.5%) were 12–60 mo</td>
<td>Clinically suspected pneumonia</td>
<td>Critical/terminal illness, acute bronchial asthma exacerbation, chronic lung disease; immunocompromise, antimicrobial agents &gt;48 h earlier</td>
<td>WHO classification</td>
<td>66; WHO classification 4 (6.1%); Not documented</td>
<td>Not documented</td>
</tr>
</tbody>
</table>

CA-LRTI, community-acquired lower respiratory tract infection; CXR, chest x-ray; FP, false-positive; IP, inpatient; OP, outpatient; Pro, prospective; Retro, retrospective; RR, respiratory rate; TP, true-positive; WHO, World Health Organization.
Of the 6975 total BCs obtained in pediatric patients with CAP, 425 were positive (6.1%). The proportion of positive BCs in studies of CAP ranged from 0.8% to 17.4% (Table 4). Studies conducted before availability of pneumococcal conjugate vaccine (PCV) had a higher positive BC rate of 7.7% (range 0.8%–17.4%), compared with the post-PCV era, which had a rate of 4.0% (range 0.9%–7.8%).

Of 382 known BC results, the most commonly isolated organisms were *S. pneumoniae* (76.7%), followed by *Haemophilus influenzae* (3.1%) and *Staphylococcus aureus* (2.1%; Table 5). In the pre-PCV era, 83.3% of isolates were *S. pneumoniae*, compared with 61.7% post-PCV. Contaminants accounted for 14.7% of isolates, which in individual studies ranged from 5.9%–75% of positive BCs.27,28,35-41 However, reporting varied across studies, with contaminants documented in all US studies but reported in only 3 studies conducted outside of the United States.27,28,35

### Severity of Disease

Severe disease was part of the inclusion criteria in 4 studies.33,35,36,42 However, only 1 study described parameters of severe disease as admission directly to the PICU or intubation in the ED for anticipated apnea.42 Diagnostic criteria

### Positive BCs

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### TABLE 3 Quality Assessment of the Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Reporting (n/11)</th>
<th>External Validity (n/3)</th>
<th>Internal Validity—bias (n/7)</th>
<th>Internal Validity—Confounding (n/6)</th>
<th>Total Score (n/26)</th>
<th>Quality Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heine et al 201337</td>
<td>9</td>
<td>2</td>
<td>6</td>
<td>3</td>
<td>20</td>
<td>Good</td>
</tr>
<tr>
<td>Kurz et al 201332</td>
<td>7</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>14</td>
<td>Fair</td>
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<tr>
<td>Lakhani et al 201334</td>
<td>6</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>14</td>
<td>Fair</td>
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<td>Myers et al 201335</td>
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<td>2</td>
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<td>3</td>
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<td>Chen et al 201236</td>
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<td>Shah et al 201140</td>
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<td>3</td>
<td>14</td>
<td>Fair</td>
</tr>
<tr>
<td>Hickey et al 199636</td>
<td>8</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>17</td>
<td>Fair</td>
</tr>
<tr>
<td>Leibovitz et al 199037</td>
<td>9</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>16</td>
<td>Fair</td>
</tr>
<tr>
<td>Isaacs 198938</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>12</td>
<td>Poor</td>
</tr>
</tbody>
</table>

### TABLE 4 BC Rates Among Studies

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Studies</th>
<th>Total Patients</th>
<th>Estimate (95% CI)</th>
<th>#</th>
<th>Observed Range of Positive BC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies22-42</td>
<td>21</td>
<td>8621</td>
<td>5.14 (3.61–7.28)</td>
<td>91.3%</td>
<td>0.8–17.4</td>
</tr>
<tr>
<td>Studies pre-PCV22–26,33,35,36,42</td>
<td>9</td>
<td>4301</td>
<td>8.06 (5.74–11.20)</td>
<td>68.6%</td>
<td>0.8–17.4</td>
</tr>
<tr>
<td>Studies post-PCV22–27,33,35,36–41</td>
<td>12</td>
<td>4320</td>
<td>3.04 (1.46–6.21)</td>
<td>83.0%</td>
<td>0.9–7.8</td>
</tr>
<tr>
<td>Prospective studies only22–26,33,35,36–41</td>
<td>15</td>
<td>6035</td>
<td>4.83 (2.98–7.73)</td>
<td>91.2%</td>
<td>0.8–17.4</td>
</tr>
<tr>
<td>Studies pre-PCV22–26,33,35,36–41</td>
<td>8</td>
<td>3892</td>
<td>6.75 (3.6–9.9)</td>
<td>89.6%</td>
<td>0.8–17.4</td>
</tr>
<tr>
<td>Studies post-PCV22,27,29–32,42</td>
<td>15</td>
<td>2143</td>
<td>3.22 (1.09–5.34)</td>
<td>88.5%</td>
<td>0.9–7.8</td>
</tr>
<tr>
<td>US studies27–41</td>
<td>5</td>
<td>2488</td>
<td>6.03 (3.40–10.48)</td>
<td>85.0%</td>
<td>2.2–10.8</td>
</tr>
<tr>
<td>US and Western Europe studies25–27,33,36–41</td>
<td>10</td>
<td>3217</td>
<td>5.79 (3.83–8.66)</td>
<td>75.2%</td>
<td>0.8–11.4</td>
</tr>
<tr>
<td>International studies22–24,26,31,33,35,42</td>
<td>11</td>
<td>5404</td>
<td>4.70 (2.62–8.29)</td>
<td>93.5%</td>
<td>0.8–17.4</td>
</tr>
<tr>
<td>Studies in children ≤523–34,36–42</td>
<td>5</td>
<td>2764</td>
<td>8.35 (6.12–11.28)</td>
<td>29.9%</td>
<td>6.1–17.4</td>
</tr>
<tr>
<td>Studies that focus on severe CAP23–34,35,36–42</td>
<td>4</td>
<td>2794</td>
<td>9.89 (6.79–14.19)</td>
<td>61.6%</td>
<td>7.1–17.4</td>
</tr>
<tr>
<td>Studies that do not focus on severe CAP22–24,31,33,35,42</td>
<td>17</td>
<td>5827</td>
<td>4.17 (2.79–6.18)</td>
<td>85.4%</td>
<td>0.8–10.8</td>
</tr>
</tbody>
</table>

BC, blood culture; CAP, community-acquired pneumonia; PCV, pneumococcal conjugate vaccine
Antimicrobial Therapy

Four studies documented the proportion of patients who were treated with antimicrobial agents before hospitalization. These studies, performed in China, Israel, the United States, and Kuwait, reported preadmission antibiotic rates of 14%, 27%, 36%, and 50%, respectively.24,31,35,41

Seven studies documented antimicrobial therapy at admission.26–28,30,36,37,41 However, these studies did not all clearly indicate whether antimicrobial therapy was given before or after BC collection, and only 3 studies documented whether BC results led to antimicrobial narrowing or broadening.38–40 In the first study, children were evaluated in the ED and appropriate changes in antimicrobial management occurred in all 6 cases of positive BCs.40 In the second, a change in antimicrobial management occurred in more than two-thirds of the positive BCs, as well as in a third of false-positive BCs.39 The third study, which reviewed BCs drawn on 409 pediatric patients in the ED and relied solely on radiographic criteria for the diagnosis of pneumonia, nevertheless found that a positive BC identified in 11 patients did not lead to any changes in their management.38 Overall, combining the data in these 3 studies, BCs led to antimicrobial management changes in 53.5% of the patients for whom BC were positive, and 2.2% of the aggregate population who had BCs drawn.

Meta-analysis Results

There was a high level of heterogeneity across the included studies (P < .001; I² = 91.32%).43 Consequently, we
applied random effects models in our meta-analysis to calculate the prevalence of positive BCs and 95% CI, for all subgroups (Table 4). Meta-regression of the subgroups showed that the only subgroup indicator that had a significant impact on prevalence of positive BCs was severe CAP ($P = 0.008$). Subgrouping also reduced the heterogeneity within the subgroup on severe CAP ($P = 0.040$), which supports our original analysis that severe CAP has a significant impact on prevalence of positive BC.

The effect of meta-regression on the other subgroups were not significant ($P > 0.05$), indicating that the prevalence can be considered the same between subgroups of US and Western Europe studies and international studies, and between subgroups of prospective and retrospective studies. The exception was the subgroup of studies on children $\leq 5$ years ($P = 0.008$). Studies not included in this subgroup covered a broader range of ages (from 0 to 21 years), and meta-regression between these 2 groups did not result in a significant $P$ value ($P = 0.06$). Hence, there is no statistical evidence that studies with children $\leq 5$ years report different prevalence than children of a broader range of ages.

The overall prevalence of positive BCs for all studies was $5.14\%$ (95% CI 3.61–7.28; Fig 2). Studies that focused on severe CAP had a prevalence of $9.89\%$ (95% CI 6.79–14.19), compared with a prevalence of $4.17\%$ (95% CI 2.79–6.18) for studies not focusing on severe CAP.

Funnel plot of the observed studies showed asymmetry and significant publication bias ($P = 0.003$; Fig 3). We then adjusted for publication bias using the trim and fill method.21 This method infers the existence of unpublished hidden studies as determined from a funnel plot, and corrects the meta-analysis by ascribing the presence of missing studies to yield an unbiased pooled estimate. With the adjusted analysis, the overall adjusted prevalence was $4.71\%$ (95% CI 3.07–6.34).

**DISCUSSION**

On the basis of meta-analysis of these studies, children with CAP had positive BCs in $5.14\%$ of cases. However, because of publication bias, the adjusted prevalence is lower at $4.71\%$. The most frequently isolated organisms from the blood of children with CAP were $S$ pneumoniae, $H$ influenzae, and $S$ aureus. These bacteria have been noted to be the predominant causes of severe pneumonia before conjugate vaccines and are similar to the literature in adults.44 Notably, 8 studies in our review were conducted before the licensure of the PCV in 2000,23–26,35,36,38,42 and a ninth study was conducted in South America in which none of the patients had received PCV.33 $S$ pneumoniae remained the predominant pathogen isolated from positive BCs even after introduction of PCV. However, in the post-PCV era, $S$ pneumoniae isolates made up 2.4% of all BC obtained in pediatric CAP compared with 5.6% pre-PCV. This is consistent with other pediatric studies demonstrating efficacy of PCV in reducing cases of invasive pneumococcal disease as well as pneumococcal pneumonia45,46 and suggests that in countries with high PCV uptake, the likelihood of a positive BC is low.

Geographic differences in BC positivity and predominant organisms isolated were evident, although no significant

![Forest plot demonstrating the pooled prevalence of positive BCs in pediatric CAP. Pooled prevalence was calculated using random effects (RE) models using the DerSimonian-Laird method.](http://hosppeds.aappublications.org/)

**FIGURE 2** Forest plot demonstrating the pooled prevalence of positive BCs in pediatric CAP. Pooled prevalence was calculated using random effects (RE) models using the DerSimonian-Laird method.
differences were seen on meta-regression. US and Western European studies had a combined BC positivity rate of 5.79% (95% CI 3.83–8.66), with *S. pneumoniae* accounting for 44.4% of isolates followed by *S. aureus* at 6.5% and *H. influenzae* at 2.4%. International studies had a combined BC positivity rate of 4.70% (95% CI 2.62–8.29) with 92.2% of isolates identified as *S. pneumoniae*, followed by *H. influenzae* at 3.5% and *K. pneumoniae* at 2.3%. We excluded studies that evaluated diagnostic methods for detection of *S. pneumoniae* in children with pneumonia to reduce selection bias. If we had included other diagnostic methods in addition to culture, such as polymerase chain reaction or antigen testing, rates of *S. pneumoniae* identification would have been even higher.

Collection of BCs in all patients with pneumonia has traditionally been considered a marker of high-quality care. The American Thoracic Society has recommended this test since the 1990s as part of the initial evaluation of patients with CAP. This recommendation was based on the belief that BC results facilitate more effective antimicrobial treatment because bacteremia reflects more severe disease and a higher risk of mortality. In adults, BC in management of pneumonia was adopted as a quality measure after a study showed that BCs obtained within 24 hours of admission were associated with lower 30-day mortality. However, there were concerns about selection bias and confounding by variations in hospital quality. In addition, the mean age of patients was 79 years, and 58% of the patients had at least 1 comorbid illness, features that are generally not applicable to the pediatric population.

The studies included in this review all lacked a study design that rigorously evaluated the value of BC in management of pediatric CAP. There were no randomized controlled studies, and the majority of studies were observational. In the few studies that listed severity of CAP as criteria for inclusion, the study’s diagnostic criteria were not always reflective of severe disease. None of the studies required collection of BC in all patients admitted with CAP. Because the majority of hospitalized patients with CAP may not have been perceived to have a high probability of bacteremia, this selection bias for BC collection in more ill-appearing patients may have resulted in higher rates of documented bacteremia.

Only 3 studies documented antimicrobial changes in management based on BC results, and all 3 studies had differing results. However, the study showing that positive BC did not lead to any change in antimicrobial management was performed almost 2 decades ago and may not reflect current management practice. In addition, none of these studies documented poor clinical outcomes for patients with either positive or negative BCs.

This impact of diagnostic testing on clinical outcomes has been an area of increasing scrutiny. Studies in the pediatric population have demonstrated that diagnostic testing has been shown to

![Funnel plot testing for publication bias in studies of positive BCs in pediatric CAP. Solid circles are observed studies. Empty circles are filled studies by the trim and fill method.](http://hosppeds.aappublications.org/)
lead to higher hospitalization rates but no significant difference in ED revisit rates, nor to significant changes in clinical management. Other studies have demonstrated the low yield of positive cultures, the lack of sensitivity in detecting bacterial pneumonia, and the low impact that positive cultures have on altering antimicrobial treatment. On the basis of the combined data from the 3 studies that documented antimicrobial changes in management, therapy changes occurred in only slightly more than of the cases. However, this accounted for 2.2% of the total population in these studies who had BCs drawn.

Our review of the literature did point out situations in which BC collection is likely to be most helpful. The highest yield of positive BCs in studies were from patients who were manifestly sick, and severe CAP was the only subgroup that had a significant effect on prevalence in the meta-regression model. However, we were unable to determine the benefit of BC collection in cases of presumed moderate CAP, as is suggested by the current guidelines, because the majority of studies did not stratify patients by severity of illness.

This is also complicated by the substantial number of false-positive BCs in these studies, ranging from 0.7% to 8.1% of all BCs collected, which correlates with findings in adult pneumonia studies. Contaminants were reported in all the US studies and this may lead to higher hospitalization rates but not to significant changes in clinical management. Other studies have demonstrated the low yield of positive cultures, the lack of sensitivity in detecting bacterial pneumonia, and the low impact that positive cultures have on altering antimicrobial treatment. On the basis of the combined data from the 3 studies that documented antimicrobial changes in management, therapy changes occurred in only slightly more than of the cases. However, this accounted for 2.2% of the total population in these studies who had BCs drawn.

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Our review was limited not only by the discrepancy in reporting of contaminants but also by the varied criteria used to diagnose pneumonia in children. Several studies used World Health Organization criteria that defines mild to moderate CAP based on cough and tachypnea. This definition is clearly limited because it is nonspecific for all types of lower respiratory tract disease. Other studies did not provide a case definition of CAP, although this was implied by their inclusion criteria and thus were included in the review. Nonetheless, this may affect the consistency of the included studies. Heterogeneity of case definitions was a major limitation, which may overestimate the true prevalence of positive BCs in hospitalized children. Although there was variation in results, there was consistency in the direction of effect, and therefore it was reasonable to calculate an average prevalence based on the included studies. We also accounted for this by performing a random effects model on the data as well as the subgroups to incorporate heterogeneity among studies, meta-regression to investigate differences for categorical explanatory variables among subgroups, and regression coefficients to evaluate differences between subgroups. However, comparisons of subgroups where there are overlapping studies may not be meaningful, as these are observational by nature and are not based on randomized comparisons.

In addition, false-negative and false-positive significance tests increase in likelihood rapidly as more subgroup analyses are performed.

Next, our review included retrospective studies, and this may lead to sampling bias, even though when we restricted our analysis to prospective studies, we had similar results, and no difference was determined on meta-regression. We did find evidence of publication bias in the included studies, but adjusted for it in our analyses. Although we excluded studies that predominantly involved patients with comorbidities, some studies did include patients with comorbidities in their analysis, most commonly asthma. The comorbid population accounted for roughly 6% of all hospitalized patients with CAP in our review, not large enough to shift the context of our findings. In addition, since the introduction of conjugate vaccines for H influenzae type b and S pneumoniae, rates of associated pneumonia in children have decreased. We attempted to account for this in our analysis by stratifying our data into pre- and post-PCV eras, but this review may consequently not reflect the current epidemiology.

This systematic review furthers our general understanding of the utility of BC in evaluation of pediatric CAP. Given that the heterogeneous study designs and case definitions may lead to overestimation of the prevalence of positive BCs, the true prevalence may be <4.71%. Additional data from ongoing projects such as the Pneumonia Etiology Research for Child Health (PERCH) will assist countries in making program decisions on health investment priorities, and provide evidence for clinicians to revise their protocols and guidelines for empirical therapy regimens. PERCH can also serve as a model for further studies in pediatric CAP, where research should attempt to quantify the true risk for bacteremia in pediatric patients with CAP, and assess the impact of bacteremia on...
clinical outcomes. Studies determining whether BC collection is cost-effective in patients hospitalized with moderate CAP may help inform whether admission to hospital is sufficient justification for this procedure. Further studies are needed to evaluate whether BCs in moderate to severe CAP in children shorten hospital stay, reduce complications, and decrease mortality.

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REFERENCES
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(Continued on First page)

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