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Draft Evidence Report

Number XXX

Diagnosis and Management of Febrile Infants (0-3 Months)

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments. To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. Comments may be sent by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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Structured Abstract

Objectives: To systematically review evidence on diagnostic accuracy of testing for serious bacterial illness (SBI) and invasive herpes simplex virus (HSV) infection; ascertain harms and benefits of various management strategies; compare prevalence of SBI and HSV between different clinical settings; and determine how well the presence of viral infection predicts against SBI for febrile infants aged 0 – 3 months. Additionally, evidence on parental compliance to return for followup assessments was reviewed in infants less than 6 months of age.

Data Sources: MEDLINE (1950 to 2010), CINAHL (1982 - 2008), EMBASE (1980 to 2010), Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews. Abstracts in the websites of relevant organizations were searched to identify any unpublished materials.

Review Methods: Two independent reviewers screened the literature (title, abstract, full text) and extracted data on population characteristics, index/diagnostic test characteristics (e.g., sensitivity, specificity). Diagnostic test accuracy studies were assessed using Quality Assessment of Diagnostic Accuracy Studies.

Results: Eighty-three studies were included. The review identified: a) combined laboratory plus clinical (e.g., Philadelphia protocol, Boston, Rochester), b) clinical, and c) laboratory criteria used for predicting SBI in febrile infants. The diagnosis of UTI accounted for the greatest proportion of SBI (> 67 percent). The prevalence rate of bacteremia and meningitis were 12.9, and 4.1 percent, respectively. *Escherichia coli* was the identified pathogen in 60 percent of cases of SBI.

The Rochester and Philadelphia demonstrated similar diagnostic accuracy in predicting risk of SBI or bacteremia (AUC: 73.0 percent and 75.0 percent, respectively). The Milwaukee criteria had a similar sensitivity for predicting SBI as Philadelphia and Rochester criteria (96.0 percent vs. 93.0-94.0 percent), however its specificity was lower (28.0 percent vs. 46.0 -56.2 percent). The Boston and Philadelphia demonstrated higher sensitivity but lower specificity in older infants (age: > 28 days) compared to neonates (age: 0 – 28 days) for total SBI or bacteremia. The Rochester criteria were more accurate in neonates vs. older infants. Laboratory criterion (procalcitonin) levels demonstrated better overall accuracy for infants older than 28 days of age (AUC: 85.0 percent) compared to neonates 28 days or younger (AUC: 73.0 percent).

Evidence on HSV was scarce. In one study, the use of cerebrospinal fluid (CSF) pleocytosis predicted risk of HSV in neonates with sensitivity of 66.6 percent and specificity of 74.6 percent.

There was little evidence on harms of delayed diagnosis/management of infants with SBI misclassified as low-risk. Most of these infants were initially discharged but later hospitalized and treated with antibiotics without any adverse outcomes. Evidence regarding benefits or harms of immediate antibiotic treatments was either lacking or poorly reported. Some complications reported in two studies were drug-related rash (0.4 percent), infiltration of intravenous line (19.0 percent), and intravenous access problems (15.6 percent).

There was a higher prevalence of SBI (mainly due to UTI) in infants without viral infection or clinical bronchiolitis compared to infants with viral infection or bronchiolitis.

In North America, prevalence rate of SBI ranged from 4.1 to 25.1 percent and in a primary care setting, this range was 9.9 -10.3 percent. Prevalence of total SBI was higher in neonates compared with older infants (12.4 vs. 8.6 percent).

The parental compliance to followup regarding return visits/reassessment of infants after initial examination across four studies ranged from 77.4 to 99.8 percent. There was no evidence to determine the influence of parental factors and clinical settings on parental compliance rates.

Conclusions: Overall, the focus of the literature has been on ruling out SBI. Harms associated with testing or management strategies have been poorly reported. Attempts to identify high risk groups, as described in the minority of reports, were not accurate. The Boston, Philadelphia, Rochester, and Milwaukee were fairly accurate in identifying a low risk group for SBI in infants younger than 3 months of age. The diagnosis of a viral infection or clinical bronchiolitis significantly decreased the chances of a serious bacterial illness. Invasive herpes simplex virus infection is a significant differential diagnosis in the febrile infant, yet the relevant literature is presented from the diagnosis rather than from the syndrome point of view, making it difficult to draw conclusions of test accuracy or management efficacy in an undifferentiated febrile infant. Although crucial to the management strategies in the low risk group, there is very little literature on factors associated with compliance in this population. Future studies should focus on identifying the risks associated with testing and observation strategies and on factors that influence compliance to followup care.

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Appendixes cited in this report are available at http://ahrq.gov/XXXXX

Executive Summary

Introduction

The febrile infant is a common clinical problem that accounts for a large number of ambulatory care visits. Young febrile infants often present with nonspecific symptoms and it is difficult to distinguish between infants with a viral syndrome and those with early serious bacterial illness (e.g. meningitis, bacteremia, urinary tract infections, and pneumonia).

The definitions of SBI vary across published literature. The identification of SBI typically includes the diagnoses of meningitis, bacteremia, and urinary tract infection. Some studies have also included pneumonia, bone and joint infections, skin and soft tissue infections, and bacterial enteritis in the definition. Invasive herpes simplex virus (HSV) infections are grouped into meningoencephalitis, disseminated, or skin, eyes and mouth. There is some overlap in these presentations.

Febrile illness in infancy is often due to viral infections and is likely to be self-limiting. Although serious bacterial illness (SBI) is relatively uncommon among febrile infants, if it is not promptly diagnosed and managed, serious morbidity may result. The clinical conundrum that practitioners often face is how to avoid missing a case of SBI versus how to avoid the risks and harms of investigating, observing, and potentially treating a febrile infant with no SBI.

The most common bacterial pathogen for SBI in the young infant is *Escherichia coli*, with Group B *Streptococcus*, *Staphylococcus aureus*, *Listeria monocytogenes,* and other gram-negative enteric bacteria being the other likely pathogens in this age group.

Although uncommon, herpes simplex virus (HSV) infections are a major cause of morbidity and mortality among neonates with a case fatality rate of 15.5 percent.[1] The prevalence of neonatal HSV infection has been reported to be between 25-50 per 100,000 live births in the United States.[2]The rate of HSV infection in a febrile neonate is 0.3 percent which is similar to the rate of bacterial meningitis in this age group.[3]

Historically, febrile infants under three months would undergo a complete evaluation for sepsis, including a lumbar puncture and would be admitted to hospital for intravenous antibiotics. The rationale for this approach is based on the high rate of SBI in this group and the difficulty with the clinical assessment for sepsis in the young infant where clinical signs of sepsis are often subtle.[4]. Infant observation scales were developed to help define infants who have severe illness but failed to reliably predict which infants were likely to have sepsis. [4-7]

Although this approach minimizes the risk of infectious complications, it leads to unnecessary hospitalization and treatment resulting in potential iatrogenic harms to infants. Several studies focused on the development of low risk criteria to help select infants who were unlikely to have SBI and could therefore be managed as outpatients. These studies developed low risk criteria such as the Philadelphia, Rochester, and Boston criteria to predict the absence of SBI. These criteria are comprised of clinical (e.g., rectal temperature, appearance) and laboratory features such as white blood cell count (WBC) in blood, urine (urinalysis) or cerebrospinal fluid (CSF), erythrocyte sedimentation rate (ESR), and absolute band counts (ABC). The application of clinical assessments combined with varying laboratory thresholds classifies infants into low-risk and not low- risk groups for having SBI. The identification of febrile infants with low risk of SBI helps to minimize unnecessary costs and harmful consequences associated with the treatment.[8-13]

The current recommendations for the evaluation and management of the young febrile infant are based on studies conducted in the late 1980's and early 1990's.[14] An up-to-date systematic review of the diagnostic tests and harms of the management strategies for febrile infants is required. This evidence report is designed to clarify the literature so that previously published guidelines may be updated.

Methods

Literature Search

Studies were identified through electronic searches in MEDLINE (1950 to September Week 2 2010, OVID interface), MEDLINE in Process (September 29, 2010), CINAHL (1982 – 2008, OVID Interface), EMBASE (1980 to 2010 Week 37, OVID interface), PsycINFO (1806 to September Week 2 2010 OVID interface), EBM Reviews, Cochrane Central Register of Controlled Trials (2nd Quarter 2010), the Cochrane Database of Systematic Reviews (2nd Quarter 2010), and PubMed (1973 to September 22nd, 2010). The websites of relevant organizations were searched to identify any unpublished materials. Additional studies were sought through contacting experts. The searches were combined into a single Reference Manager database and duplicate records were manually deleted, providing a database of unique citations.

Study Selection

The English-language studies that reported the diagnosis and/or management of infants (0 – 90 days of age for KQ1-KQ5 and 0 – 6 months of age for KQ6) with no history of major diseases predisposing to fever (rectal temperature ≥ 38°C) and/or SBI (including bacterial meningitis, bacteremia, urinary tract infection) or HSV infection admitted to an emergency department of a hospital, evaluated in an outpatient office practice or an acute care walk-in clinic were eligible. Studies conducted in North America, Australia, New Zealand, Western Europe (i.e., Belgium, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Switzerland, and United Kingdom), Northern Europe (i.e., Denmark, Finland, Norway, Sweden), Israel, Hong Kong, Japan, Taiwan, and Singapore were eligible for inclusion in the review. The inclusion was not restricted by study design (e.g., randomized or nonrandomized controlled trials, case-series, cohort, case-control, or cross-sectional/prevalence studies). Case reports, systematic reviews, cost-effectiveness analyses, editorials, or letters were excluded.

Two reviewers independently screened titles and abstracts of all identified bibliographic records and afterwards full-text reports of potentially relevant records. Discrepancies were resolved by discussion.

Data Extraction and Assessment of Study and Reporting Quality

Two reviewers independently extracted relevant information from the included studies using a data extraction form, which was verified by a third independent reviewer. Abstracted data included study and population characteristics (e.g., first author, country, design, age, ethnicity, demographics, setting). Information was extracted on index tests (e.g., criteria, laboratory thresholds) used to identify or screen bacterial or herpetic infection with treatment outcomes as well as diagnostic methods or reference standards (e.g., bacterial culture growth in blood, urine, or cerebral spinal fluid, viral culture). The test results (i.e., sensitivity, specificity, positive and negative predictive values) were directly abstracted when reported or derived whenever possible.

Other extracted information included prevalence rates of SBI or HSV infection in febrile infants and parents' compliance with followup examination visits. Efforts were made to extract relevant data separately for each age strata (i.e. 0-28; 28-60; 60-90 days), where possible.

The included studies were classified with respect to design (e.g., randomized controlled trial, cohort study, case-series). The studies reporting diagnostic accuracy data and those for which this data could be derived were classified as diagnostic accuracy studies. Two independent reviewers assessed the risk of bias of the included studies. The diagnostic test accuracy studies were assessed using a validated 14-item tool QUADAS.[15] The quality and reporting of randomized controlled trials were assessed using the 3-item Jadad scale and the Schulz questionnaire.[16,17]

Synthesis of the Evidence

The index tests (i.e., criteria, protocols, clinical symptoms, and laboratory thresholds) used for identifying infants with SBI or HSV infection, were categorized into the following groups: 1) combined clinical and laboratory criteria, 2) clinical criteria, and 3) laboratory criteria. The identified criteria were further divided into two groups: low risk and high (or not low) risk criteria. We did not prespecify the definition of SBI in this report. Instead, the definitions from original studies were presented. For each study, a two- by- two table was constructed and diagnostic accuracy parameters with the corresponding 95 percent confidence intervals (95 percent CI) were calculated, if possible. Where data allowed, diagnostic accuracy parameters were calculated for bacteremia and meningitis in addition to total SBI. The prevalence rates of SBI in virus-positive and virus-negative febrile infants were ascertained and compared using odds ratios or prevalence rate ratios. The degree of heterogeneity was examined graphically by plotting values of sensitivity and specificity and was guided by I2 and Chi-squared statistics.(10707 REF) The potential sources of heterogeneity (e.g., population, study quality, different index tests and their thresholds) were considered. The Summary Receiver Operating Characteristic (SROC) curves were constructed to assess the between-study variability in sensitivity and specificity for a given classification criteria or to detect outliers.[18]

Results

In total, 83 unique studies (91 records) were included in this review.

The diagnosis of UTI accounted for the greatest proportion of all types of SBI (bacteremia, meningitis, pneumonia, cellulitis, gastroenteritis, others). For example, the prevalence of diagnosis of UTI across studies ranged from 15.0 to 94.0 percent. In contrast, the ranges for this prevalence for bacteremia and meningitis were 0 to 41 percent and 0 to 25.9 percent, respectively. Based on the reported information (35 studies), *E. coli* was the organism found in 60 percent of total UTI cases. *Streptococcus* Group B, *E.coli,* and *Streptococcus pneumoniae* were the organisms that caused 36.4 percent, 28.0 percent, and 6.9 percent of all bacteremia cases, respectively. Similarly, *Streptococcus* Group B, *E. coli,* and *Streptococcus pneumoniae* were the organisms that caused 35.2 percent, 12.7 percent, and 8.5 percent of all meningitis cases, respectively. Other organisms were responsible for less than 4.0 percent of all bacteremia and meningitis cases.

KQ 1A: In infants < 3 months old who present with a fever, what is the evidence for the sensitivity, specificity and predictive values of individual or

combinations of clinical features (including history - including information on the mother's history and previous testing, risk factors, findings on clinical exam and formal scoring instruments based on clinical features) for identifying those with serious bacterial illness (SBI)?

This section included 61 studies. The reviewed studies reported an extensive array of classification methods (i.e., index tests) for predicting risk of SBI in febrile infants.

Combined clinical and laboratory criteria. This review identified studies using the following criteria/protocols: Boston, Philadelphia Rochester, Milwaukee, and Yale Observation Score. Other criteria were different combinations of clinical (e.g., ill or toxic appearance, impression of sepsis, age, rectal temperature) and laboratory features with varying thresholds (e.g., serum white blood cell count, erythrocyte sedimentation rate, C-reactive protein, absolute band count, urine microscopy). The presence of SBI was determined by confirming bacterial growth in blood, cerebrospinal fluid (CSF), stool, and/or urine.

For the Rochester criteria, the ranges of values for sensitivity and specificity for predicting total SBI were 52.0[19]-100.0 percent[20] and 26.0 percent[10]-69.0 percent,[20] respectively. The positive predictive values (PPV) ranged from 3.0 percent[10] to 34.0 percent[21] and the negative predictive values (NPV) ranged from 94.0 percent[10] to 100.0 percent.[20] The pooled estimates of sensitivity and specificity of the Rochester criteria for predicting SBI were 94.0 percent (95 percent CI: 91.0, 96.0) and 49.0 percent (95 percent CI: 47.0, 51.0), respectively.

For the Philadelphia protocol, the sensitivity values for predicting total SBI ranged from 84.0 percent[11] to 100.0 percent.[9,12] The values of specificity ranged from 26.0 percent[9] to 66.0 percent.[22] The corresponding PPVs ranged from 14.0 percent[12] to 27.0 percent[22] and NPVs ranged from 95.4 percent[11] to 100.0 percent.[9,12] The pooled estimates of sensitivity and specificity of the Philadelphia protocol for predicting SBI were 93.0 percent (95 percent CI: 89.0, 95.0) and 46.0 percent (95 percent CI: 44.0, 58.0), respectively.

Although the Milwaukee[10] and Boston criteria[23,24] had similar NPVs (99.3 percent and 97.0 percent-98.1 percent, respectively) in predicting total SBI, the Milwaukee protocol had a higher sensitivity (96.0 percent) but lower specificity (28.0 percent) than the Boston criteria (88.5 percent and 56.2 percent, respectively).

Based on our statistical analysis, the Rochester criteria and Philadelphia protocol did not differ in their performance for correctly discriminating febrile infants with and without SBI. For the Rochester criteria, the area under curve (AUC) and Q* statistic were 0.73 and 0.67, respectively.[20,21,25-29] The Philadelphia protocol yielded the AUC of 0.75 and Q* statistic of 0.69.[9,11,12,22,23,27]

The Boston and Rochester criteria and the Philadelphia protocol demonstrated similar degree of accuracy (i.e., sensitivity, specificity) in predicting bacteremia vs. total SBI. In general, sensitivity for detecting bacteremia did not differ across the Philadelphia protocol (75.0 percent-100.0 percent),[11,12,23] Boston (75.0 percent),[23] and Rochester criteria (75.0 percent-100.0 percent),[20,26,27,29] except for one study in which the sensitivity for the Rochester criteria was 33.3 percent.[10] The Rochester criteria[10] and Philadelphia protocol[11,23] demonstrated a slightly better sensitivity in detecting meningitis (50.0 percent[10] and 100.0 percent[11,23]) vs. bacteremia (33.3 percent,[10] 83.3 percent,[23] and 75.0 percent[11]).

Several studies reported diagnostic accuracy data for other criteria which combined various clinical (e.g., clinical/good/toxic/ill appearance, impression of sepsis, age, rectal temperature, unremarkable medical history) and laboratory criteria (e.g., serum and urine white blood cell

counts, absolute band count, erythrocyte sedimentation rate, C-reactive protein, urine dipstick result). In general, these criteria except for one study (sensitivity: 61.0 percent, specificity: 90.0 percent),[30] yielded greater values for sensitivity (range: 68.3 percent- 99.1 percent)[31,32] compared with those for specificity (range: 37.6 percent-77.8 percent).[31,33] for predicting risk of SBI. Across the same criteria, except for one (ill appearance and WBC ≥ 15,000/mm^3),[34] sensitivity (range: 84.0 percent-100.0 percent)[5,35-37] tended to be greater than specificity (range: 17.0 percent-54.0 percent)[5,36] in predicting risk of bacteremia. The sensitivity values were greater for identifying bacteremia (range: 84.0 percent-100.0 percent)[5,35-37] than SBI (range: 68.3 percent-99.1 percent).[31,32]

Clinical criteria. The identified studies reported data on diagnostic accuracy for different clinical criteria used for predicting risk of SBI. These criteria were the following: temperature ≥ 40°C,[38,39] ill appearance (i.e., presence of at least tachypnea, dyspnea, tachycardia, bradycardia, lethargy, decrease in activity/appetite), age (different categories), not ill appearance, gender (male vs. female), clinical impression of sepsis (based on physical examination, complete history, laboratory results), and no history of recent immunization. In general, the criteria of temperature (≥ 40°C or > 39.5°C) were associated with low sensitivity (range: 7.3 percent-26.1 percent) but high specificity values (range: 90.5 percent-98.8 percent) for predicting risk of SBI.[38-40] The sensitivity of using the clinical impression of sepsis in detecting bacteremia was high ranging from 80.0 percent[41] to 100.0 percent.[36,42]

Laboratory criteria. The reviewed studies reported data on diagnostic accuracy for different laboratory measures by using various thresholds: UA (microscopy, dipstick), WBC, ESR, ABC, and Procalcitonin (PCT).

In studies evaluating sensitivity and specificity of WBC (in mm^3) in identifying bacteremia at different thresholds,[43,44] lower thresholds (e.g., from 20,000/mm^3 to 5,000/mm^3) were related to greater sensitivity and lower specificity. The sensitivity values of WBC ≥ 5,000/mm^3 in these two studies were 79.0 percent[43] and 100.0 percent.[44] In two other studies,[45,46] the AUC for ABC (81.0 percent) or ANC (77.0 percent) was greater than that for WBC (61.0 percent and 69.0 percent) for detecting UTI.

In three studies,[40,47,48] the value of blood CRP levels (C-reactive protein) was shown to be greater than those of WBC, ANC, and PCT levels in predicting risk of SBI (AUC-CRP: 74.0 percent-84.0 percent vs. AUC-WBC: 68.0 percent-70.0 percent vs. AUC-ANC: 71.1 percent vs. AUC-PCT: 77.0 percent). The use of CRP yielded greater sensitivity (69.6 percent) and specificity (93.8 percent) compared to urine dipstick (43.5 percent and 82.8 percent, respectively)[40] but demonstrated lower diagnostic accuracy compared with PCT (AUC-CRP: 68.0 percent vs. AUC-PCT: 84.0 percent)[48] for predicting bacteremia.

The ranges of sensitivity and specificity values of UA (dipstick; the presence of LE or nitrite, or both) for identifying infants with UTI across the studies were 40.0 percent[49]- 85.0 percent[13] and 63.6 percent[50]– 94.0 percent,[51] respectively. In one study, the area under the curve (AUC) of ROC based on sensitivity and specificity values for different thresholds of urine microscopy (WBC: 0-2, 3-5, 6-10, 11-20, > 20/hpf) was numerically greater for the collection method using catheterization (AUC: 86.0 percent, 95 percent CI: 82.0, 91.0) vs. bag (AUC: 71.0 percent, 95 percent CI: 61.0, 82.0).[52]

KQ 1B. How do the findings on test characteristics (sensitivity, specificity and predictive values) of individual or combinations of clinical features for identifying serious bacterial illness vary within the age range 0 – 3 months?

Comparison of the diagnostic test characteristics across age groups (neonates: age ≤ 28 days vs. older infants: age > 29 days) was possible for few selected criteria (Boston, Philadelphia, Rochester, combined laboratory and clinical) reported in 14 studies.

The Boston criteria[23,24] and Philadelphia protocol[9,11,12,23] demonstrated higher sensitivity, lower specificity, smaller PPV, and similar NPV when applied to older infants (age > 28 days)[9,12,24] compared to neonates (age: 0 – 28 days)[11,23] for total SBI or bacteremia. In contrast, the application of Rochester criteria[10,19,21,26] was more accurate (higher sensitivity, specificity, and PPV) in neonates[21,26] than in older infants[10,19] for total SBI or bacteremia.

In one study,[31] the combined clinical and laboratory criteria (well appearance without focal infection, WBC: 5,000-15,000/mm^3, ABC≤ 1,500/mm^3, enhanced UA, SCF WBC < 5/mm^3 and negative gram stain) demonstrated greater specificity in infants 29 days of age or older (36.0 percent-39.0 percent) than in neonates 28 days or younger (26.3 percent-28.0 percent). The value of sensitivity (100.0 percent) did not change across the age groups (0-14, 15-28, 29-45, and 46-59 days of age).[31]

The overall diagnostic accuracy of PCT for predicting SBI was better for older infants (AUC-PCT: 85.0 percent; age > 28 days) compared with neonates (AUC-PCT: 73.0 percent; age ≤ 28 days).[53]

KQ 1C. In infants < 3 months old who present with a fever, what is the evidence for the sensitivity, specificity and predictive values of individual or combinations of clinical features (including history - including information on the mother's history and previous testing, risk factors, findings on clinical exam and formal scoring instruments based on clinical features) for identifying those with rare invasive herpes simplex virus infection (HSV)? How do these findings vary within the age range 0 to 3 months?

The reported data on the presence of Herpes Simplex Virus (HSV) in febrile infants 3 months or younger was scarce. Only four studies reported the prevalence of HSV (total of 7 cases). None of these infants had a concurrent bacterial infection. The prevalence rates of HSV amongst the febrile infants admitted across these studies (admission period range: 2 -6 years) were 2.0 percent,[28] 1.7 percent,[54] and 0.3 percent[42,55]. The diagnostic accuracy of any given criteria in predicting the risk of HSV could be calculated only for one study.[55] In this study, CSF pleocytosis (≥ 20 WBCs/mm^3 and > 1 WBC per 500 red blood cells s/mm^3) predicted the risk of HSV in neonates with sensitivity of 66.6 percent (95 percent CI: 12.5, 98.2) and specificity of 74.6 percent (95 percent CI: 71.4, 77.6). The Positive and negative predictive values in this study were 1.0 percent (95 percent CI: 0.2, 3.9) and 99.8 percent (95 percent CI: 98.9, 99.9), respectively. There were insufficient data to compare the findings in neonates and infants in older age groups.

KQ 2A. What is the evidence that clinical features alone, basic laboratory tests (e.g., complete blood count [CBC], urinalysis) alone or the combination are sufficient to identify febrile infants < 3 months who are at low risk of having a serious bacterial illness (i.e., have a high negative predictive value)?

We identified 23 studies that reported diagnostic accuracy data for low risk criteria/protocols (e.g., Boston, Philadelphia, Rochester, Milwaukee, good appearance, WBC: 5,000-15,000/mm^3, ESR < 30 mm/h, and normal urinalysis).

The evidence indicated that the identified criteria correctly classified the majority or all of the infants truly without SBI into low-risk groups. The probability that an infant classified in 'Low Risk' group was free of SBI (i.e., NPV) ranged from 90.0 percent[31] to 100.0 percent.[9] The observed high NPVs were due mostly to low prevalence of SBI in the population of febrile infants.

In all studies except for two,[10,31] the values of sensitivity of the 'Low-Risk' criteria for predicting risk of SBI ranged from 82.0 percent[23,56] to 100.0 percent.[9,20] The corresponding values for specificity ranged from 26.6 percent[9] to 68.8 percent.[20] In the two studies,[10,31] the sensitivity was below 70.0 percent and specificity below 40.0 percent. In one of the studies,[10] the Rochester criteria showed a lower discriminatory power (sensitivity: 59.0 percent and specificity: 26.3 percent) compared to other low risk criteria.

KQ 2B. What is the evidence for the potential risks resulting from a delay in the diagnosis and treatment of patients who appear low risk but have a serious bacterial illness?

Some data on management of low risk infants were reported for 18 studies. Six studies[10,39,56-59] reported to have misclassified eight cases of meningitis into low-risk for SBI using the Rochester criteria (4 missed cases),[10,56,58] a data-derived model (positive UA, WBC > 20,000/mm^3 or < 4,100/mm^3, temperature > 39.6°C, and age < 13 days; one missed case),[57] rectal temperature ≥ 40°C (one missed case),[39] and a laboratory test (WBC < 5,000/mm^3 or > 15,000mm^3 and/or ANC > 10,000/mm^3 and/or CRP > 20 mg/L and/or positive UA on LE/nitrite test for well-appearing infants with fever < 12 hours; 2 missed cases).[59] The outcomes for these cases were not reported. Three trial reports[5,22,58] failed to provide any information related to delayed diagnosis/treatment for the 12 low risk infants with SBI (UTI, bacteremia/meningitis, meningitis). In three other studies,[9,12,20] none of the low risk infants had SBI. Six of the remaining eight studies,[10,24,25,32,59,60] reported the absence of harms for the 20 low risk infants with SBI (UTI, bacteremia, enteritis, meningitis) who had been given a delayed antibiotic or antimicrobial treatment. In one study,[21] one low risk infant with UTI (caused by E. coli) had been given antibiotics for 7 days and his/her renal sonogram indicated mild dilation of the left renal pelvis, but with normal retrograde voiding cystourethrogram. In another study,[61] there was a febrile resolution in 98.3 percent of the low risk infants with UTI (n=58) after being treated with intravenous and oral antibiotics at a day treatment centre (DTC). Of the 58 treated infants in the DTC, 7 (12.0 percent) were treatment failures and were eventually hospitalized due to severe concomitant gastroesophageal reflux (n=1), hydronephrosis (n=1), and concomitant bacteremia (n=5). None of the seven infants had a serious adverse event during hospitalization. The overall

success rate of treatment given to the 58 infants with UTI in the DTC was 86.2 percent. The treatment success rate was lower (RR=0.2, 95 percent CI: 0.1, 1.1) amongst younger infants (≤ 60 days old) compared with older infants (> 60 days old).

KQ3A. What is the evidence that clinical features alone, basic laboratory tests (e.g., complete blood count [CBC], urinalysis) alone or the combination are sufficient to identify febrile infants < 3 months who are at high risk of having a serious bacterial illness (i.e., have a high positive predictive value)?

We identified 10 studies that reported diagnostic accuracy data for high risk and 'not low risk' criteria (e.g., ill appearance, WBC < 5,000/mm^3 or WBC > 15,000/mm^3 and WBC ≥ 5/high powered field). Seven studies reported criteria representing different combinations of clinical and laboratory characteristics,[30,34-37,57,62] two studies - clinical only criteria,[40,63] and one study reported laboratory only criteria.[49] These criteria were associated with low PPVs. Specifically, a large proportion of febrile infants who were classified in high-risk groups did not really have SBI. For example, in two studies reporting combined clinical and laboratory criteria for identifying SBI in infants 0 – 90 days, reported PPVs were 21.0 percent (95 percent CI: 19.0, 23.0)[57] and 60.0 percent (95 percent CI not reported).[30] Similarly, the PPVs for predicting bacteremia across 4 studies[34-36,40] ranged from 4.5 percent[36] to 27.3 percent[34]

The values of sensitivity for predicting SBI reported for the two studies (see above) were 61.0 percent (95 percent CI not reported)[30] and 82.0 percent (95 percent CI: 78.0, 86.0).[57]The corresponding values for specificity were 90.0 percent (95 percent CI not reported)[30] and 76.0 percent (95 percent CI: 75.0, 77.0).[57]

KQ 3B. What is the evidence on the benefits and harms of immediate antibiotic (antibacterial and antiviral) therapy and or hospitalization (vs. delaying until diagnostic workup is complete) in patients at high risk of serious bacterial illness?

We identified 10 studies reporting on immediate antibiotic (or antiviral) therapy administered to infants at high risk of SBI (or HSV). There was no evidence directly comparing outcomes in the immediate vs. delayed treatment groups. No treatment outcomes was reported for three studies.[10,19,59] Overall, the benefits and harms of immediate antibiotic/antiviral therapy (vs. delaying until diagnostic workup is complete) in patients at high risk of SBI (or HSV) were poorly reported.

The studies reported that febrile infants classified as being at high risk for SBI were administered immediate antibiotic therapy (vs. delaying until diagnostic workup is complete). In one study, 0.4 percent of the included infants developed drug-related rash and 18.9 percent had infiltration of an intravenous line.[12] In another study,[35] immediate intravenous antibiotic therapy administered to 13 toxic appearing infants 8 weeks or younger was reported to be without any complications. Another study reported minor intravenous access problems that had occurred in 15.6 percent of the 51 high risk infants (most of them diagnosed with UTI) treated with intravenous antibiotics for 4 days. About 67.0 percent of these infants were transferred to an outpatient day treatment centre to complete their antibiotic treatment course.[61]

KQ 4. What is the evidence that the presence of an identified viral infection predicts against a serious bacterial infection?

This section included 11 studies in which the association between the status of viral infection and the risk of SBI in febrile infants was explored. There was no evidence to assess the probability of having SBI with respect to the presence of HSV infection in febrile infants. The most frequent types of SBI in these studies were UTI (range: 5.6 percent-11.3 percent)[64,65] and bacteremia (range: 1.4 percent-3.8 percent).[29,64] The types of virus reported in most of these studies were influenza A/B and RSV. Four studies reported data on enterovirus.[28,29,64,66] Overall, the study results indicated significantly higher prevalence rates (or risk) of SBI in infants without viral infection or clinically diagnosed bronchiolitis (prevalence range: 0 percent[67] – 7.0 percent[64,68]) compared to infants with viral infection or clinically diagnosed bronchiolitis (prevalence range: 10.0 percent[69] – 20.0 percent[29]). The estimate of odds ratio across the studies ranged from 0.08[70] to 0.58.[68]

Similarly, the reviewed evidence indicated significantly lower prevalence rates of UTI in infants with viral infection or bronchiolitis versus infants free of viral infection or bronchiolitis.[68,71,72] The evidence was insufficient or inconclusive (i.e., statistically nonsignificant due to imprecision of the estimates) regarding the prevalence rates of bacteremia (range: 0 percent-2.3 percent) and meningitis (range: 0 percent-0.9 percent) due to small counts.[68,71,72]

The data on comparison of prevalence rates of SBI between virus-positive and virus–negative neonates (age: 0 – 28 days) was scarce. In one study,[68] the prevalence of SBI did not significantly differ between RSV positive and negative groups of neonates (10.1 percent vs. 14.2 percent; RR: 0.71; 95 percent CI: 0.35, 1.5).[68]

KQ 5. What is the evidence that the prevalence of serious bacterial illness varies among febrile infants presenting to primary care and emergency practice? What is the evidence that prevalence affects the predictive value of clinical and laboratory findings?

This section included 69 studies reporting prevalence rates of SBI (and/or HSV). In order to compare these rates, the studies were divided by the setting (i.e., emergency department vs. primary care) and place of conduct (North America, Taiwan, Spain, Israel, and Italy).

For studies conducted in North America in the emergency departments (n=40), the prevalence rate of total SBI ranged from 4.1 percent[10] to 25.1 percent.[27] For more than half of the studies, the prevalence rate of total SBI in emergency departments was 10.0 percent or greater. One study,[73] reported increased rate of SBI for the period of 2002 – 2006 compared to 1997 – 2001 (14.4 percent vs. 6.5 percent, p = 0.001). Of the three primary care setting study reports,[5,29,34] two reported the prevalence rates of total SBI of 9.9 percent[29] and 10.3 percent.[5] In the emergency departments of studies conducted in North America, the prevalence of SBI in neonates (age: 0 – 28 days) was higher (range: 11.5 percent[74] - 23.8 percent[54]) compared to infants older than 28 days (range: 4.1 percent[10] - 11.2 percent[75]).

For Taiwanese studies (n=3),[21,33,56] the prevalence rate of total SBI was numerically similar in emergency departments vs. primary care setting (17.7 percent-25.2 percent vs. 16.4 percent).

All three Spanish studies[65,76,77] reported prevalence rates of SBI in the emergency departments. In two of these studies, prevalence rates of SBI were 13.1 percent[65] and 18.9 percent.[76] The third study,[77] reported that the prevalence of SBI was significantly greater in infants younger than 29 days than in those older than 29 days (20.1 percent vs. 12.6 percent, p=0.04). This study did not report the crude prevalence rate of SBI based on the total sample.

Three studies conducted in Israel, in the emergency departments, reported prevalence of total SBI ranging from 10.8 percent[78] to 19.4 percent.[79] One of these studies,[79] reported an estimate of the prevalence of SBI of 19.4 percent in neonates (0 – 28 days). In this study, the prevalence rate of SBI did not differ for infants aged 3 – 7 days (21.6 percent), 8 – 18 days (26.1 percent), 15 – 21 days (17.9 percent), and 22 – 28 days (12.1 percent).[79]

In one Italian study,[59] the prevalence of SBI amongst neonates (0 – 28 days of age) was 25.3 percent.

Across all studies, the prevalence rate of total SBI was higher in the neonates (age: 0 – 28 days) ranging from 11.5 percent to 25.3 percent compared to the older infants (age: > 28 days) in whom it ranged from 4.5 percent to 13.0 percent.

The effect of prevalence rate of total SBI on the PPVs was possible to be examined only for the Philadelphia protocol[9,11,12,23,27] and the Rochester criteria[19,21,25,26,28,29] regardless of the setting it was conducted. For the Philadelphia protocol, the prevalence of total SBI did not appear to contribute to the difference observed in the PPVs. For the Rochester criteria, higher prevalence of total SBI corresponded to higher PPVs.

KQ 6. Clinicians base decisions about initial diagnostic work-up and treatment of febrile infants not solely on the infants' medical status but also on their assessments of nonclinical factors (e.g. parental understanding, parents' ability to monitor the patient, access to care). A strategy of initial observation without extensive diagnostic tests or hospitalization depends on confidence that parents will reliably bring the baby back for a timely followup appointment if conditions warrant. How likely are parents whose infants are less than six months of age and have fever or other potentially serious medical condition to comply with a provider's recommendation that the parent bring the infant back (to that provider or another) for a return appointment to reassess the condition(s) of concern?

6 A. What is the evidence that identifiable parental factors (e.g. education, insurance status, living situation, history of previous visits with the provider, time/distance required to travel to an appointment, etc.) influence the likelihood that a parent will adhere to such a recommendation?

This section included four studies conducted in North America. These studies included children with age range of 0 – 3 months. All studies reported at least some information on the degree of parental compliance to followup (range: 12 hours to 14 days after initial examination or discharge) with telephone or return visits to reassess the condition. The rate of successful followup across these studies ranged from 77.4 percent[80] to 99.8 percent.[19] For example, one study[72] reported that telephone followups were completed for 78.0 percent of the 132 infants 4-7 days after they were discharged. In another study,[61] the parental compliance for the day treatment

centre (DTC) followups was 98.3 percent. The parental compliance rates for the DTC followups did not differ between the two groups of younger (age ≤ 60 days) and older infants (age: 61- 90 days).[61] In the same study, the parental compliance to the DTC followups was greater than that to antibiotic treatment (98.3 percent vs. 80.4 percent). In one study,[80] the reported success rates for followup calls 2, 7, and 14 days after discharge were 77.4 percent, 85.4 percent, and 83.9 percent, respectively. In this study, most parents preferred discharge to hospitalization.[80]

6.B. What is the evidence that the clinical setting (community practice vs. emergency department and/or hospital outpatient clinic) in which care is sought independently influences the likelihood of compliance with a return appointment?

None of the studies reported any evidence regarding the influence of parental factors (e.g., age, education, distance/time to travel to an appointment, living situation) or clinical settings (emergency department vs. primary care office) on rates of parental compliance to telephone or return visit followups. The full report reviews the results of nine studies that were excluded from KQ6B, some of which have potentially data that could be extrapolated to the relevant patient population.

Discussion and Future Research

The clinical conundrum is how to balance the risk of missing an SBI (with potentially a devastating outcome) with the risks associated with diagnostic and management strategies for febrile infants 90 days or younger. To date, a tremendous amount of resources and effort has been focused on the development of tests, protocols, and criteria to attempt to minimize the risk of missing an SBI. However, there has been less research exploring risks associated with diagnosis and treatment of febrile infants.

The evidence synthesis for the diagnosis of serious bacterial illnesses (SBI) and invasive herpes simplex virus (HSV) infection in infants less than 90 days of life has been challenging. In general, there was a lack of standard definitions across the reviewed evidence. For example, the definitions for fever and SBI across studies varied.

The majority of SBI (greater than 65 percent) were due to urinary tract infections caused by *Escherichia coli*. Although many studies reported high negative predictive values, these should be interpreted with caution, as predictive values depend on underlying prevalence of the condition. A rare event such as bacterial meningitis will be associated with a high negative predictive value. The sensitivity, specificity, and likelihood ratios are independent of prevalence and thus are better suited for the comparison between studies.

There was very little evidence on HSV in febrile infants aged 90 days or younger to allow any definitive conclusions. Apart from these challenges, this review sought to summarize evidence on harms in the evaluation and management of febrile infants 0 – 3 months of age, to evaluate the role of viral infections or clinical bronchiolitis in the rates of SBI, and to identify the factors that influence parental compliance to followup visits. Moreover, we attempted to calculate the test accuracy characteristics from raw data for the different types of SBI (UTI, bacteremia, meningitis) and for the neonatal period, when possible.

This review revealed that certain factors either increase (e.g., neonatal age) or decrease (e.g., viral syndrome) the risk of SBI and also the test accuracy. The risks for the specific types of SBI

(e.g. UTI, bacteremia, and meningitis) were not uniform either. There was insufficient data to definitively determine the accuracy of detecting the rarer and more devastating meningitis.

Due to the heterogeneity across studies, meta-analysis was possible to be performed only for the Rochester criteria and Philadelphia protocol. There was no clear difference in the study quality (QUADAS scores) between the studies reporting combined clinical and laboratory criteria such as Rochester, Boston, Philadelphia criteria/protocol and those reporting clinical or laboratory criteria alone. In general, the combined clinical and laboratory criteria/protocol (Rochester, Philadelphia, Milwaukee, Boston) reported better test accuracy performance (high sensitivity and negative predictive values) compared with clinical criteria only (e.g., temperature, appearance, history of immunization, gender) or laboratory criteria only (e.g., blood counts). It was difficult to compare the test characteristics between detecting bacteremia and meningitis due to small counts and wide confidence intervals.

Contrary to the approach of ruling out a SBI, studies attempting to rule in an infection have not been as successful. Positive predictive values of the tests/protocols/clinical impression ranged from 4.5 percent to 64.0 percent. In the absence of better data on harms and the costs of diagnostics and therapeutics or improved positive predictive values, clinicians will continue to opt to identify low risk infants and treat a large group of SBI negative patients.

The neonatal period (0 – 28 days) has been shown to have a higher prevalence of SBI compared with older children. When separately evaluated, neonates did not have the same test characteristics as the older children or whole group of less than 3 months of age. In only one study evaluating the Rochester criteria in neonates the testing in the neonatal age group showed better numerical accuracy than in the older age group. The rest of the combined, laboratory or clinical criteria demonstrated lower sensitivity in the neonate as compared to older groups.

There is very little evidence on the risks of delayed diagnosis and management of low risk infants who were later found to have SBI. Several studies reported that such infants were subsequently hospitalized and treated with antibiotics without adverse events. Although reassuring, the absence of adverse events in these studies can be explained by underreporting and lack of followup data.

The harms and costs of immediate therapy or management in high risk patients have been poorly reported and psychological harms of testing have not been explicitly stated in the studies. Unnecessary testing may have had the unexpected consequence of the parents viewing the infant as more fragile or have more anxiety around the chance of a serious bacterial infection, although the literature has not delineated the presence or absence of such factors.

With the advent of rapid testing for viral pathogens, many clinicians now have the ability to quickly diagnose viral infections in children less than 3 months of age. This review has shown a significant inverse relationship between viral testing positive or clinical bronchiolitis and SBI. Note that this finding may not be applicable to neonates.

The majority of studies were conducted in North American emergency department settings. There appears to be a somewhat higher prevalence of SBI in the emergency department vs. primary care setting. The difference in prevalence rates may reflect a difference in the patient population that seeks care in the emergency department. The patients seen in the emergency department may be a sicker group than those who those who wait to see their primary care provider.

Follow up and reassessment of the febrile infant is an important component of their care. A clinician's decision making can be highly influenced by his/her assessment that the patient's caregivers are likely to comply with followup or further testing. Very little is known about the

factors that affect compliance for follow up in this area. Although the followup was reported in four studies, it was not the primary focus. The high rate of followup for therapy and telephone followup in these studies could in part be explained by the increased motivation of patients that are enrolled in a study. Although there were no included studies in this review on parental factors or clinical setting influencing followup, a review of the broader literature reveals some potential factors that need to be further studied in the 0-3 febrile infant population. In some studies Hispanic patients were less likely to comply with followup. The other identified parental factors such as lack of parental ability to speak English, having to make their own appointment, self-pay, lack of a primary care provider and followup greater than 24 hours seem self-evident but require further study.

To move the field further, there is a need to further delineate the risks associated with testing and also observation of this group. Well conducted studies reporting age-stratified (e.g., 0-28, 29-60, 61-90 days) outcomes are needed. Consideration should be given to exclude from such studies infants 0-6 days of age, as they are likely to represent another clinical syndrome of early onset sepsis related to perinatal factors. The focus should be on the clinical conundrum of febrile infants with no apparent source of infection - UTI, bacteremia, and meningitis.

The group of low-risk patients needs to be defined by incorporating risks associated with age group and viral or clinical syndrome status. Detailed reporting of the harms associated with the patient diagnosis and follow up observations (in or outpatient) of the low-risk group would be crucial.

Besides documenting numbers of infants with SBI, followup should be done to determine the long-term consequences of ‘missed’ or ‘delayed’ diagnosis of SBI such as decreased renal function with urinary tract infection, progression from UTI to bacteremia, and complications of meningitis. Integrated into these studies should be evaluations of the factors or interventions that increase parental compliance with return assessments in febrile infants. Optimally, these studies should be multi-centered and they should evaluate both outpatient and emergency department settings. Better data on harms of diagnostic and observation protocols would be helpful for a consensus expert panel to determine the risk-benefit balance.

Conclusion

Overall, the focus of the literature has been on ruling out SBI. Harms associated with testing or management strategies have been poorly reported. Attempts to identify high risk groups, as described in the minority of reports, were not accurate. The Boston, Philadelphia, Rochester, and Milwaukee were fairly accurate in identifying a low risk group for SBI in infants younger than 3 months of age. The diagnosis of a viral infection or clinical bronchiolitis significantly decreased the chances of a serious bacterial illness. Invasive herpes simplex virus infection is a significant differential diagnosis in the febrile infant, yet the relevant literature is presented from the diagnosis rather than from the syndrome point of view, making it difficult to draw conclusions of test accuracy or management efficacy in an undifferentiated febrile infant. Although crucial to the management strategies in the low risk group, there is very little literature on factors associated with compliance in this population. Future studies should focus on identifying the risks associated with testing and observation strategies and on factors that influence adherence to followup care.

Table 1. Summary table for executive summary

Key Question (KQ) N of studies	Results/Conclusions
KQ1-A 61 studies	<u>Combined clinical/laboratory criteria</u> Rochester criteria for SBI (AUC: 73.0%)[20,21,25-29] Philadelphia protocol for SBI (AUC: 75.0%)[9,11,12,22,23,27] Boston (sensitivity: 88.5%, specificity: 56.2%)[23,24] Milwaukee (sensitivity: 96.0%, specificity: 28.0%)[10] Rochester and Philadelphia for meningitis (sensitivity: 50.0%, 100.0%)[10,11,23] Rochester and Philadelphia for bacteremia (sensitivity: 33.3%, 83.3%)[10,11,23] Other combined clinical (e.g., clinical/good/toxic/ill appearance, impression of sepsis, age, rectal temperature) and laboratory (e.g., serum and urine WBC, ABC, ESR, CRP, urine dipstick) criteria for SBI [5,30-37,40,56-58,60,62,79] Sensitivity range: 68.3%[31]- 99.1%,[32] Specificity range: 37.6%[31]-77.8%[33] Other combined clinical and laboratory criteria for bacteremia (sensitivity range: 84.0%-100.0%, specificity range: 17.0%-54.0%).[5,35-37] <u>Clinical criteria</u> The criteria of temperature ≥ 40°C or > 39.5°C for SBI (sensitivity range: 7.3%-26.1%, specificity range: 90.5%-98.8%)[38-40] Clinical impression of sepsis for bacteremia (sensitivity range: 80.0%[41] - 100.0%[36,42]) <u>Laboratory criteria</u> UA (dipstick; the presence of LE or nitrite, or both) for UTI (sensitivity range: 40.0%[49]- 85.0%,[13] specificity range: 63.6%[50]– 94.0%[51]) UA of urine collected by catheterization (AUC: 86.0%, sensitivity: 86.0% or 43.0%, and specificity: 94.0% or 99.0%)[5,52] UA of urine collected by bag (AUC: 71.0%, sensitivity: 76.0% or 25.0%, and specificity: 84.0% or 99.0%)[5,52] AUC-WBC for UTI (61.0%, 69.0%)[45,46] AUC-ANC for UTI (77.0%)[45,46] AUC-ABC for UTI (81.0%)[45,46] AUC-CRP for SBI (range: 74.0%-84.0%)[40,47,48] AUC-WBC for SBI (range: 68.0%-70.0%) [40,47] AUC-ANC for SBI (71.1%)[40] AUC-PCT for SBI (77.0%)[48] CRP for bacteremia (AUC-CRP: 68.0%, sensitivity: 69.9%, specificity: 93.8%)[47] Urine dipstick for bacteremia (sensitivity: 43.5%, specificity: 82.8%)[40]

Table 1. Summary table for executive summary (Continued)

Key Question (KQ) N of studies	Results/Conclusions
	PCT for bacteremia (AUC-PCT: 84.0%)[48]
KQ1-B 14 studies	The Boston criteria for SBI Age > 28 days: sensitivity (88.5%), specificity (56.2%), PPV (16.2%), NPV (98.1%)[24] Age 0 – 28 days: sensitivity (82.0%), specificity (68.0%), PPV (26.0%), NPV (97.0%)[23] The Philadelphia protocol for SBI Age > 28 days: sensitivity (98.0%, 100.0%), specificity (26.6%, 42.0%)[9,12] Age 0 – 28 days: sensitivity (84.4%, 87.9%), specificity (46.8%, 55.0%)[11,23] The Philadelphia protocol for bacteremia Age > 28 days: sensitivity (100.0%)[9,12] Age 0 – 28 days: sensitivity (75.0%, 83.3%)[11,23] The Rochester criteria for SBI Age > 28 days: sensitivity (52.0%, 59.0%), specificity (26.3%)[10,19] Age 0 – 28 days: sensitivity (97.6%, 86.4%), specificity (62.2%, 46.4%), PPV (33.6%, 26.8%), and NPV (99.2%, 93.8%)[21,26] The Rochester criteria for bacteremia Age > 28 days: sensitivity (55.0%)[19] Age 0 – 28 days: sensitivity (86.4%)[26] PCT for SBI Age > 28 days: sensitivity (AUC: 85.0%)[53] Age: 0 – 28 days (AUC: 73.0%)[53]
KQ1-C 4 studies	The data on HSV was scarce[28,42,54,55] CSF pleocytosis (≥ 20 WBCs/mm^3 and > 1 WBC per 500 red blood cells s/mm^3) for HSV: sensitivity of 66.6% (95% CI: 12.5, 98.2) and specificity of 74.6% (95% CI: 71.4, 77.6)[55] Insufficient data to compare the findings across age groups
KQ2-A 23 studies	Several low risk criteria/protocols (e.g., Boston, Philadelphia, Rochester, Milwaukee, good appearance, WBC: 5,000-15,000/mm^3, ESR < 30 mm/h, normal urinalysis)[5,9-12,20-29,31,32,40,56,58,60,79,80] NPV for SBI (range: 90.0%[31]-100.0%[9]) Sensitivity for SBI (range: 82.0%[23,56]-100.0%[9,20]) Specificity for SBI (range: 27.0%[9]-69.0%[20])
KQ3-A 10 studies	Several high risk criteria (e.g., ill appearance, WBC < 5,000/mm^3 or WBC > 15,000/mm^3 and WBC ≥ 5/high powered field) for SBI[30,34-37,40,49,57,62,63] Sensitivity: 61.0%[30] and 82.0%[57] Specificity: 90.0%[30] and 76.0%[57]

Table 1. Summary table for executive summary (Continued)

Key Question (KQ) N of studies	Results/Conclusions
	PPV: 21.0%[57] and 60.0%[30]
KQ4 11 studies	Significantly higher risk of SBI in infants without viral infection compared to infants with viral infection[28,29,64-71,81] The ORs ranged from 0.08[70] to 0.58[68]
KQ5 69 studies	Prevalence of SBI (emergency vs. primary care) <u>North America (n=40)</u> Prevalence rate of SBI in emergency for all infants (range): 4.1%[10] - 25.1%[27] Prevalence rate of SBI in emergency for neonates 0-28 days (range): 11.5%[74] – 23.8[54] Prevalence rate of SBI in emergency for infants > 28 days (range): 4.1%[10] – 11.2%[75] Prevalence rate of SBI in primary care for all infants: 9.9%[29] and 10.3%[5] <u>Taiwan (n=3)</u> Prevalence rate of SBI in emergency for all infants: 17.7%[56] and 25.2%[33] Prevalence rate of SBI in emergency for all infants: 16.4%[21]
KQ6-A 4 studies	4 studies reported at least some information on the degree of parental compliance to followup () with telephone or return visits to reassess the condition[19,61,72,80] The range of rate of followup (12 hours - 14 days after initial examination or discharge): 77.4%[80] - 99.8%[19]
KQ6-B 0 studies	No evidence was identified

Chapter 1. Introduction

The febrile infant is a common problem that accounts for a large number of ambulatory care visits. Young infants often present with nonspecific symptoms and it is difficult to distinguish between infants with a viral syndrome and those with bacterial diseases. In the majority of cases febrile illness in infancy is secondary to viral infections and is self-limited. Although serious bacterial illness (SBI) is relatively uncommon, if it is not promptly diagnosed and treated, serious morbidity may result. The clinical conundrum that practitioners are faced is how to avoid missing a case of serious bacterial illness versus how to avoid the risks and harms of investigating, observing and potentially treating a febrile infant with no SBI.

Definitions

Fever in an infant is usually defined as a rectal temperature >38°C.[82] For infants <90 days old this value is approximately two standard deviations above the mean. The majority of studies that focus on the febrile infant have used this definition.

Young infant is defined as an infant less than 90 days old. Neonates are infants from birth to 28 days of age.[83]

The definitions of SBI vary across published literature. The identification of SBI typically includes the diagnoses of meningitis, bacteremia, and urinary tract infection. Some studies have also included pneumonia, bone and joint infections, skin and soft tissue infections, and bacterial enteritis in the definition.

Invasive herpes simplex virus (HSV) infections are grouped into meningoencephalitis, disseminated, or skin, eyes and mouth. There is some overlap in these presentations.

Epidemiology

The rate of SBI in young infants with fever is about 8.0 percent overall and is higher in infants aged 0–28 days (9.0 percent-13.0 percent) than in infants aged 2-3 months (7.1 percent) [11,12,23,25,29,57] The rates of SBI are highest in neonates < 2 weeks old (25.0 percent). The overall rates of bacteremia and meningitis are 2.0 percent and 0.8 percent respectively, with the highest rates seen in the youngest infants. The most common SBI is urinary tract infection (UTI) which is found in 3-11 percent of febrile infants in various reports.[62,84,85]

In the first month of life, the predominant bacterial infections involved are those acquired from the birth canal. The most common are *Group B Streptococcus* and *Escherichia coli*, with *Staphylococcus aureus*, *Listeria monocytogenes* and other *Gram-negative enteric bacteria* occurring less commonly. These organisms remain the common bacterial pathogens for the infant 4 – 12 weeks of age, but other organisms such as *Streptococcus pneumoniae* and *Neisseria meningitidis* may be seen in these older infants. *Haemophilus influenzae* type b infection is now uncommon due to widespread immunization. *Escherichia coli* is the most frequent pathogen in urinary tract infections. *Salmonella* spp. and *Shigella* spp. are the common causes of bacterial enteritis. In the past few years, the widespread use of intrapartum antibiotics prophylaxis has led to decreased prevalence of early onset *Group B Streptococcal* infections.[86]

The HSV infections are a major cause of morbidity and mortality among neonates with a case fatality rate of 15.5 percent.[87] The prevalence of neonatal HSV infection has been reported to be 25-50 per 100,000 live births in the United States.[2]The rate of HSV infection in a febrile

neonate is 0.3 percent which is similar to the rate of bacterial meningitis in this age group.[3 88] The HSV is transmitted to the newborn infant at the time of delivery and symptoms usually develop within the first 2 weeks of life. The risk of transmission is highest if the mother has primary disease, however the majority of women are asymptomatic at the time of delivery. Other risk factors include vaginal delivery, prolonged rupture of membranes, and the use of fetal scalp monitors. The HSV type 1 and type 2 are causes of disease in 30.0 percent and 70.0 percent of the infants, respectively.[88]

Clinical Assessment

The history and physical examination is the first step in the evaluation of the febrile infant. The initial clinical assessment of the infant involves deciding if the child appears unwell or "toxic". The clinical features that define toxicity include irritability, lethargy, and decreased social interaction. There may be signs of compromised circulation with poor perfusion and cyanosis or respiratory distress.

The clinical diagnosis of SBI young infants is difficult; infants at this age may have SBI in the absence of signs of toxicity. There is a limited range of behavior in the young infant and signs of serious bacterial infection may be subtle. In addition, in the young infant with meningitis there are often nonspecific symptoms with no meningeal signs.

Several studies have used observation scales to help predict SBI. In young infants, clinical observation scales have low sensitivity for the diagnosis of SBI. However, if the infant does not have a high score, the risk of SBI is low. Thus, although clinical assessment cannot adequately predict SBI, it may help define a group of infants who are at low risk for SBI.[4-7]

Large studies have not been performed on the diagnostic accuracy of clinical assessment for invasive HSV infection in an infant who presents with fever. The literature has been focused on patients with confirmed infections, thereby not allowing better understanding of the diagnostic accuracy of clinical and/or laboratory assessments.

Current Recommendations

Traditionally, it was recommended that all febrile infants <90 days of age undergo a complete evaluation for sepsis, including lumbar puncture, be admitted to hospital, and receive parenteral antibiotics for at least 48 hours pending culture results. The rationale for this approach is based on the high rate of SBI in this group and the difficulty with the clinical assessment for sepsis in the young infant where clinical signs of sepsis are often subtle.[4] Although this conservative approach minimizes the risk of infectious complications, it leads to unnecessary hospitalization and treatment with potential for iatrogenic harm to many infants.

There are several studies that have attempted to identify young infants at low risk of SBI who can be safely managed as outpatients. The criteria that are most commonly used in practice are the Rochester criteria. The Rochester criteria identified a low risk group of infants that were well appearing, were previously healthy, had no evidence of bacterial illness on examination and had normal laboratory testing. Infants in the low risk group had an overall rate of SBI of 1.0 percent but no bacteremia or meningitis. The negative predictive value for the criteria was 99.0 percent.[20,29] See Appendix F. Infants who were considered to be low risk of SBI were then managed as outpatients. Some protocols included the use of intramuscular ceftriaxone in the low risk infant group.[8]

The validity of these criteria (i.e., index tests) is measured by sensitivity and specificity. Usually, an index test classifies febrile infants into low and high (or not low) SBI risk groups.

Based on the numbers of infants in these risk groups who consequently would be diagnosed with SBI, sensitivity, specificity, and predictive values for a given index test can be calculated. The sensitivity of a test may be defined as the probability of an infant being classified in high-risk group given the presence of SBI. Specificity - the probability of an infant being classified in low-risk group given the absence of SBI. In this context, two types of error may occur: one when infants with SBI are classified into low-risk groups (false negatives) and the other when infants without SBI are classified into high-risk groups (false positives). Although it is desirable to have both highly sensitive and specific test, it is not feasible because of the tradeoff between the two indices. Predictive values (negative, positive) of a test are probabilities of having or not having SBI given the risk group an infant was classified into. For example, positive predictive value may be defined as a chance of an infant having SBI given the index test classified this infant into high-risk group. Sensitivity and specificity are characteristics of the index test and do not depend on prevalence of SBI in febrile infants. However, both positive and negative predictive values are strongly influenced by prevalence of SBI as well as by sensitivity and specificity of the index test.

The recommended management of febrile neonates, infants under 28 days of age is controversial. Given that the overall SBI rate is higher in the neonate, some experts would advocate for a full sepsis evaluation and hospitalization.[89,90]

Regardless of the local guideline or published protocols, a considerable proportion of clinicians do not adhere to them and manage the patient based on their own clinical judgment.[67,91,92]

Current Issues

The current recommendations for the evaluation and management of the young febrile infant are based on studies conducted in the late 1980's and early 1990's. An up to date systematic review of the diagnostic tests and harms of the management strategies for febrile infants is required. This evidence report was designed to clarify the literature so that previously published guidelines may be updated.

Chapter 2. Methods

Key Questions Addressed in This Report

The evidence report on Diagnosis & Management of Febrile Infants (0 – 3 months) is based on a systematic review of the scientific literature. A technical expert panel helped revise the key questions and provide expertise to the review team during the review process.

The finalized key questions (KQ) are:

KQ1A. In infants < 3 months old who present with a fever, what is the evidence for the sensitivity, specificity and predictive values of individual or combinations of clinical features (including history including information on the mother's history and previous testing, risk factors, findings on clinical exam and formal scoring instruments based on clinical features) for identifying those with serious bacterial illness (SBI)?

KQ1B. In infants < 3 months old who present with a fever, what is the evidence for the sensitivity, specificity and predictive values of individual or combinations of clinical features (including history including information on the mother's history and previous testing, risk factors, findings on clinical exam and formal scoring instruments based on clinical features) for identifying those with rare bacterial infections? How do these findings vary within the age range 0 to 3 months?

KQ1C. In infants < 3 months old who present with a fever, what is the evidence for the sensitivity, specificity and predictive values of individual or combinations of clinical features (including history - including information on the mother's history and previous testing, risk factors, findings on clinical exam and formal scoring instruments based on clinical features) for identifying those with invasive herpes simplex virus infection (HSV)? How do these findings vary within the age range 0 to 3 months?

KQ2A. What is the evidence that clinical features alone, basic laboratory tests (e.g., complete blood count [CBC], urinalysis) alone or the combination are sufficient to identify febrile infants < 3 months who are at low risk of having a serious bacterial illness (i.e., have a high negative predictive value)?

KQ2B. What is the evidence for the potential risks resulting from a delay in the diagnosis and treatment of patients who appear low risk but have a serious bacterial illness?

KQ3A. What is the evidence that clinical features alone, basic laboratory tests (e.g., complete blood count [CBC], urinalysis) alone or the combination are sufficient to identify febrile infants < 3 months who are at high risk of having a serious bacterial illness (i.e., have a high positive predictive value)?

KQ3B. What is the evidence on the benefits and harms of immediate antibiotic (antibacterial and antiviral) therapy and or hospitalization (vs. delaying until diagnostic workup is complete) in patients at high risk of serious bacterial illness?

KQ4. What is the evidence that the presence of an identified viral infection predicts against a serious bacterial infection?

KQ5. What is the evidence that the prevalence of serious bacterial illness varies among febrile infants presenting to primary care and emergency practice? What is the evidence that prevalence affects the predictive value of clinical and laboratory findings?

KQ6. Clinicians base decisions about initial diagnostic work-up and treatment of febrile infants not solely on the infants' medical status but also on their assessments of nonclinical factors (e.g. parental understanding, parents' ability to monitor the patient, access to care). A

strategy of initial observation without extensive diagnostic tests or hospitalization depends on confidence that parents will reliably bring the baby back for a timely followup appointment if conditions warrant. How likely are parents whose infants are less than six months of age and have fever or other potentially serious medical condition to comply with a provider's recommendation that the parent bring the infant back (to that provider or another) for a return appointment to reassess the condition(s) of concern?

KQ6A. What is the evidence that identifiable parental factors (e.g. education, insurance status, living situation, history of previous visits with the provider, time/distance required to travel to an appointment, etc.) influence the likelihood that a parent will adhere to such a recommendation?

KQ6B. What is the evidence that the clinical setting (community practice vs. emergency department and/or hospital outpatient clinic) in which care is sought independently influences the likelihood of compliance with a return appointment?

Data Sources and Search Strategy

Studies were identified through electronic searches in MEDLINE (1950 to September Week 2 2010, OVID interface), MEDLINE in Process (September 29, 2010, OVID interface), CINAHL (1982 to July Week 2 2008, OVID interface), EMBASE (1980 to 2010 Week 37, OVID interface), EBM Reviews, Cochrane Central Register of Controlled Trials (2nd Quarter 2010, OVID interface), the Cochrane Database of Systematic Reviews (2nd Quarter 2010, Wiley interface), PsycINFO (1806 to September Week 2 2010) and PubMed (Updated to September 22nd, 2010). Whenever possible, the electronic searches were limited to 1973 onwards, as this was the year that the first study examining bacteremia in a walk-in clinic was published.[93]

We searched for abstracts in the websites of relevant organizations (i.e., Society of Academic Emergency Medicine, American College of Emergency Physicians, Canadian Association of Emergency Physicians, American Academy of Pediatrics and the Society of Pediatric Research) to identify any unpublished materials. Additional studies were sought from the authors' personal files and by contacting experts.

The search strategies are presented in Appendix A. The electronic search strategies were developed and executed by two experienced information specialists. The main electronic search strategy (MEDLINE) was also peer reviewed using PRESS (Peer Review of Electronic Search Strategies.[94] The searches were combined into a single Reference Manager database and duplicate records were manually deleted, providing a database of unique citations (i.e., titles and abstracts). An update search of the electronic databases was run on October 6th, 2008.

Study Eligibility and Screening

Studies were eligible if they reported the diagnosis of serious bacterial infection (e.g., bacterial meningitis, bacteremia, urinary tract infection) or herpes and/or management of infants (0-90 days of age) with no history of major disease(s), presenting with fever (rectal temperature ≥ 38°C) to a hospital clinic, an emergency department, an acute care clinic, or an outpatient office. Given the lack of relevant evidence found for KQ6 with respect to infants 0 – 90 days of age, the eligibility criteria were expanded to include children aged 0 – 6 months. The diagnostic test accuracy results for infants older than 90 days of age reported in some studies were not considered in this review (KQ1a). Such studies were included in the review only if they reported other relevant data (e.g., prevalence of SBI, outcomes related to management of febrile infants).

Reports of studies examining participants from North America, Australia, New Zealand, Western Europe (i.e., Belgium, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Switzerland, and United Kingdom), Northern Europe (i.e., Denmark, Finland, Norway, Sweden), Israel, Hong Kong, Japan, Taiwan, and Singapore were eligible to be included.

The eligibility for inclusion was not restricted by study design (e.g., randomized or nonrandomized controlled trials, case-series, cohort, case-control, or cross-sectional/prevalence studies). Case reports, systematic reviews, cost-effectiveness analyses, articles with no patient data specific to our inclusion criteria (e.g., editorials without any data, decision analyses), and those written in languages other than English were excluded. A list of the citations (i.e., titles and abstracts) that were potentially relevant but written in languages other than English was retained and provided to the technical expert panel for their review and is available upon request. Studies were included regardless of their publication status.

Two reviewers (GN, ACT) independently screened titles and abstracts of all identified bibliographic records by using a prespecified study relevance form. Two reviewers (CH, ACT) independently screened full-text reports of potentially relevant records. Discrepancies were resolved by discussion or the involvement of a third reviewer (DM).

Data Extraction

Initially, a draft standardized data extraction form was developed by the review team and circulated to the technical expert panel members who provided additional expert input after which the form was accordingly modified. Then, two reviewers (ACT, AT) piloted the modified version of the data extraction form before the actual data extraction process began. Two reviewers (ACT, AT) independently extracted relevant information from the included study reports. Afterwards, a third independent reviewer (FY) verified the extracted data.

Abstracted data included study characteristics (e.g., first author, country of research origin, study design), population examined (e.g., age, ethnicity, mother's demographics), methods used to identify or screen for bacterial or herpetic infection, and treatment or management outcomes of the febrile infants. The diagnostic test results (i.e., sensitivity, specificity, positive and negative predictive values) were directly abstracted when reported. Where possible, the test results were derived from the information provided in studies.

The primary outcome was the set of accuracy indices of an index test (e.g., various laboratory and/or clinical criteria, protocols, laboratory thresholds) against a reference standard (e.g., bacterial culture growth in blood, urine or cerebral spinal fluid, viral culture, molecular testing) in predicting the presence of serious bacterial or herpes simplex virus infections. Secondary outcomes were any events or potential risks associated with a delayed diagnosis/treatment of infants with serious bacterial or herpes simplex virus infection or those associated with immediate treatment (antibacterial or antiviral) for infants classified at a high risk for having a serious bacterial or herpes simplex virus infection. Another outcome of interest was the prevalence of serious bacterial infection in febrile infants stratified by the status of viral infection and a clinical setting of presentation (emergency department vs. outpatient clinic). The rate of parents' compliance in followup examination visits was also one of the relevant outcomes.

Risk of Bias (Study and Reporting Quality)

The study reports were categorized by study design as follows: randomized controlled trial (including quasi-randomized trials), controlled clinical trial, quasi-experimental (e.g., prepost

study), cohort, nested case-control, case-control, cross-sectional, case series, and chart review. Studies reporting diagnostic accuracy data, as well as those for which this data could be derived were classified as diagnostic accuracy studies. Two independent reviewers (ACT, AT) assessed the risk of bias (i.e., study and reporting quality) for the included studies. The reviewers were not blinded to any study details.[95]

The diagnostic test accuracy studies were assessed using the QUADAS tool.[15] This validated instrument consists of 14 items (i.e., questions) asking if a study reported information on the applicability, description of selection criteria, and explanation of study withdrawals. The QUADAS items are rated as 'Yes', 'No', or 'Unclear'. For potential convenience and to efficiently summarize the quality data, the reviewers for each study assigned a score of 1 to 'Yes' rating and score of 0 to 'No' or 'Unclear' rating across all 14 items. For example, a study that reported or described information for 7 out of 14 QUADAS items received a score of 7. For randomized trials we used the three-item Jadad scale, which helps to assess the reporting of randomization generation, blinding, and dropouts/withdrawals.[16] The adequacy of allocation concealment was also assessed for the randomized trials.[17]

We did not assess the study quality of single arm/single cohort studies (for Q2b and Q3b) and chart reviews, as we could not identify a validated way of conducting such appraisals.

Data Synthesis and Analysis

The identified studies were grouped according to the criteria/protocols (i.e., classification methods, index test) used to predict the risk of serious bacterial infection (or herpes simplex virus) in febrile infants. We did not prespecify the definition of SBI in this report. Instead, the definitions from original studies were presented. The classification criteria were categorized into the following groups: a) combined (clinical and laboratory) criteria (Boston, Philadelphia, Rochester, Milwaukee, Yale Observational Score), b) clinical criteria, and c) laboratory criteria. Further, the identified formal protocols and criteria were categorized as 'Low-Risk' and 'Not Low-Risk.'

For each study, two by two tables (i.e., cross-tabulation of infant counts classified by index tests and reference standards used for the diagnosis of serious bacterial or herpes simplex virus infection) were constructed in order to calculate all the necessary diagnostic accuracy parameters with the corresponding 95 percent confidence intervals (95 percent CI). The diagnostic accuracy parameters for index tests against the reference test (i.e., diagnosis) for correctly classifying febrile infants with or without serious bacterial infection into respective 'low risk', 'not low risk', and 'high risk' categories were calculated. Where possible, these parameters were ascertained and calculated for separate types of serious bacterial infection (e.g., bacteremia, meningitis, and bacteremia/meningitis). The performance characteristics of different criteria or thresholds were assembled in tables and were qualitatively compared across studies.

Prevalence rates (with 95 percent CIs) of serious bacterial infection in virus-positive and virus-negative febrile infants were ascertained, calculated, and compared by means of prevalence rate ratios and odds ratios with accompanying 95 percent CIs. The prevalence rates of serious bacterial infection (or herpes simplex virus infection) were qualitatively compared between the two types of setting (i.e., emergency department vs. primary care) through matching the studies by the country of conduct.

The diagnostic accuracy parameters were pooled if they were based on the application of the same criteria/protocol in similar populations of infants for predicting the specific type of bacterial infection (e.g., total serious bacterial infection, urinary tract infection, and bacteremia).

The degree of heterogeneity across the study results was examined graphically by plotting values of sensitivity and specificity. The assessment of heterogeneity was guided by I2 and Chi-squared statistics and corresponding p-values.[96] The potential sources of heterogeneity considered a priori were patient population age (0 – 28 days vs. > 28 days), prevalence of serious bacterial infection (or herpes simplex virus infection), different index tests (i.e., laboratory/clinical criteria, protocols), and different thresholds for any given index test.

The Summary Receiver Operating Characteristic (SROC) curves based on pairs of sensitivity and specificity values were also constructed to assess the between-study variability in sensitivity and specificity for a given classification criteria or to detect outliers.[18] For each SROC, area under curve (AUC) and Q* statistic were generated to assess the overall diagnostic performance of an index test (i.e., classification criteria/protocol). The AUC may be defined as the probability of any given index test (i.e., protocol/criteria) correctly classifying randomly chosen pair of infants with and without SBI into high- and low-risk groups, respectively. The Q* statistic is the value of true positive rate at which the curve intersects the diagonal line of identity (i.e., where sensitivity and specificity are equal).[97] This statistic measures the overall degree of test accuracy based on SROC data. For example, the Q* statistic of 0.6 indicates a very low degree of discrimination (both sensitivity and specificity of 60.0 percent). Whereas, the Q* statistic of 1.0 signifies perfect discriminatory ability of the test (both sensitivity and specificity of 100.0 percent).

For an index test, the heterogeneity in overall diagnostic performance was examined by generating diagnostic odds ratios (DOR) and the degree of their variability across studies. In the absence of statistically significant heterogeneity, the DOR were pooled using the DerSimonian and Laird random effects model. The DOR is the difference between the log odds of true positive and false positive rates (TPR and FPR); it indicates the degree of test accuracy in discriminating patients with and without disease; a greater magnitude of DOR is suggestive of a better diagnostic performance of an index test. [98]

The SROC is a method of summarizing the performance of a diagnostic test across different studies regardless of thresholds used in them. It represents a plot of the TPR (i.e., sensitivity) as a function of the FPR (1 – specificity).[99] Initially, logit transformations of the TPR and FPR are performed to specify two parameters: the sum of the two transforms (i.e., logit TPR + logit FPR) denoted as ‘s’ and the difference between the two transforms (i.e., logit TPR - logit FPR) denoted as ‘D’ (i.e., the DOR). Then, the association (i.e., slope and y-intercept) between ‘s’ and ‘D’ is estimated using a linear regression, where ‘s’ is regressed on ‘D’. The SROC curve is constructed on an ROC plan by plugging the values for slope and y-intercept into the SROC equation.[18,99] The statistical analyses were performed using Meta-Disc (version 1.4).[100]

Chapter 3. Results

Literature Search

In total, 83 unique studies (91 records) were included in this review. The study flow process is depicted in Figure 1 (PRISMA flow chart).

Five studies were reported in multiple publications: Bilavsky et al. (2009/2010),[46,78] Levine et al. (2004/2005/2009),[68,72,101] Maniaci et al. (2008),[53,102] Chen et al. (2008 and 2009),[63,103] and the PROS study by Pantell et al. (2002/2004/2005/2008).[5,52,67,104]

The flow of the included studies for each key question is as follow:

- KQ1a: All criteria used to identify risk of SBI in febrile infants (n = 61).[5,9-13,19,21-27,31,32,35,38,39,42,43,45,50,51,56,57,60,62,84,105,106,20,28-30,33,34,36,37,40,41,44,46-49,53,55,58,59,63,65,79,80,107-113]
- Combined criteria/protocols to identify infants at risk of SBI (n = 19)[9-12,19-29,38,80,106,110]
- Other combined criteria to identify infants at risk of SBI (n = 16)[5,30-37,40,56-58,60,62,79]
- Clinical criteria alone to identify infants at risk of SBI (n = 15)[5,34-36,38-42,63,65,79,108,112,113]
- Laboratory criteria alone to identify infants at risk of SBI (n = 27)[5,13,34-36,40-51,53,55,57,59,79,84,105,107,109,111]
- KQ1b: Test characteristics of criteria to identify SBI in febrile infants- variation within age ranges (n = 14) [9-12,19,21,23,24,26,31,34,51,53,108]
- KQ1c: Test characteristics of criteria to identify HSV in febrile infants (n = 4)[28,42,54,55]
- KQ2a: Test characteristics of Low Risk criteria (n = 23)[5,9-12,20-29,31,32,40,56,58,60,79,80]
- KQ2b : Management of Low Risk febrile infants- Delayed antibiotic treatment (n = 15)[5,9,10,12,20-22,24,25,32,58-61,77]
- KQ3a: Test characteristics of High Risk criteria (n = 10)[30,34-37,40,49,57,62,63]
- KQ3b: Management of High Risk febrile infants- Immediate antibiotic treatment (n = 10)[9,10,12,19,35,59,61,73,76,114]
- KQ4: Evidence for viral coinfections in febrile infants (n = 11) [28,29,64-71,81]
- KQ5: Prevalence of SBI in primary vs. emergency care (n = 69)[5,9-13,19,21,23-27,31,35,38,39,43,45,50,51,54,56,57,66,68,70,74,75,84,105,10628,29,33,34,36,37,40-42,44,46,47,53,55,60,62,64,65,71,73,76-79,107-112,115-121]
- KQ6: Evidence for identifying parental and clinical setting factors affecting adherence to provider's recommendation (n = 4)[19,61,68,80]

Study Populations

The reviewed studies included febrile infants aged 0 – 90 days with fever (rectal temperature ≥ 38°C) and with no history of major disease(s) who had been admitted and assessed in an emergency department, an outpatient clinic, or a primary care physician's office. The source of fever for most of these infants was described as not known (fever without a source or FWS). These studies excluded infants who had a current or previous antibiotic treatment. Of the 83 included studies, 58 (69.9 percent) were conducted in North America, 8 (9.6 percent) in Western Europe, and 7 (8.4 percent) in Asia (Taiwan or Korea). Information on ethnicity and socioeconomic status were poorly reported in majority of reports. Span of data collection for these studies ranged from 1974 to 2009. Twelve of the studies included more than one hospital/office sites including the Pediatric Research in Office Settings (PROS) study, which included 219 physicians' office practice sites. The remaining studies were conducted at a single

site. Twenty two studies reported information on neonates (0 – 28 day old). The detailed information for all included studies is presented in Appendix C (Evidence Tables 1 – 8).

Methods for Classification (i.e., Screening Tests to Predict SBI) and Diagnosis of SBI and Viral Infection

The reviewed studies reported a wide array of index tests (i.e., criteria) for predicting the risk of serious bacterial infection in febrile infants assessed in emergency departments or outpatient clinics. These criteria were comprised of either clinical or laboratory features alone or represented a variety of combinations of clinical features and laboratory thresholds which were tested in febrile infants in order to predict serious bacterial infection. Some of these tests were commonly used criteria such as the Boston,[23,24] Philadelphia,[9,11,12,22,23,27,80] Rochester, [10,19-21,25-29,38] Milwaukee [10], and Yale scoring criteria.[101,110] (Appendix F) Other reported criteria were various of clinical (e.g., ill or toxic appearance, impression of sepsis, age, rectal temperature) and/ or laboratory features using different techniques with varying thresholds such as serum WBC counts, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), absolute band count (ABC), cerebrospinal fluid (CSF) (e.g. presence of pleocytosis), Procalcitonin levels (PCT), and urine analysis (e.g., microscopy: WBC of spun urine, dipstick: leukocyte esterase/nitrite).[5,20,29,31-39,41,42,47,56-58,60,62,108]

The presence of serious bacterial infection was determined by confirming bacterial growth in blood, cerebrospinal fluid, stool, and/or urine. The definition of urinary tract infection was based on supra-pubic tap > 1,000 colony forming units/mL or catheterization > 10,000 colony forming units/mL) although one report employed the higher threshold of > 20,000 colony forming units/mL with a single organism.[5] Although serious bacterial infection studies consistently reported on bacteremia, meningitis and urinary tract infection, some other studies chose to include osteomyelitis, suppurative arthritis, soft tissue infections (cellulites, abscess, mastitis), gastroenteritis, and pneumonia. The following bacterial isolates were considered as pathogens: *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Klebsiella* species, *Salmonella* species, Group A *Streptococcus*, Group B *Streptococcus*, *Haemophilus influenzae* type b, *Staphylococcus aureus*, *Moraxella catarrhalis*, *Escherichia coli*, *Listeria monocytogens*, or other enteric gram-negative rods. Urine cultures were thought contaminated if the symptoms of febrile infants disappeared without appropriate treatment or if the isolated bacteria were not regarded as a pathogen.

E-coli, was found to be the pathogen for 68 percent of UTI cases (1040/1533, range 37.5 percent to 100 percent). *E-coli* was the organism for 30 percent (25/38) of cases of bacteremia, and 14 percent (11/77) of cases of bacterial meningitis. In total, *E-coli* was the organism found for 60 percent of total SBI cases (1136/1890).

The presence of influenza A was confirmed by documented positive direct antigen Flu A testing or positive viral culture. Enterovirus (EV) was diagnosed using polymerase chain reaction or culture (blood, cerebrospinal fluid, nasopharyngeal and throat swabs). The diagnosis of respiratory syncytial virus (RSV) was documented by rapid immunoassay or viral culture.[29,66,68,71,81,122]

Study Outcomes

The outcomes of reviewed studies were performance characteristics (i.e., accuracy indices: sensitivity, specificity, positive and negative predictive value, the area under receiver operating

curve, likelihood ratios) of variety of classification methods in predicting the risk of serious bacterial infection in febrile infants (Questions 1a, 1b, 2a, 3a) or herpes simplex virus (HSV) infection (Question 1C). Other studies compared the rates of serious bacterial infection in febrile infants between those with or without viral infection (prevalence rates, odds ratios) (Question 4).[28,29,66-68,71,81]

Several studies in 'low-risk' or 'not low-risk' groups of infants (as classified by index tests or criteria) explored and reported outcomes such as rates of hospitalization, total health care costs associated with hospitalization, incidence of serious bacterial infection, treatment-related harms (e.g., infiltrated intravenous lines, drug-related rush, diarrhea), parents' rate of compliance, or rates of culture (blood, urine, cerebrospinal fluid) contamination.[5,9,10,12,19-22,24,25,31,32,58,60,114]

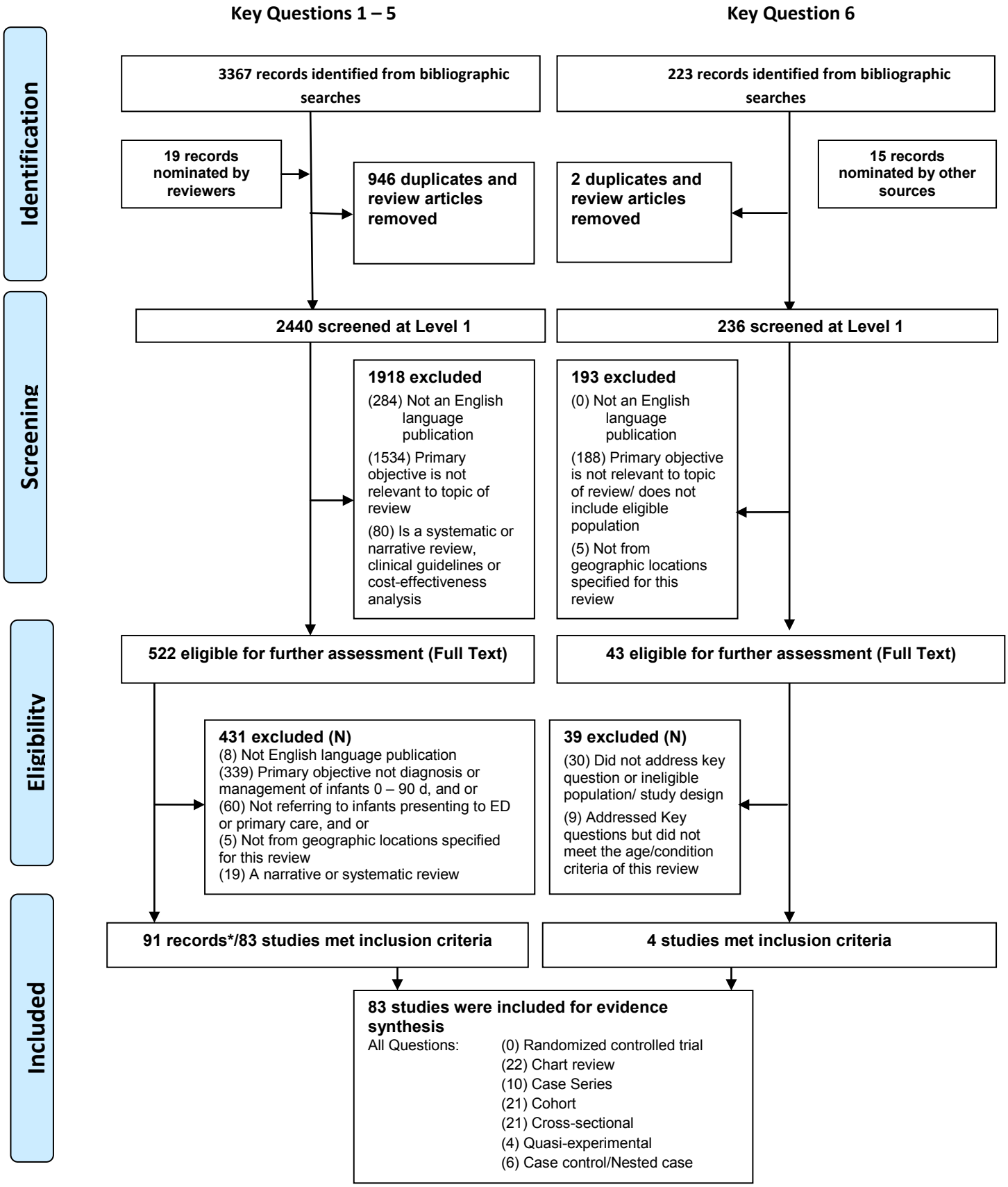
Risk of Bias (Study and Reporting Quality)

The study and reporting quality of the included in the review studies were assessed using the Quality Assessment of Studies of Diagnostic Accuracy Included in Systematic Reviews (QUADAS). (Appendix G)

The mean (range) quality score based on 14-item QUADAS tool for included studies was 10.2 [44,107]-14[9,60]). For example, the study with lowest quality score of 3 was rated 'Yes' on only 3 items and the study with the highest score was rated 'Yes' on all 14 items. About 86.9 percent of the studies clearly described selection criteria, 91.3 percent used a valid reference standard for the diagnosis, and in 68.1 percent of studies there was a short period of time between reference standard and index test. The reference standard and index tests were reported to be independent in about 75.4 percent of the studies. Only 28.9 percent of the studies explicitly reported that test results were interpreted without knowledge of either reference standard, or index test results (33.3 percent). The withdrawals were explained in 54.7 percent of the studies.

Based on qualitative assessment, study quality did not seem to account for the observed discrepancies in the diagnostic accuracy parameters for a specific criteria or protocol across the studies. For Boston, Rochester, Philadelphia, Milwaukee criteria, comparison of results according to QUADAS score was not possible due to: a) relative lack of variability in quality, b) different combinations of clinical criteria used, c) various laboratory criteria (or thresholds) used, and/or d) various target conditions for which a given index test was evaluated (e.g., serious bacterial infection, bacteremia, meningitis).

Figure 1. Quorum flow chart - Febrile infant (0 – 3 months)



KQ 1A. In infants < 3 months old who present with a fever, what is the evidence for the sensitivity, specificity and predictive values of individual or combinations of clinical features (including history including information on the mother's history and previous testing, risk factors, findings on clinical exam and formal scoring instruments based on clinical features) for identifying those with serious bacterial illness (SBI)?

The prevalence of SBI amongst all febrile infants (0 – 90 days of age) is about 9.0 percent. The prevalence of SBI is greater in neonates aged 0 – 28 days (11.5-25.0 percent) compared to older infants aged 60 – 90 days (7.0-9.0 percent). The most common bacterial illness is urinary tract infection (6.0-7.0 percent). Bacteremia and meningitis occur in about 1 percent and 0.3 percent, respectively.[10,11,23,123-125] The most common bacterial pathogen for SBI in the young infant is *Escherichia coli*, with *group B Streptococcus*, *Staphylococcus aureus*, *Listeria monocytogenes,* and other gram-negative enteric bacteria being the other likely pathogens in this age group.

In total, 56,813 infants were enrolled in the included studies, from which 5,153 were diagnosed with SBI (9.1 percent). Across all studies, the prevalence rate of total SBI was higher in the neonates (age: 0 – 28 days) ranging from 11.5 percent[74] to 25.3 percent[59] compared to the older infants (age > 28 days) in whom it ranged from 4.1 percent[10] to 12.6 percent.[77]

The type of SBI was not defined in 16 studies. [33,64,66,68,70,74-77,77,113,115-117,117,119] Some studies did not report on various types of SBI but only focused on one type (e.g., bacteremia or UTI only). Such studies are discussed in detail throughout the results section but were not used to calculate the proportion of UTI and other types of SBIs. Therefore, 45 studies reporting on various diagnoses were used to calculate the rate of UTI, bacteremia, and meningitis among infants 0 – 90 days of age.

According to these studies, the rate of total SBI was 10.5 percent. Proportion of various type of SBI included: 67.8 percent UTI; 12.9 percent bacteremia; 4.1 percent bacterial meningitis; 2.1 percent bacteremia + UTI; 2.0 percent pneumonia; 1.1 percent bacteremia + meningitis; and 9.9 percent other types of infections (cellulitis, gastroenteritis, others).

The diagnosis of UTI accounted for the greater proportion of all types of SBI (bacteremia, meningitis, pneumonia, cellulitis, gastroenteritis, others. For example, the prevalence of diagnosis of UTI across studies ranged from 15.0 to 94.0 percent. In contrast, the ranges for this prevalence for bacteremia and meningitis were 0 to 41 percent and 0 to 25.9 percent, respectively (with the exception of one study reporting a rate of 34 percent bacterial meningitis for infants 0 – 60 days of age[106]).

In total, *E. coli* was the organism found in 60 percent of total SBI cases (1136/1890) where the information was reported (35 studies). [9,11,12,19,21-23,25,30-32,35,36,38,41,44,46-50,53,55-57,60,62,79,80,101,105,106,109,112]

Thirty five studies reported the occurrence of bacteremia and information about the associated type of isolated organisms (401 cases).[9-12,19-24,26,30,31,34,36,38,40-42,44,46,47,53,55-57,59,60,63,65,106,107,109,110] In these studies, *Streptococcus* Group B and *E. coli* were the organisms that caused 36.4 percent and 28.0 percent of all bacteremia cases, respectively. *Streptococcus pneumoniae* accounted for 6.9 percent of bacteremia cases. *Staphylococcus aureus* and *Streptococcus* group A/C were found in only 4.5% and 1.5% of bacteremia cases, respectively. Other organisms (*Neisseria Meningitidis*, S*almonella species*, *Klebsiella pneumoniae*, *Listeria monocytogenes*, *enterococci, Enterobacter cloacae*, *Streptococcus bovis*, *Yersinia enterocolitica*,

Proteus mirabilis, *Gram negative rod*, *Pseudomonas stutzeri*, *Enterobacter coacae*, *Streptococcus pyogenes*, *S. epidermidis*, and *Streptococcus group D*) were responsible for less than 4.0 percent of all bacteremia cases.

Thirty five studies reported the occurrence of meningitis and information about the associated type of isolated organisms (142 cases).[5,9,11,12,22-24,26,30,30-32,34,36-38,40-42,44,46-48,55,57-60,63,65,79,106,107,109,126] In these studies, *Streptococcus* group B and *E-coli* were the organisms that caused 35.2 percent and 12.7 percent of all meningitis cases, respectively. *Streptococcus pneumoniae*, *Listeria monocytogenes*, and *Neisseria meningitidis* accounted for 8.5 percent, 5.6 percent, and 4.5 percent of meningitis cases, respectively. Other organisms (*S. epidermidis, Klebsiella pneumonia, Listeria monocytogenes, Proteus mirabilis, Streptococcus bovis, Listeria meningitis, Enterobacter coacae, Pseudomonas stutzeri, and Salmonella meningitis*) were responsible for less than 4.0 percent of all meningitis cases.

Screening Tests and Their Performance

This review included 62 studies that reported data on the performance characteristics (i.e., accuracy indices: sensitivity, specificity, PPV, NPV, ROC-AUC, LRs) of variety of criteria used in predicting the risk of SBI in febrile infants admitted to emergency departments or outpatient clinics (Tables 2-5).

In this section, the classification criteria (i.e., index tests) for predicting the risk of SBI were divided into the following four broad groups: 1) Combined classification criteria (clinical and laboratory), 2) Clinical criteria, and 3) Laboratory criteria.

Combined Clinical and Laboratory Criteria/Protocols

Philadelphia, Boston, Rochester, Milwaukee criteria, and Yale observation scores.

Total serious bacterial infection. The use and performance characteristics of the Philadelphia, Boston, and Rochester, Milwaukee criteria, and Yale Observation Score (YOS) for predicting the risk of SBI in febrile infants was reported in and/or ascertained from 19 studies (Table 2). [9-12,19-29,38,80,106,110]

The Rochester criteria was evaluated for identifying SBI in 10 studies.[10,19-21,25-29,38] The sensitivity of Rochester criteria in these studies ranged from 52.0 percent[19] to 100.0 percent.[20] The infants' age eligibility for the Rochester criteria is 56 days or younger. Note that in the study,[19] with the lowest value of sensitivity for the Rochester criteria (52.0 percent), the age of infants exceeded 56 days and was up to 89 days. The corresponding values for specificity ranged from 26.3 percent[10] to 68.8 percent.[20] The PPV values for Rochester criteria in 8 studies were 3.3 percent (95 percent CI: 1.9, 5.8),[10] 12.3 percent (95 percent CI: 9.6, 15.6),[25] 12.3 percent (95 percent CI: 10.0, 16.0),[27]16.6 percent (95 percent CI: 13.8, 20.0),[28] 23.8 (95 percent CI: 15.7, 34.3),[20] 24.7 (95 percent CI: 16.4, 35.2),[29] 26.8 percent (95 percent CI: 17.2, 38.8),[26] and 33.6 percent (95 percent CI: 25.1, 42.1).[21] All NPV values across the 8 studies[10,20,21,25-29] ranged from 94.0 percent to 100.0 percent. The use of Rochester criteria[10] and similar criteria[56,58] reported to have missed four cases of bacterial meningitis.

The evaluation of the Philadelphia protocol for identifying infants with SBI was reported for seven studies.[9,11,12,22,23,27,80] Overall, the sensitivity of this protocol was high, ranging from 84.4 percent (95 percent CI: 67.0, 95.0)[11] to 100.0 percent.[9,12] The specificity ranged from 26.6 percent (95 percent CI: 22.3, 31.4)[9] to 66.6 percent (95 percent CI: 62.0, 71.0).[22] The range of

PPVs was 14.0 percent - 26.5 percent. In all 7 studies,[9,11,12,22,23,27,80] the NPVs for Philadelphia protocol ranged from 95.0 percent[11] to 100.0 percent.[9,12]

In three studies, the Boston criteria[23,24,38] were evaluated for predicting risk of total SBI. The sensitivity for total SBI across three studies ranged from 82.0 percent[23] to 99.5 percent.[38] Note that the study with the lowest sensitivity[23] included infants 28 days or younger, that is, outside the protocol's age eligibility (i.e., 28 - 89 days). The NPVs for the Boston criteria were also high ranging from 97.0 percent[23] to 98.0 percent.[24]

The performance of the Milwaukee protocol for predicting risk of total SBI was reported in one study.[10] This protocol demonstrated a high sensitivity (96.0 percent, 95 percent CI: 88.0, 100.0) and low specificity (28.0 percent, 95 percent CI: 23.0, 36.0).

The Young Infant Observation Scale (YIOS) was evaluated for predicting risk of total SBI in one study of febrile infants 60 days or younger.[106] The YIOS included three variables (i.e., affect, respiratory status, and peripheral perfusion) as statistically significant factors revealed in a stepwise discriminant analysis. These factors were scored as 1 (no compromise), 3 (intermediate level of compromise), or 5 (severe compromise). For predicting the risk of total SBI, the YIOS score ≥7 yielded the sensitivity, specificity, and NPV of 76.0 percent 75.0 percent, and 96.0 percent, respectively.[106]

In two studies,[101,110] the Yale Observation Score (YOS) was tested to predict urinary tract infection (UTI) in febrile infants 60 days or younger[101] and total SBI in 29-56 days old infants.[110] In the first study,[101] the application of the YOS > 10 (denoting a high risk of SBI given ill appearance) in predicting UTI was associated with low sensitivity (4.4 percent, 95 percent CI: 1.4, 11.5) and PPV (5.6 percent, 95 percent CI: 1.8, 14.5). The specificity and NPV were 92.6 percent (95 percent CI: 90.6, 94.1) and 90.5 percent (95 percent CI: 88.5, 92.3), respectively. In the second study,[110] the YOS > 10 criterion demonstrated higher sensitivity (33.3 percent, 95 percent CI: 11.3, 64.5) in identifying total SBI. The sensitivity of this test in predicting bacterial sepsis was 75.0 percent (95 percent CI: 21.9, 98.6).[110]

Statistical analysis (Rochester criteria and Philadelphia protocol). The Summary Receiver Operating Characteristic (SROC) curves based on pairs of sensitivity and specificity values across the studies were constructed for Rochester criteria[20,21,25-29] and Philadelphia protocol (see Figures 2-3).[9,11,12,22,23,27] The SROC is a method of summarizing the performance of a diagnostic test across different studies regardless of thresholds used in them.

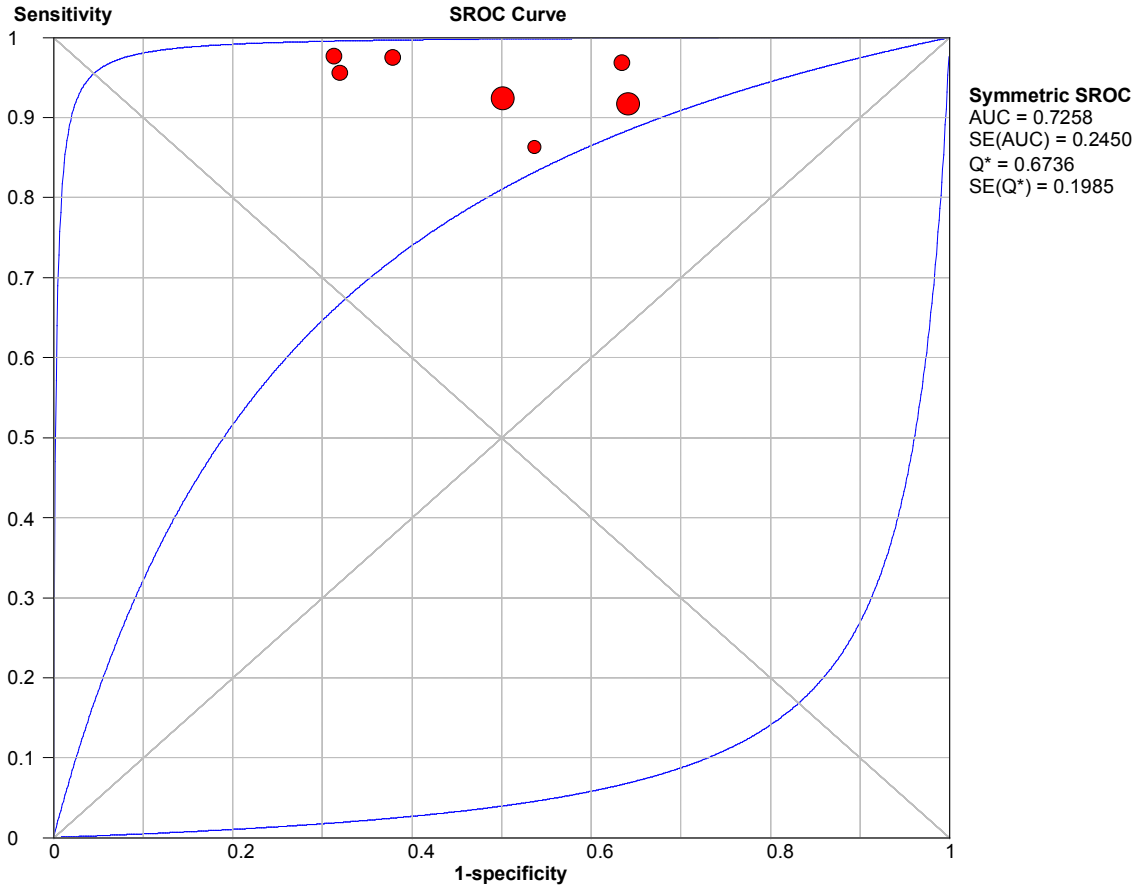
The initial analysis revealed an outlier pair of sensitivity and specificity values for Rochester criteria observed in one study.[10] This study was excluded from the analyses because it failed to report the inclusion, exclusion criteria as well as baseline characteristics of infants which prevented from exploring sources of heterogeneity contributed by this study. The exclusion of this study led to a reduction of heterogeneity for sensitivity of the Rochester criteria from I2 = 78.6 percent (Chi-squared = 23.39) to I2 = 24.5 percent (Chi-squared = 7.94, p = 0.24). The pooled estimate of sensitivity for the Rochester criteria was 94.0 percent (95 percent CI: 91.0, 96.0).[20,21,25-29] There was a statistically significant heterogeneity in specificity values for the Rochester criteria (I2 = 95.9 percent, Chi-squared = 147.0, p<0.01). The pooled specificity was 49.0 percent with individual specificity values ranging from 36.0 percent to 69.0 percent. (Figures 3-4)

For the Philadelphia protocol,[9,11,12,22,23,27] there was a statistically significant heterogeneity with respect to both sensitivity and specificity values (Chi-squared = 20.4, p=0.001 and Chi-squared = 157.1, p<0.001, respectively). The pooled estimates (ranges) for sensitivity and

specificity of the Philadelphia protocol were 92.9 percent (84.4 percent-100.0 percent) and 46.1 percent (26.6 percent-66.7 percent), respectively. (Figures 5-6)

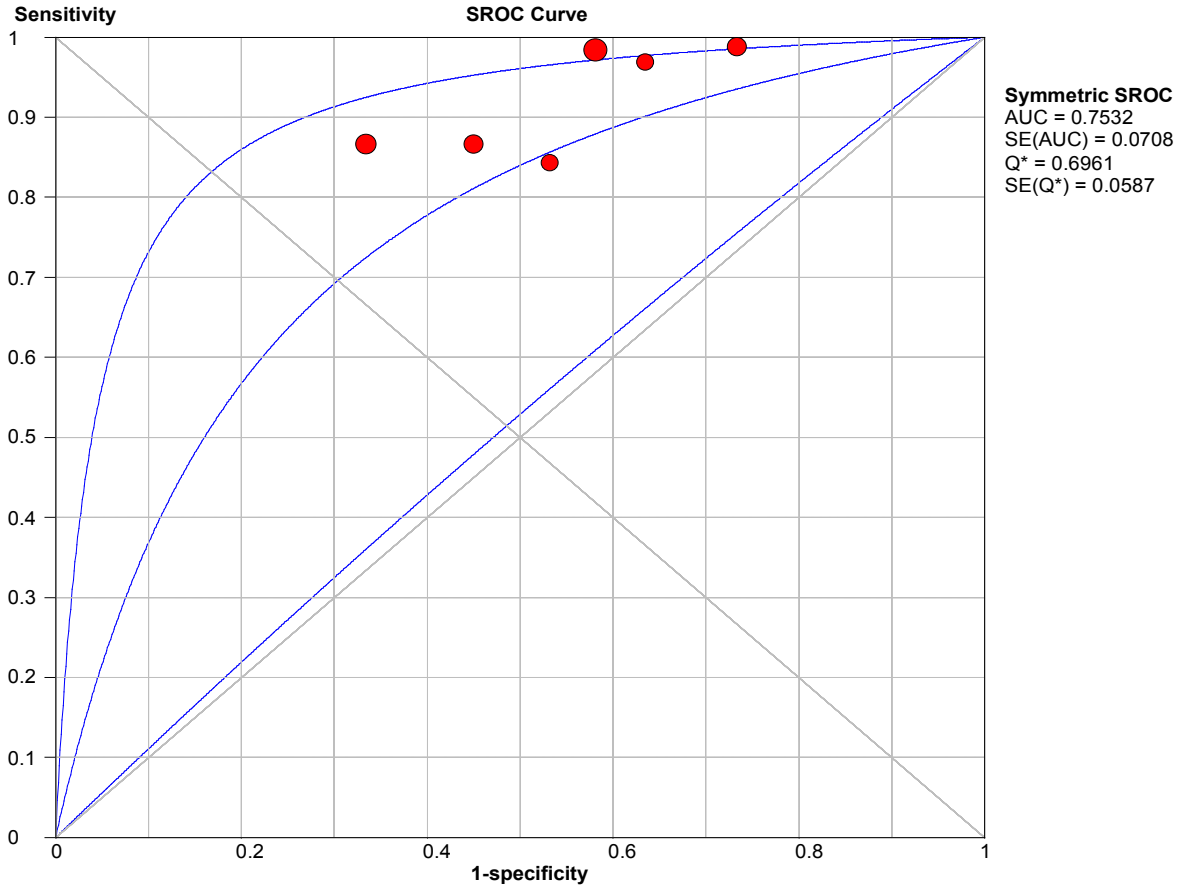
For the Rochester criteria, the area under curve (AUC) and Q* statistic were 0.73 (SE=0.25) and 0.67 (SE=0.20), respectively. The Philadelphia protocol yielded the AUC of 0.75 (SE=0.07) and Q* statistic of 0.69 (SE=0.06). The heterogeneity across diagnostic odds ratios (DOR) was statistically nonsignificant for both Philadelphia protocol (Chi-squared = 7.15, p = 0.21) and Rochester criteria (Chi-squared = 12.0, p = 0.06). The pooled estimates of DOR (based on random effects model) for the Rochester criteria and Philadelphia protocol were 14.25 (95 percent CI: 6.89, 29.46) and 11.0 (95 percent CI: 6.1, 19.8), respectively.

Figure 2. Summary receiver operating characteristic curve (Rochester criteria)



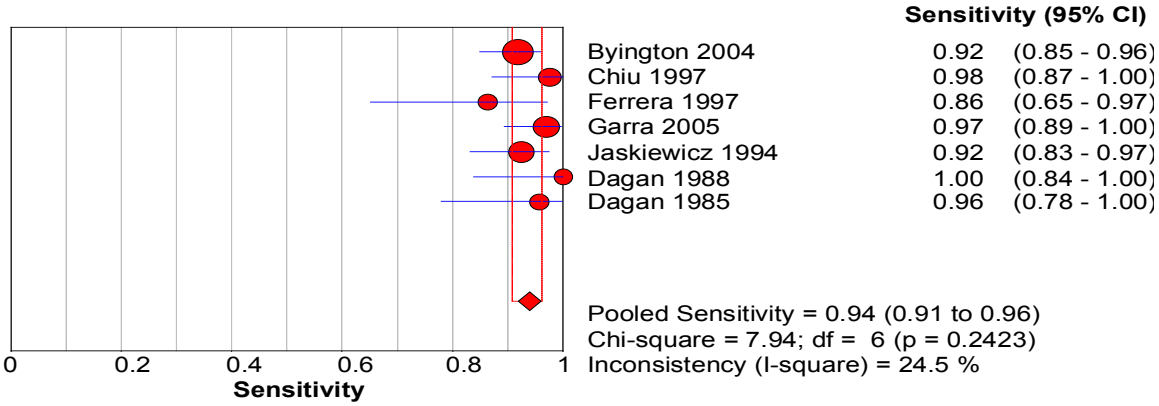
Abbreviations
SROC: Summary Receiver Operating Characteristic Curve
AUC: Area Under Curve
SE: standard error
Q*: Q-statistic
Note: The AUC of 0.72 is interpreted as the 72.0% probability of the Rochester criteria correctly classifying randomly chosen pair of infants with and without SBI into high-risk (or not low-risk) and low-risk (or not high-risk) groups, respectively

Figure 3. Summary receiver operating characteristic curve (Philadelphia protocol)



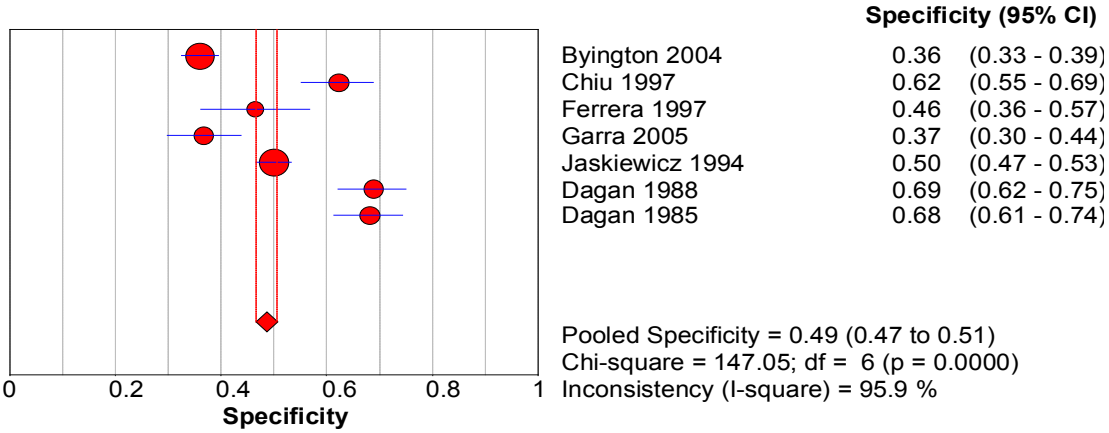
Abbreviations
SROC: Summary Receiver Operating Characteristic Curve
AUC: Area under Curve
SE: standard error
Q*: Q-statistic
Note: The AUC of 0.75 is interpreted as the 75.0% probability of the Philadelphia protocol correctly classifying randomly chosen pair of infants with and without SBI into high-risk (or not low-risk) and low-risk (or not high-risk) groups, respectively

Figure 4. Sensitivity plots (Rochester criteria)



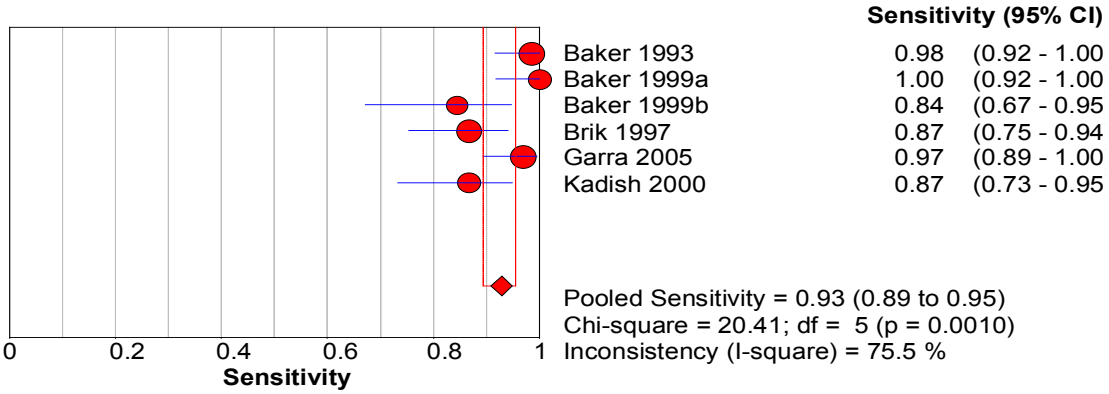
References: Byington 2004, [28] Chiu 1997, [21] Ferrera 1997, [26] Garra 2005, [27] Jaskiewicz 1994, [25] Dagan 1988, [20] and Dagan 1985. [29]

Figure 5. Specificity plots (Rochester protocol)



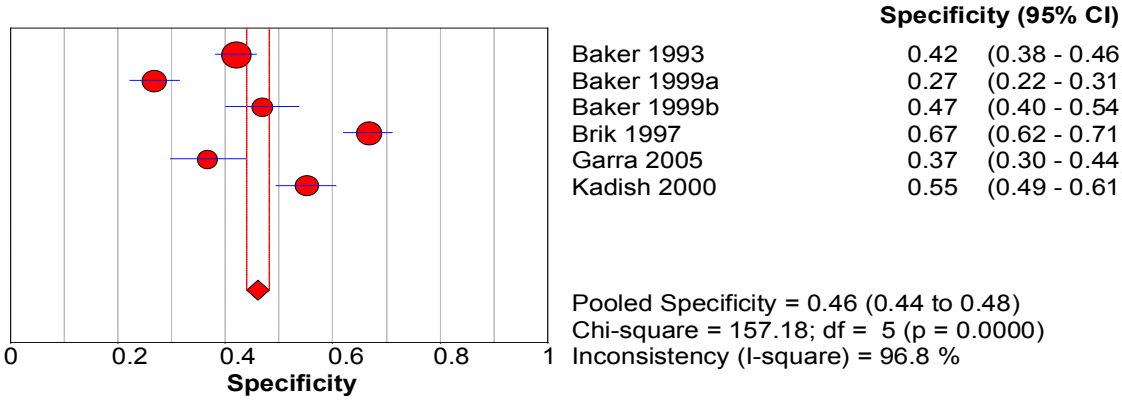
References: Byington 2004, [28] Chiu 1997, [21] Ferrera 1997, [26] Garra 2005, [27] Jaskiewicz 1994, [25] Dagan 1988, [20] and Dagan 1985.[29]

Figure 6. Sensitivity plots (Philadelphia protocol)



References: Baker 1993, [12] Baker 1999a, [9] Baker 1999b, [11] Brik 1997, [22] Garra 2005, [27] and Kadish 2000 [23]

Figure 7. Specificity plots (Philadelphia protocol)



References: Baker 1993, [12] Baker 1999a, [9] Baker 1999b, [11] Brik 1997, [22] Garra 2005, [27] and Kadish 2000 [23]

Specific types of serious bacterial infection. The accuracy indices of Boston,[23] Philadelphia,[9,11,12,22,23,27] and Rochester [10,19-21,25-27,29] protocols/criteria for identifying febrile infants with specific types of SBI (e.g., bacteremia, meningitis, bacteremia/meningitis) were ascertained for 14 studies. These criteria (not reported for the Milwaukee protocol[10]) performed similarly in terms of sensitivity, specificity, and NPV in predicting bacteremia and total SBI (Table 2). For all these criteria, the PPVs were much lower for identifying infants with bacteremia (range: 0.5 percent[10]- 10.1 percent[29]) or meningitis (range: 0.5 percent[10] – 2.7 percent[11]) compared to those for identifying total SBI (range: 3.3 percent[10] – 33.6 percent[21]), reflecting a lower prevalence rate of bacteremia and meningitis. In three studies, Rochester criteria[10] and Philadelphia protocol[11,23] demonstrated a slightly better sensitivity for correctly identifying infants with meningitis (50.0 percent[10]and 100.0 percent,[11,23]) than infants with bacteremia (33.3 percent,[10] 83.3 percent,[23] and 75.0 percent,[11] respectively). Numerically, sensitivity for identifying bacteremia did not differ across the Philadelphia protocol (75.0 percent,[11] 83.3 percent,[23]and 100.0 percent[12]), Boston (75.0 percent[23]), and Rochester criteria (75.0 percent[27] and 100.0 percent [20,26,29]), except for one study in which the sensitivity value for the Rochester criteria was 33.3 percent.[10] There was insufficient data to compare the validity indices across these criteria with respect to the identification of infants with meningitis.

Table 2. Test results – Combined clinical & laboratory criteria I (Boston criteria, Milwaukee protocol, Philadelphia protocol, Rochester criteria, and Yale observation score)

Study ID	N/n* Age range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
			Boston Criteria				
Kadish (2000)[23]	394/372 1 – 28 d	Total: 45 (12.1) UTI: 32 Bacteremia: 12 Meningitis: 5 Cellulitis: 3 Septic arthritis: 1 Gastroenteritis: 1 Pneumonia: 1	82.0 [67.4, 91.5]	68.0 [62.8, 73.1]	26.0 [19.4, 34.4]	97.0 [93.0, 98.4]	LR^+=2.58 LR-= 0.26
		Bacteremia: 12	75.0 [42.8, 93.3]	63.3 [58.1, 68.3]	6.4 [3.1, 12.1]	98.7 [96.0, 99.6]	LR^+=2.04 LR-= 0.39
Kaplan (2000)[24]	3,166/2,190 28 – 90 d	Total: 191 (8.7) Types of SBI: NR	88.5 [82.8, 92.5]	56.2 [54.0, 58.4]	16.2 [14.0, 18.6]	98.1 [97.0, 98.7]	LR^+= 2.02 LR-= 0.20
Stanley (2005)[38]	5,279/5,279 0 – 90 d	Total: 480 (9.1) UTI: 305 Meningitis: 10 Bacteremia: 39 Bacteremia/meningitis: 8 Bacteremia/UTI: 11 Pneumonia: 70 Cellulitis: 26 Bacterial enteritis: 11	99.5 [98.3, 99.9]	NR	NR	NR	NR
			Milwaukee Protocol				
Bonadio (1993)[10]	534/534 29 – 60 d	Total: 24 (4.5) UTI: 11 Bacterial meningitis: 4 Bacteremia: 6 Bacterial enteritis: 2 Pneumonia: 1	96.0 [88.0, 100.0]	28.0 [23.0, 36.0]	5.9 [3.6, 8.2]	99.3 [98.0, 100.0]	LR^+= 1.33 LR-= 0.15
			Philadelphia Protocol				

Table 2. Test results – Combined clinical & laboratory criteria I (Continued)

Study ID	N/n* Age range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
Baker (1999)[11]	254/254 3 – 28 d	Total: 32 (12.5) UTI: 17 Bacteremia: 8 Meningitis: 4 Cellulitis: 1 Gastroenteritis: 2 Peritonitis: 1 Osteomyelitis: 1	84.4 [67.0, 95.0]	46.8 [40.0, 53.0]	18.6 [12.0, 25.0]	95.4 [90.0, 99.0]	LR^{+}=1.58 LR-= 0.33
		Bacteremia: 8	75.0 [35.6, 95.5]	43.5 [37.2, 49.9]	4.1 [1.7, 9.1]	98.1 [92.7, 99.7]	LR^{+}=1.32 LR-= 0.57
		Meningitis: 4	100.0 [39.6, 100.0]	43.6 [37.4, 49.9]	2.7 [0.9, 7.3]	100.0 [95.7, 100.0]	LR^{+}=1.77 LR-= 0
Kadish (2000)[23]	394/372 1 – 28 d	Total: 45 (12.1) UTI: 32 Bacteremia: 12 Meningitis: 5 Cellulitis: 3 Septic arthritis: 1 Gastroenteritis: 1 Pneumonia: 1	87.0 [72.5, 94.4]	55.0 [49.5, 60.5]	21.0 [15.5, 27.6]	97.0 [92.8, 98.7]	LR+=1.92 LR-= 0.24
		Bacteremia: 12	83.3 [50.8, 97.0]	51.1 [45.8, 56.3]	5.3 [2.7, 9.9]	98.9 [95.6, 99.8]	LR+=1.70 LR-= 0.32
		Meningitis: 5	100.0 [46.3, 100.0]	50.7 [45.5, 55.9]	2.6 [0.9, 6.5]	100.0 [97.4, 100.0]	LR+=2.03 LR-= 0
Baker (1993)[12]	747/747 29 – 56 d	Total: 65 (8.7) UTI: 24 Bacteremia: 19 Meningitis: 9 Cellulitis: 6 Gastroenteritis: 13 Adenitis: 1	98.0 [92.0, 100.0] 100.0‡ [93.0, 100.0]	42.0 [38.0, 46.0] 42.0‡ [38.3, 45.9]	14.0 [11.0, 17.0] 14.1‡ [11.1, 17.7]	99.7 [98.0, 100.0] 100.0‡ [98.3, 100.0]	LR^{+}=1.69 LR-= 0.03 LR^{+}=1.72 LR-= 0
		Bacteremia: 19	100.0‡ [79.0, 100.0]	39.4‡ [35.8, 43.0]	4.1‡ [2.5, 6.5]	100.0‡ [98.3, 100.0]	LR^{+}=1.65 LR-= 0
		Meningitis: 9	100.0‡ [62.8, 100.0]	38.9‡ [35.4, 42.5]	2.0‡ [0.9, 3.8]	100.0‡ [98.3, 100.0]	LR^{+}=1.63 LR-= 0

Table 2. Test results – Combined clinical & laboratory criteria I (Continued)

Study ID	N/n* Age range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
Condra (2010) [80]	1,672/240 29 – 60 d	*Data on only low risk infants (n=62)* Total: 2 (NR) UTI: 2	NR	NR	NR	96.7 [NR]	NR
Baker (1999)[9]	422/422 29 – 60 d	Total: 43 (10.2) UTI: 17 Bacteremia: 9 Meningitis: 5 Gastroenteritis: 5 Cellulitis: 5 Chlamydia pneumonia: 2 Enterocolitis: 1 Osteomyelitis: 1 Septic arthritis: 1	100.0 [89.7, 100.0]	26.6 [22.3, 31.4]	14.0 [10.0, 17.7]	100.0 [96.0, 100.0]	LR+= 1.36 LR-= 0
		Bacteremia: 9	100.0 [62.9, 100.0]	24.4 [20.4, 28.9]	2.8 [1.4, 5.4]	100.0 [95.4, 100.0]	LR+= 1.32 LR-= 0
		Meningitis: 5	100.0 [46.3, 100.0]	24.2 [20.3, 28.7]	1.5 [0.6, 3.8]	100.0 [95.4, 100.0]	LR+= 1.31 LR-= 0
Garra (2005)[27]	302/259 0 – 56 d	Total: 65 (25.1) UTI: 51 Bacteremia/UTI: 5 Bacteremia: 8 Bacteremia/Meningitis:1	98.5 [92.0, 100.0]	41.9 [38.0, 46.0]	13.9 [11.0, 17.0]	99.7 [98.0, 100.0]	LR+= 1.70 LR-= 0.03
		Bacteremia: 8	87.5 [46.7, 99.3]	19.1 [13.6, 25.9]	4.7 [2.1, 9.9]	97.0 [82.9, 99.8]	LR+= 1.08 LR-= 0.65
Brik (1997)[22]	492/492 0 – 90 d	Total: 60 (12.3) UTI: 40 Meningitis: 2 Bacteremia: 10 Gastroenteritis: 4 Cellulitis: 2 Adenitis: 1	86.6 [74.8, 93.6]	66.6 [62.0, 71.0]	26.5 [20.6, 33.4]	97.3 [94.5, 98.7]	LR+= 2.60 LR-= 0.20
Rochester Criteria							

Table 2. Test results – Combined clinical & laboratory criteria I (Continued)

Study ID	N/n* Age range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
Chiu (1997)[21]	250/250 4 – 28 d	Total: 41 (16.4) UTI: 16 Bacteremia/Meningitis: 7 Bacteremia/Enteritis: 3 Enteritis: 2 Bacteremia/Osteomyelitis: 1 Others: NR	97.6 [92.9, 100.0]	62.2 [55.6, 68.8]	33.6 [25.1, 42.1]	99.2 [97.7, 100.0]	LR+= 2.58 LR-= 0.04
		Bacteremia/Meningitis: 7 Bacteremia/Enteritis: 3 Bacteremia/Osteomyelitis: 1	100.0 [67.8, 100.0]	54.8 [48.2, 61.2]	9.2 [4.9, 21.2]	100.0 [96.4, 100.0]	LR+= 2.21 LR-= 0
Ferrera (1997)[26]	188/134 0 – 28 d	Total: 22 (16.4) UTI: 13 UTI/meningitis: 1 Bacteremia: 4 Bacteremia/UTI: 1 Bacteremia/meningitis: 1 Listeria meningitis: 1 Pneumonia: 1	86.4 [64.0, 96.4]	46.4 [36.3, 56.7]	26.8 [17.2, 38.8]	93.8 [81.8, 98.4]	LR+=1.61 LR-= 0.29
		Bacteremia: 4	100.0 [39.5, 100.0]	41.7 [32.7, 51.3]	5.6 [1.8, 14.3]	100.0 [90.2, 100.0]	LR+=1.71 LR-= 0
Bonadio (1993)[10]	534/532 29 – 60 d	Total: 22 (4.1) UTI: 11 Meningitis: 4 Bacteremia: 6 Klebsiella pneumoniae: 1	59.0 [36.6, 78.5]	26.3 [22.5, 30.3]	3.3 [1.9, 5.8]	93.7 [88.0, 96.9]	LR+=0.80 LR-= 1.55
		Bacteremia: 6	33.3 [6.0, 75.9]	26.3 [22.5, 30.3]	0.5 [0.09, 2.1]	97.1 [92.3, 99.0]	LR+=0.45 LR-= 2.53
		Meningitis: 4	50.0 [9.1, 90.8]	26.7 [23.0, 30.7]	0.5 [0.08, 2.1]	98.6 [94.5, 99.7]	LR+=0.68 LR-= 1.87
Dagan (1988)[20]	237/236 < 60 d	Total: 22 (9.3) Bacteremia: 8 UTI: 6 Otitis media: 6 Gastroenteritis: 1 Bacteremia: 1 (not included)	100.0 [80.7, 100.0]	68.8 [62.1, 74.8]	23.8 [15.7, 34.3]	100.0 [96.8, 100.0]	LR+= 3.20 LR-= 0

Table 2. Test results – Combined clinical & laboratory criteria I (Continued)

Study ID	N/n* Age range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
		Bacteremia: 8	100.0 [59.7, 100.0]	64.9 [58.3, 71.0]	9.0 [4.3, 17.6]	100.0 [96.8, 100.0]	LR+= 2.85 LR-= 0
Garra (2005)[27]	302/259 0 – 56 d	Total: 65 (25.1) UTI: 51 Bacteremia/UTI: 5 Bacteremia: 8 Bacteremia/Meningitis: 1	92.4 [84.0, 97.0]	49.9 [47.0, 53.0]	12.3 [10.0, 16.0]	98.9 [97.0, 100.0]	LR+=1.84 LR-= 0.15
		Bacteremia: 8	75.0 [35.5, 95.5]	28.3 [22.9, 34.3]	3.2 [1.3, 7.3]	97.3 [89.6, 99.5]	LR+=1.04 LR-= 0.88
		Bacteremia/UTI: 5	100.0 [46.3, 100.0]	28.7 [23.3, 34.8]	2.6 [0.9, 6.5]	100.0 [93.6, 100.0]	LR+=1.40 LR-= 0
Jaskiewicz (1994)[25]	1057/931 0 – 60 d	Total: 66 (7.0) UTI: 34 Skin/soft tissue infection: 18 Bacteremia: 16 Gastroenteritis: 4 Pneumonia: 1	92.4 [82.5, 97.2]	50.0 [46.5, 53.3]	12.3 [9.6, 15.6]	98.9 [97.2, 99.6]	LR+=1.84 LR-= 0.15
		Bacteremia: 16 (1.7)	87.5 [60.4, 97.8]	47.5 [44.2, 50.8]	2.8 [1.6, 4.8]	99.5 [98.2, 99.9]	LR+= 1.66 LR-= 0.26
Baskin (1992)[19]	503/501 28 - 89 d	Total: 27 (5.4) Bacteremia: 8 UTI + bacteremia: 1 UTI: 8 Gastroenteritis: 10	52.0 [31.7, 71.6]	NR	NR	NR	NR
		Bacteremia: 8	55.5 [22.6, 84.6]	NC	NC	NC	NC
Stanley (2005)[38]	5,279/5,279 0 – 90 d	Total: 480 (9.1) UTI: 305 Meningitis: 10 Bacteremia: 39 Bacteremia/meningitis: 8 Bacteremia/UTI: 11 Pneumonia: 70 Cellulitis: 26 Bacterial enteritis: 11	99.8 [98.6, 99.9]	NR	NR	NR	NR

Table 2. Test results – Combined clinical & laboratory criteria I (Continued)

Study ID	N/n* Age range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
Byington (2004)[28]	894/888 (infants without viral infections) 1 – 90 d	Total: 109 (12.3) Types of SBI: bacteremia, UTI, meningitis, pneumonia	91.7 [84.5, 95.9]	36.0 [32.6, 39.4]	16.6 [13.8, 20.0]	96.9 [94.0, 98.5]	LR+= 1.43 LR-= 0.23
YIOS score ≥ 7 (affect, respiratory status/effort, peripheral perfusion)							
Bonadio (1993)[106]	242/233 0 – 29 d	Total: 29 (12.4) Meningitis: 10 Bacteremia: 12 UTI: 7	76.0 [56.0, 88.9]	81.9 [75.7, 86.7]	37.3 [25.3, 50.8]	96.0 [91.6, 98.2]	ROC given
Yale Observation Scale (YOS) > 10							
Zorc (2005)[101]	1,513/995 1 – 60 d	Total: 91 (9.0%) UTI	4.4 [1.4, 11.5]	92.6 [90.6, 94.1]	5.6 [1.8, 14.5]	90.5 [88.5, 92.3]	LR+=0.60 LR-= 1.03
Baker (1990)[110]	126/126 29 – 56 d	Total: 12 (9.5%) UTI: 5 Bacterial sepsis: 4 Other: 3	33.3 [11.3, 64.5]	72.8 [63.5, 80.5]	11.4 [3.7, 27.6]	91.2 [82.9, 95.8]	LR+= 1.22 LR-= 0.91
		Bacterial sepsis: 4	75.0 [21.9, 98.6]	73.7 [64.8, 81.1]	8.5 [2.2, 24.1]	98.9 [93.1, 99.9]	LR+= 2.85 LR-= 0.33

d=day(s); UTI=urinary tract infection; NR=not reported; SBI=serious bacterial infection; YIOS=Young Infant Observation scale; PPV= positive predictive value; NPV= negative predictive value

‡ Values based on Philadelphia protocol + no immunodeficiency syndrome, band-to-neutrophil ratio < 0.2

* N/n: number of infants enrolled/ number of infants with culture and test results

Other combined criteria (clinical and laboratory). The data on the diagnostic accuracy of different combinations of clinical (e.g., clinical/good/toxic/ill appearance, impression of sepsis, age, rectal temperature, unremarkable medical history) and laboratory features such as serum and urine WBC (with different thresholds), ABC ≥ 5,000/μL, ESR < 30 (or 20) mm/h, C-reactive protein (CRP) < 20 mg/L, or urine dipstick result (leukocyturia and/or nitrituria) were reported for 16 studies (Table 3).[5,30-37,40,56-58,60,62,79]

Of the studies that applied 'Low-Risk' criteria, similar combination of clinical appearance and laboratory values (WBC: 5,000-15,000/mm^3, ESR < 30 mm/h, normal UA: LE/nitrites or WBC < 10/hpf, ABC ≤ 1,500/mm^3) were used in two studies.[31,32] The overall accuracy for predicting total SBI was numerically higher in the first study[32] (sensitivity: 99.1 percent, specificity: 59.3 percent, PPV: 48.6 percent, NPV: 99.4 percent) compared to the second study (sensitivity: 68.3 percent, specificity: 37.6 percent, PPV: 12.9 percent, NPV: 89.7).[31] The authors in the second study,[31] also examined the effect of age on the accuracy indices of the criteria. Overall, there was no discernable numerical trend in the values of sensitivity and specificity across the age groups (0 – 14, 15 – 28, 29 – 45, and 46 - 59 days). In one study,[60] the estimates of sensitivity, specificity, PPV, and NPV of the 'Low-Risk' set of clinical judgment criteria (i.e., "nonbacterial illness", "did not appear ill", "benign physical examination", and "unremarkable initial laboratory screen") in predicting total SBI were 90.5 percent (95 percent CI: 78.6, 96.5), 55.4 percent (95 percent CI: 50.3, 60.3), 21.6 percent (95 percent CI: 16.5, 27.7), and 97.7 percent (95 percent CI: 94.5, 99.1), respectively. In another study,[56] the 'Low-Risk' criteria included the following: no findings consistent with soft tissue, skeletal, ear, or eye infection, UA: < 10 (or 25) WBC/hpf, WBC: 5,000-15,000/mm^3 and ABC ≤ 1,500/mm^3. In this study, the criteria demonstrated a higher sensitivity for identifying infants with bacteremia and meningitis (92.3 percent, 95 percent CI: 62.0, 99.6) than for identifying total SBI (82.2 percent, 95 percent CI: 67.4, 91.5).

In one study,[40] of 1,018 febrile infants aged 90 days or younger, the combined criteria of general appearance (well-appearing vs. not well-appearing) and urine dipstick result (leukocyturia and/or nitrituria vs. normal) yielded a sensitivity of 87.0 percent (95 percent CI: 67.9, 95.5) for detecting bacteremia with an NPV value of 99.4 percent (95 percent CI: 98.2, 99.8).

One study,[79] applied a combined low risk clinical (not ill appearing) and laboratory criteria (peripheral WBC of 10,000 – 15,000/mm^3, absence of leukocyte esterase in noncentrifuged urine on dipstick test, < 23 WBC/hpf on microscopic examination of the CSF)to exclude SBI in 449 febrile neonates (0 – 28 days). Overall, 87 (19.4 percent) of neonates had SBI which included bacteremia+ meningitis + UTI (2.3 percent), bacteremia + meningitis (1.1 percent), bacteremia + UTI (11.5 percent), bacteremia (1.1 percent), UTI (80 percent, more than sixty percent were male), pneumonia (22.5 percent), and omphalitis (1.1 percent). These criteria identified 226 neonates at low risk of SBI, of whom 14 (6.2 percent) were diagnosed with SBI including one case of bacteremia + meningitis and 13 cases of UTI (NPV = 93.8 percent, 95 percent CI: 90.1, 96.4).

In one study,[5] the criteria for predicting bacteremia/bacterial meningitis in infants aged 0 to 90 days were: ill appearance in combination with laboratory values (WBC < 5,000/mm^3 or WBC > 15,000/mm^3 and WBC ≥ 5/hpf) which yielded a sensitivity of 87.1 percent and a specificity of 50.7 percent. In another study,[34] the classification of infants aged 0 – 30 days and 30-60 days with respect to risk of bacteremia, using a similar criteria of ill appearance and WBC ≥

15,000/mm,3 resulted in lower sensitivity values of 28.5 percent (95 percent CI: 5.1, 69.7) and 75.0 percent (95 percent CI: 21.9, 98.6), respectively.

The criteria of test positive for LE or nitrate with WBC > 20,000/mm^3 and WBC < 4,100/mm^3, rectal temperature of 39.6°C, and age less than 13 days in predicting risk of total SBI were associated with a sensitivity of 82.0 percent (95 percent CI: 78.0, 86.0) and a specificity of 76.0 percent (95 percent CI: 75.0, 77.0).[57] The corresponding PPV and NPV were 21.0 percent (95 percent CI: 19.0, 23.0) and 98.3 percent (95 percent CI: 97.8, 98.7), respectively.[57] Use of this criteria misclassified one case of bacterial meningitis into low risk.[57] The corresponding NPV for bacteremia and bacterial meningitis of this model was 99.6 (95 percent CI: 99.4, 99.8).

In one study,[35] the addition of either ABC ≥ 5,000/mL or C-reactive protein positive test to the criterion of toxic appearance (increased irritability, decreased eye contact, unwillingness to feed, and the state of alertness) in predicting risk of bacteremia did not change values of sensitivity (100.0 percent), specificity (48.0 percent-49.0 percent), and predictive values (PPV: 16.6 percent - 17.2 percent and NPV: 100.0 percent).

In three studies,[36,37,62] the classification criteria used were similar: impression of sepsis, either WBC > 15,000/mm^3 or ESR > 30 mm/h, or both (or negative impression of sepsis and both WBC > 15,000/mm^3 and ESR > 30 mm/h). In two studies,[36,37] the sensitivity in correctly identifying infants with either bacteremia or bacteremia/meningitis was 100.0 percent. In the third study,[62] the sensitivity for identifying infants with UTI was much lower (46.0 percent).

In one study,[33] a logistic regression model was constructed (based on data from 99 infants) which showed that sex (male), spun urine WBC count (≥ 10/hpf), and CRP (≥3.6 mg/L) were statistically significant predictors of SBI. A probability cutoff for the model was selected to be 0.265 (at which specificity and sensitivity were equal: 80 percent) above which the values indicated high risk for a febrile infant of having an SBI. This model yielded sensitivity and specificity values of 77.8 percent for predicting SBI.

In one study,[30] the combined criteria (CRP ≥ 1.87 mg/dL, lack of mild upper respiratory tract infection symptoms (URI), and no URI symptoms in the patient's sibling) applied to 221 febrile infants aged 0 – 90 days in order to distinguish the infants with and without SBI, resulted in sensitivity, specificity, PPV, and NPV values of 61.0 percent, 90.0 percent, 60.0 percent, and 91.0 percent, respectively. After excluding infants with UTI (n=28), the corresponding values for the combined criteria (CRP ≥ 1.87 mg/dL and lack of mild URI symptoms) were 38.0 percent, 94.0 percent, 31.0 percent, and 95.0 percent, respectively.

Table 3. Test results –combined clinical & laboratory criteria II (Other combinations)

Criteria	Study ID	N/n* Age range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
Clinical Impression of Sepsis/ Appearance of infant + Laboratory Markers								
Low risk: -ve or ambivalent impression of sepsis and both WBC < 15,000/mm^3 and ESR < 30 mm/h High risk: 1) strong, or ambivalent *impression* of sepsis with either WBC ≥ 15,000 /mm^3 , or ESR ≥ 30 mm/h, or 2) -ve impression of sepsis and both WBC and ESR criteria	Crain (1988)[37]	46/35 0 – 15 d	Total: 3 (8.5) Sepsis/meningitis	100.0 [31.0, 100.0]	75.0 [56.2, 87.9]	27.3 [7.3, 60.7]	100.0 [82.8, 100.0]	LR^+=4.0 LR^-=0
Not ill appearing + WBC 5000 – 15,000/mm^3; absence of LE in noncentrifuged urine on dipstick test CSF-WBC < 23 /hpf	Schwartz (2009)[79]	449/449 0 – 28 d	SBI: 87 (19.4)	83.9 [75.6, 90.0]	58.6 [56.6, 60.0]	32.7 [29.5, 35.1]	93.8 [90.6, 96.1]	LR^+= 2.02 LR^-=0.27
Ill appearance WBC ≥ 15,000/mm^3	Caspe (1983)[34]	305/107 0 – 30 d	Total: 7 (6.5) (bacteremia)	28.5 [5.1, 69.7]	NR	NR	NR	NR
		305/198 30 – 60 d	Total: 4 (2.0) (bacteremia)	75.0 [21.9, 98.6]	95.8 [91.7, 98.0]	27.3 [7.3, 60.6]	99.4 [96.6, 99.9]	LR^+=18.1 LR^-=0.26
No findings consistent with soft tissue, skeletal, ear, eye, or umbilical infection and UA: WBC < 10 /hpf, ESR < 30 mm/h, CRP < 20 mg/L, WBC: 5,000-15,000/mm^3,	Chiu (1994)[56]	254/254 4 – 31 d	Total: 45 (17.7) UTI: 16 Bacteremia/meningitis: 13 Enterocolitis: 2 Abscess: 2 Peritonitis: 1	82.2 [67.4, 91.5]	60.3 [53.3, 66.9]	30.8 [22.9, 40.0]	94.0 [88.2, 97.2]	LR^+= 2.07 LR^-= 0.29

Table 3. Test results – Combined clinical & laboratory criteria II (Continued)

Criteria	Study ID	N/n* Age range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
1,500 band forms/ mm^3			Omphalitis: 10 Pustulosis: 1 Purulent conjunctivitis: 1					
			Bacteremia/meningitis: 13	92.3 [62.0, 99.6]	55.2 [48.6, 61.5]	10.0 [5.5, 17.1]	99.2 [95.3, 99.9]	LR^+= 2.06 LR^-= 0.13
Well appearance without focal infection, full term, no underlying illness, no previous hospitalization, no perinatal antibiotics (if < 14 days old), no sibling with group GBS disease; WBC: 5,000-15,000/ mm^3, ABC ≤ 1,500/mm^3, enhanced UA (WBC ≤ 9 mm^3; -ve Gram stain), CSF WBC ≤ 5/mm^3 and –ve Gram stain	Herr (2001)[31]	434/344 < 59 d	SBI: 41 (12.0) UTI: 25 Pneumonia: 8 Bacteremia: 3 Meningitis: 2 Gastroenteritis: 1 Chlamydia: 1	68.3 [51.7, 81.4]	37.6 [32.2, 43.3]	12.9 [8.8, 18.2]	89.7 [82.8, 94.2]	LR+=1.09 LR-=0.84
		434/42 0 – 14 d	SBI: 3 (7.1)	100.0 [31.0, 100.0]	28.2 [15.5, 45.1]	9.6 [2.5, 26.9]	100.0 [67.8, 100.0]	LR^+=1.39 LR^-=0
		434/104 15 – 28 d	SBI: 9 (8.6)	100.0 [62.8, 100.0]	26.3 [18.0, 36.5]	11.3 [5.6, 21.0]	100.0 [83.0, 100.0]	LR^+=1.35 LR^-=0
		434/138 29 – 45 d	SBI: 19 (13.7)	100.0 [79.0, 100.0]	39.5 [30.7, 48.9]	20.8 [13.3, 30.9]	100.0 [90.5, 100.0]	LR^+=1.65 LR^-=0
		434/113 46 – 59 d	SBI: 10 (8.7)	100.0 [65.5, 100.0]	35.9 [26.8, 46.0]	13.1 [6.8, 23.3]	100.0 [88.2, 100.0]	LR^+=1.56 LR^-=0
Toxic appearance (↑ irritability, ↓ eye contact, unwillingness to feed, and the state of alertness) and	Broner (1990)[35]	NR/52 4 – 56 d	Total: 5 (9.6) (bacteremia)	100.0 [46.3, 100.0]	49.0 [34.3, 63.7]	17.2 [6.5, 36.5]	100.0 [82.2, 100.0]	LR+=1.95 LR-= 0

Table 3. Test results – Combined clinical & laboratory criteria II (Continued)

Criteria	Study ID	N/n* Age range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
ABC ≥ 5,000 /μL								
Toxic appearance and CRP positive				100.0 [46.3, 100.0]	48.0 [32.4, 61.7]	16.6 [6.3, 35.4]	100.0 [81.5, 100.0]	LR+=1.88 LR-= 0
Toxic appearance and ABC ≥ 5,000 ABC/μL and WBC ≥ 15,000 /μL				100.0 [46.3, 100.0]	49.0 [34.3, 63.7]	17.2 [6.5, 36.5]	100.0 [81.5, 100.0]	LR^+=1.96 LR^-=0
Clinical impression of sepsis [-ve] (infant's level of activity, irritability, responsiveness, ability to be consoled, feeding pattern) and WBC ≥ 15,000/mm^3 + ESR ≥ 30 mm/h	Crain (1982)[36]	134/134 0 – 60 d	Total: 5 (3.7) (bacteremia)	100.0 [46.3, 100.0]	17.0 [11.2, 24.9]	4.5 [1.6, 10.6]	100.0 [81.5, 100.0]	LR^+=1.20 LR^-= 0
Clinical impression of sepsis [strong or ambivalent] and WBC ≥ 15,000/mm^3 or ESR ≥ 30 mm/h				100.0 [46.3, 100.0]	17.0 [11.2, 24.9]	4.5 [1.6, 10.6]	100.0 [81.5, 100.0]	LR^+=1.20 LR^-=0
Impression of sepsis + either WBC > 15,000 /mm^3 or ESR > 30 mm/h, or both; or –ve impression of sepsis + both WBC > 15,000 /mm^3 and ESR > 30 mm/h	Crain (1990)[62]	442/442 8 – 57d	Total: 33 (7.4) (UTI)	46.0 [31.1, 66.1]	98.0 [95.7, 98.9]	64.0 [42.6, 81.3]	95.9 [93.4, 97.5]	LR^+=22.0 LR^-=0.52

Table 3. Test results – Combined clinical & laboratory criteria II (Continued)

Criteria	Study ID	N/n* Age range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
Previously healthy infants without physical finding of OM, skin or musculoskeletal infection + WBC: 5,000-15,000/mm^3, ABC ≤ 1,500/mm^3, UA- WBC ≤ 10/hpf, and stool- WBC ≤ 5 /hpf (in infants with diarrhea)	McCarthy (1990)[58]	86/NR 0 – 60 d	SBI: 1 (NR) (data given only on 1 infant with SBI out of 86 infants classified as 'low risk')	NR	NR	NR	98.8 [92.7, 99.9]	NR
General appearance (well appearing vs. not well appearing) and Urine - UA: dipstick (LE$^+$, nitrite, $^+$ or both vs. normal)	Gomez (2010) [40]	1,125/ 1,018 0 – 90 d	Total: 23 (2.2) Bacteremia: 9 UTI/bacteremia: 8 Meningitis: 4 Sepsis: 2	87.0 [67.9, 95.5]	NR/NC	NR/NC	99.4 [98.2, 99.8]	NR/NC
Unremarkable medical history, good appearance, no focal/physical signs of infection + ESR < 30 mm/h, WBC 5,000-15,000/mm^3, normal UA (dipstick: LE, nitrites)	Marom (2007)[32]	449/386 0 – 90 d	Total: 108 (28.0) UTI: 54 Acute OM: 13 Gastroenteritis: 2 Meningitis: 2 Others: NR	99.1 [94.2, 99.9]	59.3 [53.3, 65.1]	48.6 [41.8, 55.4]	99.4 [99.3, 99.5]	LR$^+$=2.43 LR$^-$=0.01
Clinical appearance; WBC < 5,000/ mm^3 or WBC >15,000/mm^3	Pantell (2004)[5]	3,066/ 1,746 0 – 90d	Total: 63 (3.6) (Bacteremia/bacterial meningitis	83.9 [NC]	54.0 [NC]	NR	NR	LR$^+$=1.82 LR$^-$=0.29

Table 3. Test results – Combined clinical & laboratory criteria II (Continued)

Criteria	Study ID	N/n* Age range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
Clinical appearance; WBC < 5,000/ mm^3 or WBC >15,000/mm^3; WBC ≥ 5/hpf		3,066/ 1,746 0 – 90d	Total: 63 (3.6) (Bacteremia/bacterial meningitis)	87.1 [NC]	50.7 [NC]	NR	NR	LR^+=1.75 LR^-=0.25
Low risk: not ill appearing, no bacterial illness + benign laboratory screening findings (undefined)	Wasserman (1990)[60]	NR/443 < 90 d	Total: 53 (12.0) Bacteremia: 8 Meningitis: NR Soft tissue infection: NR UTI: NR Enteritis: NR	90.5 [78.6, 96.5]	55.4 [50.3, 60.3]	21.6 [16.5, 27.7]	97.7 [94.5, 99.1]	LR^+=2.10 LR^-=0.17
Other Clinical Criteria + Laboratory Markers								
Age < 13 d; T > 39.6°C UA (LE+ or nitrite+) WBC < 4,100/mm^3, > 20,000/mm^3	Bachur (2001)[57]	5,279/ 5,279 0 – 90 d	Total: 373 (7.0) UTI: 297 Meningitis: 17 Bacteremia: 40 Bacteremia/ meningitis: 8 Bacteremia/UTI: 11	82.0 [78.0, 86.0]	76.0 [75.0, 77.0]	21.0 [19.0, 23.0]	98.3 [97.8, 98.7]	LR+=3.48 LR-=0.23
			Bacteremia or meningitis: 48	NR	NR	NR	99.6 [99.4, 99.8]	LR+=2.36 LR-= 0.48
Sex of infant (male) spun urine + WBC ≥ 10/hpf, and CRP ≥ 3.6 mg/L (probability > 0.265 based on logistic regression model)	Chen (2009) [33]	135/135 0 – 90 d	Total: 34 (25.2)	77.8 [NR]	77.8 [NR]	NR	NR	NR

Table 3. Test results – Combined clinical & laboratory criteria II (Continued)

Criteria	Study ID	N/n* Age range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
Lack of mild upper respiratory tract infection symptoms, and no upper respiratory tract infection symptoms in the patient's siblings + CRP ≥ 1.87 mg/dL,	Shin (2009) [30]	NR/211 0 – 90 d	Total: 51 (23.0) UTI: 28 Bacteremia: 6 Meningitis: 4 UTI/ bacteremia: 3 Other: 10	61.0 [NR]	90.0 [NR]	60.0 [NR]	91.0 [NR]	NR
Lack of mild upper respiratory tract infection symptoms+ CRP ≥ 1.87 mg/dL		NR/183 (excluding 28 infants with UTI) 0 – 90 d	Total: 23 (10.4) Bacteremia: 6 Meningitis: 4 UTI/bacteremia: 3 Miscellaneous: 10	38.5 [NR]	93.5 [NR]	31.3 [NR]	95.2 [NR]	NR

h=hour; d=day(s); UTI=urinary tract infection; NR=not reported; LE=leukocyte esterase; WBC=white blood cell count; UA=urinalysis; T=temperature; NC=not calculable; ESR=erythrocyte sedimentation rate; CRP=C-reactive protein; ABC=absolute band count ; NC=not calculable; CSF=cerebrospinal fluid; GBS=group B streptococcal disease; LR=likelihood ratio; PPV= positive predictive value; NPV= negative predictive value; ↑= increased; ↓ = decreased; -ve=negative; OM=otitis media

*N/n: number of infants enrolled/ number of infants with test and culture results

Clinical Criteria Alone

The use and performance characteristics of clinical criteria for predicting the risk of SBI in febrile infants was reported in and/or ascertained from 15 studies (Table 4).[5,34-36,38-42,63,65,79,108,112,113]

In two studies,[38,39] temperature ≥ 40°C was evaluated as a predictor of SBI in infants admitted to emergency departments. The results of both studies demonstrated that this criterion had a low sensitivity in identifying infants with SBI (7.3 percent, 95 percent CI: 5.2, 10.1[38] and 21.0 percent, 95 percent CI: 9.3, 38.4[39]) and high specificity in identifying those without SBI (98.8 percent, 95 percent CI: 98.4, 99.1 and 97.0 percent, 95 percent CI: 95.2, 98.0, respectively). Correspondingly, NPVs for both studies ranged from 91.4 percent[38] to 95.8 percent.[39] Likewise, in the two studies,[38,39] the use of temperature ≥ 40°C as a criterion in predicting the risk of bacteremia, meningitis, or meningitis/bacteremia was associated with low sensitivity (range: 12.5 percent-25.0 percent).The use of rectal temperature ≥ 40°C criterion was reported to have missed one case of bacterial meningitis.[39]

In one study[63] the use of ill appearance (presence of at least one of the following: tachypnea, dyspnea, tachycardia, bradycardia, decrease of activity, lethargy, and decrease of appetite) was associated with a PPV of 52.3 percent (95 percent CI: 36.8, 67.3); test accuracy characteristics could not be ascertained.

In one study,[5] the criteria of ill appearance and age ≤ 30 days (vs. well appearance and age > 30 days), used to predict the risk of bacteremia was associated with sensitivity and specificity values of 95.2 percent and 35.49 percent, respectively. In the same study, the criteria of moderately or very ill appearance, age < 25 days, and temperature ≥ 38.6°C yielded sensitivity of 93.6 percent and specificity of 27.3 percent. In two other studies,[34,108] the application of 'ill appearance' ("inconsolable when held or fed or unresponsive to their environment;"[34] not defined for one study[108]) in predicting the risk of bacteremia resulted in different sensitivity values of 37.5 percent (95 percent CI: 10.2, 74.1)[108] and 91.0 percent (95 percent CI: 57.1, 99.5).[34] Besides, the results of the latter study[34] indicated a numerically higher sensitivity of the criteria for identifying bacteremia in older (≥30 days: 100.0 percent, 95 percent CI: 40.0, 100.0) vs. younger infants (< 30 days: 85.7 percent, 95 percent CI: 42.0, 99.2). Note that, the number of infants with bacteremia was small (n = 7) and the confidence intervals around the two estimates mostly overlapped.

In one study,[79]clinical observation (not ill appearance) in neonates (0 – 28 days) was associated with an overall sensitivity of 21.0 percent, and an NPV value of 82.5 percent (95 percent CI: 78.5, 86.0). In this study, the NPV values obtained through repeated testing for infants aged 3 – 7, 8 – 14, 15- 21, and 22 – 28 days, tended to improve for infants after 2nd week of life.

In another study,[40] of 1,018 febrile infants (≥ 38.0°C) aged 90 days or younger, the probability of having bacteremia in infants was increased with respect to general appearance (not well-appearing vs. well appearing; OR=8.01, 95 percent CI: 2.76, 23.05) and highest temperature detected (≥ 39.5°C vs. 38.0°C to 39.4°C; OR=3.37, 95 percent CI: 1.16, 9.36). For the two criteria, sensitivity was 26.1 percent with specificity values ranging from 90.5 percent (highest temperature) to 95.8 percent (general appearance). The prevalence rates of bacteremia did not significantly differ across the age (≤ 30 days vs. > 30 days; OR=1.72, 95 percent CI: 0.66, 4.39) and gender groups (male vs. female; OR=2.13, 95 percent CI: 0.78, 6.09), therefore showing low

values of sensitivity (range: 34.8 percent-73.9 percent) and specificity (range: 42.9 percent-76.4 percent).

The use of clinical impression of sepsis as criteria for predicting the presence of bacteremia was reported in three studies.[36,41,42] The definitions of these criteria were based on infant's physical examination, complete history, initial laboratory results (qualitative impression, no specific cut-offs were employed),[42] irritability, level of activity, and/or responsiveness.[36,41] In the three studies, the impression of sepsis criteria were shown to have sensitivity values of 80.0 percent [41] and 100.0 percent[36,42] in predicting the risk of bacteremia. The corresponding specificity values were 66.0 percent,[42] 37.5 percent [41] and 58.1 percent.[36]

In one study,[112] of 1,978 febrile infants (≥ 38.0°C) aged 45-90 days, the prevalence of SBI was compared between the infants who had been recently immunized (72 hours preceding the ED visit) and those who had not been recently immunized (with inactivated polio virus, hepatitis B, *Haemophilus influenzae* B, diphtheria-tetanus-acellular pertussis, pneumococcal conjugate, and rotavirus vaccines). The absence of immunization in predicting the presence of definite SBI (excluding possible SBI cases) was associated with sensitivity and specificity values of 95.4 percent and 11.3 percent, respectively (NPV=97.2 percent and PPV=7.1 percent). The study results indicated a higher prevalence of SBI (UTI, bacteremia, meningitis, pneumonia) in 'not recently immunized' infants (7.0 percent, 95 percent CI: 5.9, 8.3) compared to recently immunized infants (2.8 percent, 95 percent CI: 0.6, 5.1). The prevalence of SBI in infants immunized 24 hours prior to presentation was even lower (0.6 percent, 95 percent CI: 0, 0.9). The recently immunized infants (72 hours preceding the ED visit) were at lower risk of having SBI compared with 'not recently immunized' infants (RR=0.41, 95 percent CI: 0.19, 0.90). Infants immunized 24 hours prior to presentation were even at a lower risk of having SBI than 'not recently immunized' infants (RR=0.09, 95 percent CI: 0.01, 0.64).

The association between grunting respiration and the presence of SBI was assessed in one case-control study,[113] in which, 40 cases (infants aged 90 days or younger presenting with grunting) and 40 controls (infants aged 90 days or younger with no grunting) admitted to emergency department of a hospital in 2005-2006 were matched on age, day of hospitalization, and fever. The association between grunting and SBI was not significant with 3 infants with SBI in the case group vs. two infants with SBI in the control group (7.5 percent vs. 5.0 percent; OR=1.54, 95 percent CI: 0.19, 14.1).

Table 4. Test results – Clinical criteria alone

Criteria	Study ID	N/n* Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV % [95% CI]	Other
Appearance at Presentation								
Not ill appearing	Shwartz (2008)[79]	644/449 0 – 28 d	Total: 87 (19.4) Bacteremia + meningitis + UTI: 2 Bacteremia + meningitis: 1 Bacteremia + UTI: 10 UTI: 70 Pneumonia: 2 Omphalitis: 1	21.0 [NR]	NR	NR	82.5 [78.5, 86.0]	NR
Ill appearance	Bonadio (1994)[108]	367/356 60 – 90 d	Total: 33 (9.3) UTI: 17 Meningitis: 5 Bacteremia: 8 Salmonella: 3	33.3 [18.5, 51.9]	NR	NR	NR	NR
			Bacteremia: 8 (2.2)	37.5 [10.2, 74.1]	NR	NR	NR	NR
			UTI: 17 (4.7)	17.6 [4.6, 44.2]	NR	NR	NR	NR
			Salmonella: 3 (0.8)	0.0 [NA]	NR	NR	NR	NR
			Meningitis: 5 (1.4)	100.0 [46.3,100.0]	NR	NR	NR	NR
Toxic appearance (i.e., increased irritability, decreased eye contact, unwillingness to feed, and the state of alertness)	Broner (1990)[35]	NR/52 4 – 56 d	Total: 5 (9.6) (bacteremia)	80.0 [29.8, 98.9]	80.0 [66.2, 90.3]	30.7 [10.3, 61.1]	97.4 [84.5, 99.8]	LR^+=4.17 LR^-=0.24

Table 4. Test results – Clinical criteria alone (Continued)

Criteria	Study ID	N/n* Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV % [95% CI]	Other
Clinical impression of sepsis (infant's level of activity, irritability, responsiveness, ability to be consoled, feeding pattern)	Crain (1982)[36]	134/134 0 – 60 d	Total: 5 (3.7) (bacteremia)	100.0 [46.3,100.0]	58.1 [49.1, 66.6]	8.5 [3.1, 19.4]	100.0 [93.9, 100.0]	LR^+=2.38 LR^-=0
Septic appearance (yes, no, unsure) based on physical examination, complete history, initial laboratory results	King (1987)b[42]	NR/97 < 60 d	Total: 4 (5.4) Bacteremia or meningitis	100.0 [39.6,100.0]	66.0 [54.9, 74.9]	11.1 [3.6, 27.0]	100.0 [92.6, 100.0]	LR^+=2.90 LR^-=0
Clinical impression of sepsis (irritable, toxic, lethargic)	Rosenberg (1985)[41]	122/122 0 – 60 d	Total: 5 (4.0) (bacteremia)	80.0 [29.9, 98.9]	37.5 [28.7, 47.2]	5.4 [1.7, 13.9]	97.6 [86.2, 99.8]	LR^+=1.28 LR^-=0.53
Ill appearance (inconsolable when held or fed or unresponsive to their environment)	Caspe (1983)[34]	305/305 0 – 90 d	Total: 11 (3.6) (bacteremia)	91.0 [57.1, 99.5]	56.6 [49.3, 63.5]	10.4 [5.4, 18.7]	99.1 [94.4, 99.9]	LR^+=2.10 LR^-=0.16
		305/107 0 – 30 d	Total: 7 (6.5) (bacteremia)	85.7 [42.0, 99.2]	73.2 [63.4, 81.3]	18.2 [76.1, 36.0]	98.6 [91.8, 99.9]	LR^+=3.20 LR^-=0.19
		305/198 30 – 60 d	Total: 4 (2.0) (bacteremia)	100.0 [39.6,100.0]	69.6 [62.5, 75.9]	6.3 [2.0, 16.2]	100.0 [96.5, 100.0]	LR^+=3.28 LR^-=0
		305/305 0 – 90 d	UTI 7 (2.3)	42.8 [11.8, 79.8]	NR	NR	NR	NR
Ill appearance (at least one of the following: tachypnea, dyspnea, tachycardia, bradycardia, decrease of activity, lethargy, and decrease of appetite)	Chen (2008)[63]	44/NR 0 – 90 d	Total: 23 (NR) UTI: 17 Bacteremia: 2 Meningitis: 2 Other: 2 (data given only on 23 infants with SBI out of 44 infants classified as 'high risk')	NR	NR	52.3 [36.8, 67.3]	NR	NR

Table 4. Test results – Clinical criteria alone (Continued)

Criteria	Study ID	N/n* Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV % [95% CI]	Other
Ill appearing (based on appearance, respiratory, and circulatory functioning)	Gomez (2010)[40]	1,125/ 1,018 0 – 90 d	Total: 198 (19.4) UTI: 172 Bacteremia: 9 UTI/bacteremia: 8 Meningitis: 4 Sepsis: 2 Cellulitis: 2 Otitis media: 1	NR/NC	NR/NC	NR/NC	NR/NC	NR/NC
Not well appearing (based on appearance, respiratory, and circulatory functioning) vs. well- appearing			Total: 23 (2.2) Bacteremia: 9 UTI/bacteremia: 8 Meningitis: 4 Sepsis: 2	26.1 [11.3, 47.2]	95.8 [95.4, 96.3]	12.5 [5.4, 22.6]	98.2 [97.9, 98.7]	LR^+=6.18 LR^-=0.77
Clinical appearance	Pantell (2004)[5]	3,066/ 3,066 0 – 90d	Total: 63 (3.6) (Bacteremia/bacterial meningitis)	58.1 [NC]	68.1 [NC]	NR	NR	LR^+=1.82 LR^-=0.61
Age/ Gender of Infant Alone or in Combination with Other Clinical Criteria								
Age ≤ 30 days vs. > 30 days	Gomez (2010)[40]	1,125/ 1,018 0 – 90 d	Total: 23 (2.2) Bacteremia: 9 UTI/bacteremia: 8 Meningitis: 4 Sepsis: 2	34.8 [17.3, 56.9]	76.4 [76.0, 76.9]	3.3 [1.6, 5.4]	98.1 [97.5, 98.7]	LR^+=1.47 LR^-=0.85
Gender (male vs. female)	Gomez (2010)[40]	1,125/ 1,018 0 – 90 d	Total: 23 (2.2) Bacteremia: 9 UTI/bacteremia: 8 Meningitis: 4 Sepsis: 2	73.9 [51.6, 88.9]	42.9 [42.4, 43.3]	2.9 [2.0, 3.5]	98.6 [97.4, 99.4]	LR^+=1.29 LR^-=0.60
High risk: age < 30 d and ill-appearing Low risk: age > 30 d and well-appearing	Pantell (2004)[5]	3,066/ 1,746 0 – 90d	Total: 63 (3.6) (Bacteremia/bacterial meningitis)	95.2 [NC]	35.49 [NC]	NR	NR	LR^+=1.47 LR^-=0.13
Well or minimally ill age < 25 d		3,066/ 3,066 0 – 90 d		93.6 [NC]	27.3 [NC]	NR	NR	LR^+=1.28 LR^-=0.23

Table 4. Test results – Clinical criteria alone (Continued)

Criteria	Study ID	N/n* Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV % [95% CI]	Other
Well or minimally ill appearance, Temperature < 38.6°C, age ≥ 25 d		3,066/ 3,066 0 – 90 d	Total: 14 (0.7) (Bacteremia/bacterial meningitis)	71.4 [42.0, 90.4]	56.8 [54.5, 59.1]	1.2 [0.6, 2.4]	99.6 [98.9, 99.8]	LR^+=1.65 LR^-=0.50
Fever Temperature								
Temperature > 40.0°C	Bonadio (1991)[39]	683/683 30 – 60 d	Total: 34 (5.0) Meningitis: 6 Bacteremia: 8 UTI: 16 Enteritis: 4	21.0 [9.3, 38.4]	97.0 [95.2, 98.0]	26.0 [11.8, 46.6]	95.8 [94.0, 97.2]	LR^+=6.68 LR^-=0.81
			Bacteremia: 8	12.5 [0.6, 53.3]	96.1 [94.3, 97.4]	3.7 [0.2, 20.8]	98.9 [97.7, 99.5]	LR^+=3.24 LR^-=0.91
			Meningitis: 6	33.3 [5.9, 75.9]	96.3 [94.5, 97.5]	7.4 [1.3, 25.7]	99.4 [98.3, 99.8]	LR^+=9.02 LR^-=0.69
	Stanley (2005)[38]	5,279/ 5,279 0 – 90 d	Total: 480 (9.1) UTI: 305 Meningitis: 10 Bacteremia: 39 Bacteremia/meningitis: 8 Bacteremia/UTI: 11 Pneumonia: 70 Cellulitis: 26 Bacterial enteritis: 11	7.3† [5.2, 10.1]	98.8 [98.4, 99.1]	38.0 [28.3, 48.8]	91.4 [90.6, 92.1]	LR^+=6.13 LR^-=0.93
			Bacteremia: 39	5.1 [0.9, 18.6]	98.3 [97.8, 98.6]	2.1 [0.3, 8.3]	99.3 [99.0, 99.5]	LR^+=2.98 LR^-=0.96
			Bacteremia/meningitis: 8	25.0 [4.4, 64.4]	98.3 [97.8, 98.6]	2.2 [0.4, 8.4]	99.8 [91.6, 99.6]	LR^+=0 LR^-=0.76
			Meningitis: 10	0 [0, 34.4]	98.2 [97.8, 98.6]	0 [0, 5.0]	99.8 [99.6, 99.9]	LR^+=14.6 LR^-=1.01
Temperature ≥ 39.5°C vs. 38°C–39.4°C	Gomez (2010)[40]	1,125/1018 0 – 90 d	Total: 23 (2.2) Bacteremia: 9 UTI/bacteremia: 8 Meningitis: 4 Sepsis: 2	26.1 [11.2, 48.0]	90.5 [90.2, 91.0]	6.1 [2.6, 11.3]	98.1 [97.7, 98.7]	LR^+=2.75 LR^-=0.81

Table 4. Test results – Clinical criteria alone (Continued)

Criteria	Study ID	N/n* Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV % [95% CI]	Other
Clinical History								
Not previously healthy vs. previously healthy	Gomez (2010)[40]	1,125/ 1,018 0 – 90 d	Total: 23 (2.2) Bacteremia: 9 UTI/bacteremia: 8 Meningitis: 4 Sepsis: 2	21.7 [8.4, 43.6]	88.5 [88.2, 89.0]	4.2 [1.6, 8.4]	98.0 [97.7, 98.6]	LR^+=1.89 LR^-=0.88
Rapid influenza test (negative vs. positive)	Mintegi (2009)[65]	520/381 0 – 90 d	Total: 50 (13.1) UTI: 34 Bacteremia: 8 Meningitis: 5 Other: 3	94.0 [83.1, 98.4]	33.2 [31.6, 33.9]	17.5 [15.5, 18.4]	97.3 [92.5, 99.3]	LR^+=1.4 LR^-=0.18
No history of recent immunization (72 hrs preceding the ED visit)[£]	Wolff (2009) [112]	2,247/1,978 45 – 90 d	Total: 130 (6.6) UTI: 105 Bacteremia: 11 Bacteremia/UTI: 4 Meningitis: 3 Pneumonia: 7	95.4[μ] [90.0, 98.1]	11.3 [10.9, 11.5]	7.1 [6.7, 7.3]	97.2 [93.8, 98.8]	LR^+=1.07 LR^-=0.4

d=day(s); UTI= urinary tract infection; NR=not reported; T=temperature; NC=not calculable; hpf=high-power field; LR=likelihood ratio; PPV= positive predictive value; NPV= negative predictive value

*N/n: number of infants enrolled/ number of infants with test and culture results

£ Inactivated polio virus, hepatitis B, Haemophilus Influenzae B, diphtheria-tetanus-acellular pertussis, pneumococcal conjugate, rotavirus, and Pediarix (pentavalent vaccine) vaccines; μ 28 cases of possible SBI were excluded from the calculations of the test accuracy indices

Laboratory Criteria Alone

The use and performance characteristics of laboratory thresholds for predicting the risk of SBI or bacteremia in febrile infants was reported in and/or ascertained from the reports of 27 studies (Table 5).[5,13,34-36,40-51,53,55,57,59,79,84,105,107,109,111]

A wide variety of laboratory variables and thresholds were applied alone or combination across the reviewed studies. Some of the examples are UA (microscopy, dipstick),[13,40,40,49-52,57,105] WBC,[34,35,41-47,59,105,107,109] ESR,[36,42,105] ABC,[35,45,107,109] and procalcitonin (PCT).[48,53,102]

Blood cell count (WBC; ABC; ANC). In studies evaluating sensitivity and specificity of WBC (in mm^3) in identifying bacteremia at different thresholds,[43,44] moving towards the lower thresholds (e.g., from ≥ 20,000/mm^3 to ≥ 5,000/mm^3) was related to an increase in sensitivity and decrease in specificity, as a result of trade-off between the two indices. The sensitivity values of WBC ≥ 5,000/mm^3 in the two studies were 79.0 percent[43] and 100.0 percent[44] Similar pattern of trade-off between sensitivity and specificity was observed for thresholds of ABC for predicting bacteremia (sensitivity: 80.0 percent at ABC ≥ 5,000/mm^3)[35] or bacteremia/meningitis (sensitivity: 88.0 percent at ABC ≥ 500/mm^3).[107] In one study,[41] WBC < 5,000/mm^3 or ≥ 15,000/mm^3 demonstrated only 60.0 percent sensitivity in identifying infants with bacteremia. In one study,[59] 99 well appearing febrile neonates age 7 – 28 days (< 12 hours in duration) were screened by absolute neutrophil count (ANC: > 10,000/ mm^3), and WBC (threshold: <5,000/ mm^3 or > 15,000/ mm^3) at admission. Serious bacterial infection (UTI, bacteremia, meningitis, pneumonia, cellulitis, osteomyelitis, septic arthritis) was found in 25 (25.3 percent) of the neonates. The areas under ROC were 0.78 (95 percent CI: 0.69, 0.86) for ANC, and 0.59 (95 percent CI 0.49, 0.69) for WBC. A repeated blood examination after 12 hours of fever persistence for infants with initial normal laboratory tests (n=58) was performed. Five of these neonates were diagnosed with SBI. Two of the misclassified infants into low risk group had bacterial meningitis. The area under ROC calculated for repeated tests resulted in improved values for CRP (0.99, 95 percent CI: 0.92, 1.0), ANC (0.85, 95 percent CI: 0.73, 0.93) and WBC (0.79, 95 percent CI: 0.66, 0.88). This study concluded that laboratory markers are more accurate and reliable predictors of SBI when performed after 12 hours of initiation of fever.[59] In one study, the AUC for ABC (AUC: 81.0 percent; thresholds: 250, 500, 1,000, 2,000, and 3,000/mm^3) was shown to be statistically significantly greater compared to that for total WBC (AUC: 61.0 percent; thresholds: 3,000, 10,000, 12,000, 18,000, and 20,000/mm^3) in identifying infants with and without UTI.[45] Authors of another study[44] reported a higher value of AUC (72.3 percent, 95 percent CI: 56.6, 87.9) based on different thresholds of total WBC (5,000, 10,000, 12,000, 15,000, 17,000, 20,000, and 25,000/mm^3) for identifying infants with total SBI. Another study,[46] included 1,257 febrile infants aged ≤ 60 days and investigated predictive value of absolute neutrophil count (ANC with thresholds: > 4.65, > 10, > 12.5 K/µL), WBC (various thresholds: > 15, >20, > 20 or < 4.1, > 15 or <5 K/µL), and ratio percent of ANC/WBC. The area under the ROC curve for ANC was 0.77 (95 percent CI: 0.67, 0.78) and for WBC was 0.69 (95 percent CI: 0.61, 0.73). For infants ≤ 28 days old, the AUC was 0.73 (95 percent CI: 0.67–0.78) for percent WBC, 0.70 (95 percent CI: 0.65–0.76) for percent ANC, and 0.67 (95 percent CI: 0.61–0.73) for WBC. *Escherichia coli* was responsible for 83 percent of the UTI infections. *Streptoccocus pneumoniae*, *Streptoccocus pyogenes* and *Streptococcus* Group B were responsible for isolated bacteremia.

Erythrocyte sedimentation rate (ESR). All three studies,[36,42,105] that tested criterion of ESR > 30 mm/h demonstrated high values of specificity (range: 75.7 percent - 93.6 percent) for bacteremia or UTI. The sensitivity values for bacteremia (or meningitis) differed in two studies: 80.0 percent[36] and 25.0 percent.[42] In the third study, ESR > 30 mm/h predicted the risk of UTI with sensitivity of 73.0 percent (95 percent CI: 50.0, 88.4).[105]

C-reactive protein (CRP). In one study,[47] the predictive ability of blood CRP levels (> 2 mg/dL, > 4 mg/dL, > 8 mg/dL) was shown to better than WBC levels (> 15 K/µL, > 20 K/µL, > 15 or < 5 K/ µL) in terms of sensitivity, specificity, and the values of likelihood ratio. The areas under the ROC curve (AUC) for CRP and WBC for predicting SBI were 74.0 percent (95 percent CI: 67.0 percent, 80.0 percent) and 70.0 percent (95 percent CI: 64.0 percent, 76.0 percent), respectively. In one study,[40] the use of CRP (at 70 g/L) resulted in higher sensitivity and specificity (69.6 percent and 93.8 percent, respectively) for predicting bacteremia compared to urine dipstick (43.5 percent and 82.8 percent, respectively) in 1,018 febrile infants (≥ 38.0°C) aged 90 days or younger. Likewise, the AUC for CRP (84.7 percent) was significantly greater than AUCs for WBC (67.9 percent) and absolute neutriphil count (ANC; 71.1 percent).[40] In one study,[59] CRP (> 20 mg/L) was used to predict SBI in 99 febrile neonates (7 – 28 days) at admission (duration of fever < 12 hours). Serious bacterial infection (UTI, bacteremia, meningitis, pneumonia, cellulitis, osteomyelitis, septic arthritis) was found in 25 (25.3 percent) of the neonates. The area under ROC for CRP, was 0.77 (95 percent CI: 0.67, 0.85).

Procalcitonin (PCT). In a study by Maniaci (2008),[53] the performance of procalcitonin (PCT) for identifying SBI (bacteremia, UTI, meningitis, pneumonia, bacterial GI) or possible SBI (UTI with urine culture of 10,000 to 49,000, or bacterial pneumonia as a chest radiograph interpreted by an attending radiologist) for febrile infants ≤ 90 days of age was examined. Overall, 30/234 (12.8 percent), and 12 /234 (5.12 percent) of infants were identified with definite SBI and possible SBI, respectively. At a cut off value of 0.13 ng/mL, procalcitonin had a sensitivity of 96.7 percent (95 percent CI: 81.0 percent–99.8 percent), specificity of 30.3 percent (95 percent CI: 24.0, 37.5), and NPV of 98.3 percent (95 percent CI: 89.7, 99.9). In discriminating definite plus possible SBIs and no SBI, a cutoff value of 0.12 ng/mL yielded a sensitivity of 95.2 percent (95 percent CI: 83.0, 99.0), specificity of 25.5 percent (95 percent CI: 20.0, 32.0), and NPV of 96.1 percent (95 percent CI: 85.4, 99.3). With either of these cutoff values, 2 patients with low-colony count UTIs with negative urinalysis results would have been misclassified as being at low risk for SBIs. All 6 patients with bacteremia would have been correctly identified as being at high risk for SBIs. In a second publication of the same study the authors reported elevated procalcitonin values for infants with SBI compared with infants without SBI both with and without recent immunizations. The median procalcitonin levels in this study were 0.53, 0.29, and 0.17 ng/mL for infant with SBI, infant with recent immunization, and infants with no recent immunization, respectively.[102] A recent study,[48] compared the ability of C-reactive protein, and procalcitonin (PCT) to predict SBI in 347 febrile infants younger than 90 days of age. Serious bacterial infection (bacteremia; meningitis; sepsis such as hemodynamic instability, tissue perfusion; UTI; pneumonia by chest x ray; gastroenteritis; cellulitis) was diagnosed in 82 (23.6 percent) of infants (65 UTI, 4 UTI + bacteremia, 5 bacteremia, 2 cellulitis, 4 sepsis, 1 acute bacterial gastroenteritis, and 1 pneumonia). *Escherichia coli* was responsible for 86 percent of the UTI infections. The most common organisms for bacteremia were *Streptococcus agalactiae* B, *Streptococcus pneumoniae*, and Gram negative bacilli. In this study the area under the ROC curve (AUC) for PCT was 0.77 (95 percent CI: 0.72, 0.81) and for CRP it was 0.79 (95 percent

CI: 0.75, 0.84). In 15 infants with more invasive infection (sepsis, bacteremia, bacterial meningitis), the diagnostic value of PCT (AUC 0.84, 95 percent CI: 0.79, 0.88) was higher than CRP (AUC 0.68, 95 percent CI: 0.63, 0.73).

Cerebrospinal fluid (CSF). In two studies, the presence of CSF pleocytosis as a criterion was evaluated to predict total SBI, bacteremia and bacterial meningitis in neonates[55] and infants aged 0 – 90 days.[111] The definition of CSF pleocytosis for neonates differed in these studies. In the first study,[55] the definition of pleocytosis was ≥ 20 WBC/mm^3 and > 1 WBC per 500 red blood cells/mm^3.[55] In the second study,[111] the criterion was WBC ≥ 25 cells/ µL. In this study, WBC ≥ 10 cells/µL was used as the criterion for infants aged 29 – 90 days. The sensitivity values for detecting total SBI in the two studies were 31.1 percent[55] and 12.5 percent.[111] Since one of these studies[111] reported sensitivity for the entire group of infants (0 – 90 days), these results were not comparable. In both studies the use of CSF pleocytosis resulted in a better sensitivity for detecting bacteremia (range: 28.0 percent- 34.5 percent) and bacterial meningitis (71.4 percent- 91.6 percent) compared to total SBI (12.5 percent- 31.1 percent).

Urine analysis (UA). The ranges of sensitivity and specificity values of UA (dipstick; the presence of LE or nitrite, or both) for identifying infants with UTI across the studies were 81.0 percent[57]- 85.0 percent[13] and 63.6 percent[50]– 94.0 percent,[51] respectively.[13,50-52,57] In one study, the sensitivity of urine dipstick was lower in identifying UTI in neonates (73.2 percent) with NPV of 94.1 percent (95 percent CI: 91.7, 96.3).[79] For three studies, the microscopy of spun urine (WBC ≥ 5/hpf) yielded sensitivity of 59.0 percent,[105] 65.0 percent,[13] and 40.0 percent.[49] The specificity values for the same studies were 92.4 percent[13] 93.0 percent,[105] and 85.0 percent.[49] In one study,[5,52] two methods of urine collection (gold standard of >100 000 cfu/mL for a bag specimen; >20 000 cfu/mL for catheterization specimen), catheterization and bag were compared in terms of specificity and sensitivity of UA (the presence of LE or nitrite) in identifying infants with UTI. Regardless of the criteria used (LE or nitrites), the UA of urine collected by catheterization had a better sensitivity (86.0 percent or 43.0 percent) and specificity (94.0 percent or 99.0 percent) compared to sensitivity (76.0 percent or 25.0 percent) and specificity (84.0 percent or 99.0 percent) for urine collected with bag. In general, the presence of nitrites taken as a criterion had a lower sensitivity for both collection methods (catheterization: 43.0 percent and bag: 25.0 percent) than LE taken alone (catheterization: 94.0 percent and bag: 84.0 percent). Similarly, the area under the curve (AUC) of ROC based on sensitivity and specificity values for different thresholds of urine microscopy (WBC: 0-2, 3-5, 6-10, 11-20, > 20/hpf) was numerically greater for the collection method using catheterization (AUC: 86.0 percent, 95 percent CI: 82.0, 91.0) vs. bag (AUC: 71.0 percent, 95 percent CI: 61.0, 82.0).[52]In another study,[40] the use of urine dipstick result (leukocyturia and/or nitrituria vs. normal) yielded a sensitivity of 43.5 percent and specificity of 82.8 percent in correctly identifying bacteremia in 1,018 febrile infants (≥ 38.0°C) aged 90 days or younger.

Table 5. Test results - Laboratory criteria

Criteria	Study ID	N/n Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV (%) [95% CI]	Other
Blood Markers in Neonates (0 – 28 d)								
WBC > 15,000/mm^3	Bonadio (1987)[109]	55/55 0 – 28 d	Total: 8 (14.5) UTI: 3 Gastroenteritis: 2 Meningitis: 2 Bacteremia: 1	0.0 [NA]	NR	NR	NR	NR
ABC >1,500/mm^3				50.0 [17.4, 82.5]	NR	NR	NR	NR
CBC Differential Ratio < 1 (Low risk)				87.5 [46.6, 99.3]	NR	NR	NR	NR
WBC < 5,000, or > 15,000 (fever < 12 hours duration)	Bressan (2010)[59]	99/99 7 – 28 d	Total: 25 (25.3) UTI: 15 Meningitis: 3 Bacteremia: 3 Bacteremia + UTI: 2 Pneumonia: 1 Osteomyelitis: 1	28.0 [14.3, 47.6]	87.7 [78.2, 93.4]	43.75 [23.1, 66.8]	78.1 [68.0, 85.6]	LR^+ = 2.3 LR^- = 0.8
WBC < 5,000, or > 15,000/mm^3 (fever > 12 hours duration)		99/58 7 – 28 d	Total: 5 (8.6) only low risk infants determined by the same criteria	80.0 [37.6, 96.4]	90.6 [79.7, 95.9]	44.4 [18.9, 73.3]	98.0 [89.3, 99.6]	LR^+ = 8.5 LR^- = 0.2
ANC > 10,000/mm^3 (fever < 12 hours duration)		99/99 7 – 28 d	Total: 25 (25.3)	20.0 [8.9, 39.1]	97.3 [90.6, , 99.3]	71.4 [35.9, 91.8]	78.0 [68.5, 85.3]	LR+ = 7.3 LR- = 0.8
ANC > 10,000/mm^3 (fever > 12 hours duration)		99/58 7 – 28 d	Total: 5 (8.6) only low risk infants determined by the same criteria	80.0 [37.6, 96.4]	100.0 [93.2, 100.0]	100.0 [51.0, 100.0]	98.2 [90.2, 99.7]	LR^+ = NR LR^- = 0.2
CRP > 20 mg/L (fever < 12 hours duration)		99/99 7 – 28 d	Total: 25 (25.3)	48.0 [30.3, 66.5]	93.2 [85.1, 97.1]	70.6 [46.9, 86.7]	84.2 [74.7, 90.5]	LR^+ = 7.1 LR^- = 0.6
CRP > 20 mg/L (fever > 12 hours duration)		99/58 7 – 28 d	Total: 5 (8.6) only low risk infants determined by the same criteria	100.0 [56.6, 100.0]	96.2 [87.2, 99.0]	71.4 [35.9, 91.8]	100.0 [93.0, 100.0]	LR^+ = 0.2 LR^- = 0
WBC 10,000/mm^3	Brown (2005)[44]	71/69 < 28 d	Total: 8 (12.0) UTI: 4	100.0 [60.0, 100.0]	31.0 [19.9, 44.7]	17.0 [8.0, 30.7]	100.0 [78.1, 100.0]	LR^+ = 1.40 LR^- = 0

Table 5. Test results - Laboratory criteria (Continued)

Criteria	Study ID	N/n Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV (%) [95% CI]	Other
WBC 12,000/mm^3			Bacteremia: 2 Other: NR	75.0 [35.5, 95.5]	53.0 [41.6, 68.0]	18.0 [7.8, 37.0]	94.0 [78.9, 98.9]	LR^+ = 1.60 LR^- = 0.50
WBC 15,000/mm^3				50.0 [17.4, 82.5]	74.0 [64.4, 87.0]	21.0 [7.8, 50.2]	91.0 [79.5, 97.3]	LR^+ = 1.90 LR^- = 0.70
WBC 17,000/mm^3				38.0 [9.0, 76.0]	89.0 [78.1, 95.7]	33.0 [9.0, 69.0]	91.0 [80.0, 96.7]	LR^+ = 3.80 LR^- = 0.70
WBC 5,000/mm^3				100.0 [NC]	2.0 [NC]	12.0 [NC]	100.0 [NC]	LR^+ = 1.00 LR^- = 0
WBC within 5,000 - 10,000; 12,000 - 15,000; 17,000 - 20,000; 22,000 - 25,000/mm^3				NA	NA	NA	NA	ROC (AUC) = 72.3, 95% CI: 56.6, 87.9
WBC ≥ 15,000/mm^3	Caspe (1983)[34]	305/107 0 – 30 d	Total: 7 (6.5) (bacteremia)	28.6 [5.1, 69.7]	NR	NR	NR	NR
ESR ≥ 30 mm/h	Crain (1982)[36]	134/99 0 – 60 d	Total: 5 (5.0) (bacteremia)	80.0 [29.8, 98.9]	93.6 [86.0, 97.3]	40.0 [13.7, 72.6]	99.0 [93.0, 99.9]	LR^+ =12.50 LR^- = 0.21
Blood Markers in Infants 0 – 60 d								
PMN ≥ 10,000/mm^3				38.0 [NC]	93.0 [NC]	NR	NR	LR^+ = 5.42 LR^- = 0.66
WBC ≥ 15,000/mm^3				50.0 [NC]	77.0 [NC]	NR	NR	LR^+ = 2.17 LR^- = 0.64
WBC ≥ 15,000/mm^3 + PMN ≥ 10,000/mm^3	Berkowitz (1985)[107]	434/239 < 60 d	Total: 10 (4.2) Sepsis/meningitis	38.0 [NC]	94.0 [NC]	NR	NR	LR^+ = 6.33 LR^- = 0.65
WBC ≥ 15,000/mm^3 + ABC ≥ 500/mm^3				63.0 [NC]	84.0 [NC]	NR	NR	LR^+ = 3.93 LR^- = 0.44
ABC ≥ 500/mm^3				88.0 [NC]	61.0 [NC]	NR	NR	LR^+ = 2.25 LR^- = 0.19
Total WBC/mm^3 (3,000, 10,000, 12,000, 18,000, 20,000)	Bonadio (1992)[45]	1,009/ 1,009 4 – 60 d	Total: 81 (8.0) Meningitis: 21 UTI: 29 Bacteremia: 23	NA	NA	NA	NA	ROC (AUC): 0.61 (SE: 0.038)

Table 5. Test results - Laboratory criteria (Continued)

Criteria	Study ID	N/n Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV (%) [95% CI]	Other
WBC >10,000/mm^3			Enteritis: 8	69.0 [57.7, 78.6]	52.0 [48.2, 54.7]	11.0 [8.5, 14.2]	95.0 [92.6, 96.7]	LR^+ = 1.43 LR^- = 0.59
WBC >12,000/mm^3				51.0 [39.6, 61.8]	72.0 [68.9, 74.8]	14.0 [10.0, 18.1]	94.0 [92.3, 95.9]	LR^+ = 1.82 LR^- = 0.68
WBC >15,000/mm^3				31.0 [21.3, 42.2]	88.0 [85.5, 89.8]	18.0 [12.3, 25.7]	94.0 [91.6, 95.0]	LR^+ = 2.58 LR^- = 0.78
WBC >20,000/mm^3				16.0 [9.1, 26.2]	97.0 [96.2, 98.3]	35.0 [20.7, 52.6]	93.0 [91.1, 94.5]	LR^+ = 5.33 LR^- = 0.86
WBC >8,000/mm^3				74.0 [62.9, 82.9]	28.0 [25.4, 31.4]	8.0 [6.4, 10.6]	93.0 [88.7, 95.2]	LR^+ = 1.02 LR^- = 0.92
ABC (250, 500, 1,000, 2,000, and 3,000/mm^3)				NA	NA	NA	NA	ROC (AUC): 0.81 (SE: 0.025)
ABC > 250/mm^3				93.0 [82.4, 96.1]	44.0 [40.8, 47.3]	13.0 [9.9, 15.4]	99.0 [96.4, 99.3]	LR^+ = 1.66 LR^- = 0.15
ABC > 500/mm^3				80.0 [76.5, 92.7]	61.0 [55.5, 63.0]	16.0 [12.3, 19.2]	98.0 [96.4, 99.0]	LR^+ = 2.05 LR^- = 0.32
ABC >1,000/mm^3				74.0 [62.9, 82.9]	80.0 [76.9, 82.1]	24.0 [19.0, 30.0]	97.0 [95.7, 98.2]	LR^+ = 3.70 LR^- = 0.32
ABC>2,000/mm^3				42.0 [31.2, 53.4]	93.0 [91.2, 94.6]	35.0 [25.5, 45.0]	96.0 [93.1, 96.1]	LR^+ = 6.00 LR^- = 0.62
ABC>3,000/mm^3				19.0 [11.0, 29.0]	98.0 [97.0, 98.9]	47.0 [29.5, 64.9]	93.0 [91.4, 94.7]	LR^+ = 9.50 LR^- = 0.82
ABC>1,500/mm^3				50.0 [17.4, 82.5]	NR	NR	NR	NR
CBC Differential Ratio < 1 (Low risk)				87.5 [46.6, 99.3]	NR	NR	NR	NR
WBC > 15,000/μL	Bilavsky (2010)[46]	1,257/ 1,257 0 – 60 d	Total SBI: 134 (10.7%) UTI: 104 Bacteremia + UTI: 9 Isolated bacteremia: 4	38.8 [31.0, 47.3]	84.6 [82.4, 86.6]	NR	NR	LR^+ = 2.5 LR^- = 0.7
WBC > 20,000/μL				16.4 [11.1–23.6]	95.6 [94.3, 96.7]	NR	NR	LR^+ = 3.8 LR^- =0.9
WBC < 4,100 or > 20,000/μL				17.2 [11.7, 24.4]	93.2 [91.6, 94.6]	NR	NR	LR^+ = 2.5 LR^- = 0.9

Table 5. Test results - Laboratory criteria (Continued)

Criteria	Study ID	N/n Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV (%) [95% CI]	Other
WBC < 5,000 or > 15,000/µL			Bacteremia + enteritis: 3 Pneumonia: 13 Enteritis: 1 Bacterial meningitis: 0	42.5 [34.5, 51.0]	79.3 [76.9, 81.6]	NR	NR	LR^+ = 2.1 LR^- = 0.7
ANC >4.650/µL				70.9 [62.7, 77.9]	63.3 [60.5, 66.1]	NR	NR	LR^+ = 1.9 LR^- = 0.5
ANC>10,000/µL				28.4 [21.4, 36.5]	95 [93.6, 96.0]	NR	NR	LR^+ = 5.7 LR^- = 0.8
ANC>12.500/µL				11.9 [7.5, 18.5]	97.8 [96.7, 98.5]	NR	NR	LR^+ = 5.4 LR^- =0.9
ANC/WBC > 20%				98.5 [94.7, 99.6]	7.2 [5.8, 8.9]	NR	NR	LR^+ = 1.0 LR^- =0.2
ANC/WBC > 40%				76.1 [68.2, 82.6]	50.0 [47.0, 52.9]	NR	NR	LR^+ = 1.5 LR^- = 0.5
ANC/WBC > 60%				27.6 [20.1, 35.7]	89.6 [87.7, 91.2]	NR	NR	LR^+ = 2.7 LR^- = 0.8
WBC ≥ 15,000 /µL	Broner (1990)[35]	NR/52 4 – 56 d	Total: 5 (9.6) (bacteremia)	20.0 [1.0, 70.0]	80.0 [66.2, 90.3]	10.0 [0.5, 45.8]	90.4 [76.4, 96.9]	LR^+ = 1.00 LR^- = 1.00
ABC ≥ 5,000 /µL				80.0 [29.8, 98.9]	57.0 [42.2, 71.4]	16.6 [5.4, 38.1]	96.4 [79.7, 99.8]	LR^+ = 1.86 LR^- = 0.35
CRP $^+$ve				64.0 [17.0, 92.7]	67.0 [52.7, 80.4]	16.6 [4.4, 42.2]	94.1 [78.9, 98.9]	LR^+ = 1.93 LR^- = 0.53
ESR ≥ 30 mm/h				25.0 [1.0, 70.1]	87.0 [73.5, 94.7]	14.3 [0.7, 58.0]	91.1 [77.8, 97.1]	LR^+ = 1.92 LR^- = 0.86
WBC ≥ 15,000/mm^3	Caspe (1983)[34]	305/198 30 – 60 d	Total: 4 (2.0) (bacteremia)	75.0 [21.9, 98.7]	NR	NR	NR	NR
Bacteriuria (Any number of bacteria by hpf)	Hoberman (1993)[84]	NR/306 0 – 59 d	Total: 14 (UTI)	64.0 [35.6, 86.0]	NR	NR	NR	NR
% Immature neutrophils ≥ 20%	King (1987)a[42]	NR/321 < 60 d	Total: 16 (5.0) Bacteremia or meningitis	69.0 [41.5, 87.9]	75.0 [69.7, 79.7]	12.6 [6.8, 21.9]	97.0 [94.8, 99.2]	LR^+ = 2.76 LR^- = 0.41
WBC ≤ 5,000 /mm^3		NR/342 < 60 d		44.0 [20.7, 69.4]	96.0 [93.1, 97.7]	35.0 [16.3, 59.0]	97.0 [94.5, 98.6]	LR^+ = 11.00 LR^- = 0.58
ESR ≥ 30 mm/h		NR/74 < 60 d	Total: 4 (5.4) Bacteremia or meningitis	25.0 [1.3, 78.0]	75.7 [63.7, 84.8]	5.5 [0.2, 29.3]	94.6 [84.2, 98.6]	LR^+ = 1.04 LR^- = 0.99

Table 5. Test results - Laboratory criteria (Continued)

Criteria	Study ID	N/n Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV (%) [95% CI]	Other
WBC > 15,000 / µL	Lin (2000) [105]	223/162 < 60 d	Total: 22 (13.5) (UTI)	36.0 [18.0, 59.1]	80.0 [72.2, 86.0]	22.2 [10.7, 39.6]	88.9 [81.7, 93.5]	LR^+ = 1.80 LR^- = 0.80
CRP > 20 mg/L				59.0 [36.6, 78.5]	90.0 [83.5, 94.2]	48.1 [29.1, 67.6]	93.3 [87.3, 96.7]	LR^+ = 5.90 LR^- = 0.40
ESR > 30 mm/h				73.0 [49.5, 88.4]	78.0 [69.9, 84.2]	34.0 [21.3, 49.4]	94.7 [88.5, 97.8]	LR^+ = 3.30 LR^- = 0.30
Blood Markers in Infants 0 – 90								
WBC > 15,000/µL	Bilavsky (2009) [47]	892/892 0 – 90 d	Total: 102 (11.3) UTI: 84 Bacteremia: 6 Pneumonia: 11 Meningitis: 1	48.0 [38.6, 57.6]	84.1 [81.4, 86.5]	NR	NR	LR^+ = 3.00 LR^- = 0.60
WBC > 20,000/µL	Bilavsky (2009) [47]	892/892 0 – 90 d	Total: 102 (11.3) UTI: 84 Bacteremia: 6 Pneumonia: 11 Meningitis: 1	21.6 [14.7, 30.5]	95.2 [93.5, 96.5]	NR	NR	LR^+ = 4.50 LR^- = 0.80
WBC > 15,000/µL or WBC < 5,000/µL	Bilavsky (2009) [47]	892/892 0 – 90 d	Total: 102 (11.3) UTI: 84 Bacteremia: 6 Pneumonia: 11 Meningitis: 1	50.0 [40.5, 59.5]	78.1 [75.0, 80.8]	NR	NR	LR^+ = 2.30 LR^- = 0.60
WBC < 5,000/mm^3	Bonsu (2003)[43]	3,961/ 3,810 0 – 89 d	Total: 38 (1.0) (bacteremia)	-	-	-	-	LR = 3.90
WBC < 5,000 or WBC ≥ 15,000/mm^3				66.0 [49.0, 80.0]	72.0 [71.0, 74.0]	2.3 [1.5, 3.5]	99.5 [99.1, 99.7]	LR^+ = 2.37 LR^- = 0.47
WBC < 5,000 or WBC 20,000/mm^3				45.0 [29.0, 62.0]	88.0 [87.0, 89.0]	3.6 [2.2, 5.8]	99.3 [99.0, 99.6]	LR^+ = 3.70 LR^- = 0.62
WBC ≥ 10,000/mm^3				61.0 [43.0, 76.0]	42.0 [40.0, 44.0]	1.0 [0.6, 1.5]	99.0 [98.4, 99.4]	LR^+ = 1.04 LR^- = 0.94
WBC ≥ 15,000/mm^3				45.0 [29.0, 62.0]	78.0 [76.0, 79.0]	2.0 [1.2, 3.2]	99.3 [98.9, 99.5]	LR^+ = 2.00 LR^- = 0.71
WBC ≥ 20,000/mm^3	Bonsu (2003)[43]	3,961/ 3,810	Total: 38 (1.0) (bacteremia)	24.0 [11.0, 40.0]	93.0 [92.0, 94.0]	3.4 [1.6, 6.6]	99.1 [98.8, 99.4]	LR^+ = 3.50 LR^- = 0.81

Table 5. Test results - Laboratory criteria (Continued)

Criteria	Study ID	N/n Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV (%) [95% CI]	Other
WBC ≥ 5,000/mm^3		0 – 89 d		79.0 [63.0, 90.0]	5.0 [4.0, 6.0]	0.8 [0.6, 1.2]	96.2 [92.3, 98.2]	LR^+ = 0.83 LR^- = 3.95
WBC ≤5,000 - ≤15,000/mm^3				NA	NA	NA	NA	LR = 0.40
ANC ≥ 10,000/mm^3	Gomez (2010) [40]	1,125/1018 0 – 90 d	Total: 23 (2.2) Bacteremia: 9 UTI/bacteremia: 8 Meningitis: 4 Sepsis: 2	NR/NC	NR/NC	NR/NC	NR/NC	AUC=71.1% [58.5, 83.8]
WBC ≥ 15,000/mm^3				NR/NC	NR/NC	NR/NC	NR/NC	AUC=67.9% [55.3, 80.4]
PCT at 0.13 ng/mL	Maniaci (2008)[53]	435/234 0 – 90 d	Total: 30 (12.8) Bacteremia: 4 Bacteremia + UTI: 2 UTI: 24	96.7 [81.0, 99.8]	30.3 [24.0, 37.5]	NR	98.3 [89.7, 99.9]	NR
PCT-Q (semi-quantitative PCT) ≥ 0.5 ng/mL	Olaciregui (2008)[48]	375/347 0 – 90 d	Total: 82 (23.6) UTI: 69 (4 with bacteremia) Bacteremia: 5 Cellulitis: 2 (1 with bacteremia) Sepsis: 4 (2 with bacteremia) Gastroenteritis: 1 with bacteremia	63.0 [52.0, 74.0]	87.0 [83.0, 91.0]	59.0 [48.0, 70.0]	89.0 [85.0, 93.0]	LR+ = 4.8 LR- = 0.42
Leucocyte count (5,000 – 15,000), CRP (<30), PCT (<0.5), good general state and –ve urine dipstick				96.0 [88.0, 99.0]	35.0 [29.0, 42.0]	32.0 [25.0, 38.0]	96.0 [92.0, 100]	LR+ = 1.48 LR- = 0.11
PCT-Q (semi-quantitative PCT) > 0.5 ng/mL			Bacteremia: 5 (1.4)	86 .0 [58.0, 100.0]	93.0 [90.0, 96.0]	35.0 [19.0, 51.0]	99.0 [98.0, 100.0]	LR+ = 12.3 LR- = 0.15
Leucocyte count (5,000 – 15,000), CRP (<30), PCT (<0.5), good general state and –ve urine dipstick				100 [74.0, 100.00]	29 [24.0, 35.0]	6 [3.0, 9.0]	100 [96.0, 100.0]	LR+ = 1.4 LR- = 0
CRP > 8 mg/dL	Bilavsky (2009)[47]	892/892 0 – 90 d	Total: 102 (11.3) UTI: 84	23.5 [16.4, 32.6]	98.2 [97.1, 98.9]	NR	NR	LR^+ = 13.30 LR^- = 0.80

Table 5. Test results - Laboratory criteria (Continued)

Criteria	Study ID	N/n Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV (%) [95% CI]	Other
CRP > 4 mg/dL	Gomez (2010)[40]	1,125/ 1,018 0 – 90 d	Bacteremia: 6 Pneumonia: 11 Meningitis: 1	44.1 [34.9, 53.8]	92.2 [90.1, 93.8]	NR	NR	LR^+ = 5.60 LR^- = 0.60
CRP > 2 mg/dL				55.9 [46.2, 65.1]	82.2 [79.3, 84.7]	NR	NR	LR^+ = 3.10 LR^- = 0.50
CRP at 70 g/L			Total: 23 (2.2) Bacteremia: 9 UTI/bacteremia: 8 Meningitis: 4 Sepsis: 2	69.6 [49.1, 89.4]	93.8 [92.1, 95.1]	20.5 [14.1, 25.3]	99.3 [98.5, 99.6]	LR^+ = 11.17 LR^- = 0.32 AUC=84.7% [75.4, 94.0]
CRP at 20 g/L				73.9 [53.5, 87.5]	74.8 [72.0, 77.5]	6.3 [4.4, 7.6]	99.2 [98.5, 99.7]	LR^+ = 2.93 LR^- = 0.34 AUC=84.7% [75.4, 94.0]
CRP ≥ 30 mg/L	Olaciregui (2008)[48]	375/347 0 – 90 d	Total: 82 (23.6) UTI: 69 (4 with bacteremia) Bacteremia: 5 Cellulitis: 2 (1 with bacteremia) Sepsis: 4 (2 with bacteremia) Gastroenteritis + bacteremia: 1	59.0 [48, 70]	89.0 [85.0, 93]	63.0 [52.0, 74.0]	87.0 [83.0, 91.0]	LR+ = 5.4 LR- = 0.46
CRP ≥ 20 mg/L				64.0 [54.0, 74.0]	84.0 [80.0, 88.0]	55 [45.0, 65.0]	88.0 [84.0, 92.0]	LR+ = 4.0 LR- = 0.43
CRP > 30 mg/L			Bacteremia: 5 (1.4)	56.0 [32.0, 80]	74.0 [69.0, 79.0]	9,6 [4.0, 16.0]	97 [95.0, 99.0]	LR+ = 2.15 LR- = 0.59
Cerebro-Spinal Fluid (CSF) Markers								
CSF pleocytosis (≥ 20 WBC/mm^3 and > 1 WBC per 500 red blood cells/mm^3)	Caviness (2008)[55]	960/800 0 – 28 d	Total: 119 (14.8) UTI: 78 Bacteremia: 29 Meningitis: 12	31.1 [23.1, 40.3]	75.5 [72.0, 78.6]	18.1 [13.2, 24.2]	86.2 [83.1, 88.8]	LR^+ = 1.26 LR^- = 0.91
			Bacteremia: 29	34.5 [18.6, 54.3]	74.8 [71.6, 77.8]	4.9 [2.5, 9.1]	96.8 [95.0, 98.0]	LR^+ = 1.37 LR^- = 0.87

Table 5. Test results - Laboratory criteria (Continued)

Criteria	Study ID	N/n Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV (%) [95% CI]	Other
			Meningitis: 12	91.6 [59.7, 99.5]	75.5 [72.3, 78.4]	5.4 [2.8, 9.6]	99.8 [98.9, 99.9]	LR^+ = 3.74 LR^- = 0.11
CSF pleocytosis (neonates: WBC ≥ 25 cells/ µL; age 29 – 90 d: WBC ≥ 10 cells/ µL)	Meehan (2008)[111]	2,820/ 2,003 0 – 90 d	Total: 192 UTI: 160 Bacteremia: 25 Meningitis: 7	12.5 [8.3, 18.2]	91.6 [90.2, 92.8]	13.6 [9.1, 19.8]	90.8 [89.3, 92.0]	LR^+ = 1.48 LR^- = 0.95
			Bacteremia: 25	28.0 [12.8, 49.6]	91.4 [90.1, 92.6]	3.9 [1.7, 8.3]	99.0 [98.4, 99.4]	LR^+ = 3.27 LR^- = 0.78
			Meningitis: 7	71.4 [30.2, 94.8]	91.4 [90.1, 92.6]	2.8 [1.0, 6.8]	99.9 [99.5, 99.9]	LR^+ = 8.33 LR^- = 0.31
Urine Markers								
Urine - UA: dipstick (LE^+, nitrite, $^+$ or both) and microscopy (pyuria: ≥ 5 WBC/hpf)	Bachur (2001)[51]	NR/868 0 – 29 d	UTI: 73 (8.4)	82.0 [71.0, 90.0]	92.0 [90.0, 94.0]	48.4 [39.4, 57.5]	98.2 [96.9, 99.0]	LR^+ = 10.25 LR^- = 0.19
Urine dipstick– UA (absence of LE)	Schwartz (2009)[79]	644/449 0 – 28 d	Total: 87 (19.4) UTI: 82	73.2 [NR]	NR	NR	94.1 [91.7, 96.3]	NR
Urine - Any LE alone	Dayan (2002)[13]	246/193 1 - 60 d	UTI: 27(14.0)	80.0 [62.5, 97.5]	94.2 [90.7, 97.7]	67.7 [48.5, 82.6]	96.3 [91.7, 98.5]	LR^+ = 13.80 LR^- = 0.21
Urine - Any nitrite alone				35.0 [14.1, 55.9]	97.7 [95.4, 99.9]	69.2 [38.8, 89.6]	90.0 [84.4, 93.8]	LR^+ = 15.10 LR^- = 0.67
Urine - Gram stain, any organisms				80.0 [62.5, 97.5]	99.4 [93.8, 100.0]	95.6† [76.0, 99.8]	96.8 [92.9, 98.9]	LR^+ = 138.40 LR^- = 0.20
Urine - Nitrite + LE				30.0 [10.0, 50.0]	100.0 [98.3, 100.0]	100.0 [60.0, 100.0]	89.7 [84.2, 93.5]	LR^+ = ∞ LR^- = NA
Urine - UA (LE^+ or $nitrite^+$)				85.0 [69.4, 100.0]	91.9 [87.8, 96.0]	62.1 [44.8, 77.0]	97.4 [93.1, 99.1]	LR^+ = NA LR^- = 0.16
Urine –Microscopy of spun urine (≥ 5 WBC/hpf)				65.0 [44.1, 85.9]	92.4 [88.6, 96.4]	56.6 [37.6, 74.0]	93.8 [88.7, 96.8]	LR^+ = 8.60 LR^- = 0.38

Table 5. Test results - Laboratory criteria (Continued)

Criteria	Study ID	N/n Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV (%) [95% CI]	Other
Urine –Microscopy of spun urine (≥ 10 WBC/hpf)				45.0 [23.2, 66.8]	97.6 [95.4, 99.9]	75.0 [47.4, 91.6]	91.5 [86.1, 95.0]	LR^+ = 19.50 LR^- = 0.56
Urine –UA Microscopy (hemocytometer; ≥ 10 WBC/µL)	Lin (2000)[105]	223/162 < 60 d	UTI: 22 (13.5)	82.0 [59.0, 94.0]	94.0 [88.6, 97.3]	69.2 [48.1, 84.9]	97.0 [92.2, 99.0]	LR^+ = 12.70 LR^- = 0.20
Urine – UA Microscopy (spun urine; ≥ 5 WBC/hpf)				59.0 [36.7, 78.5]	93.0 [86.9, 96.3]	56.5 [34.8, 76.1]	93.5 [87.7, 96.8]	LR^+ = 8.30 LR^- = 0.40
Urine - UA: dipstick (LE^+, nitrite, $^+$ or both) and microscopy (pyuria: ≥ 5 WBC/hpf)	Bachur (2001)[51]	NR/2,283 29 – 89 d	UTI: 172 (7.5)	82.0 [75.0, 87.0]	94.0 [93.0, 95.0]	52.6 [46.4, 58.7]	98.4 [97.8, 98.9]	LR^+ = 13.60 LR^- = 0.20
Urine - UA (LE^+ or nitrite$^+$)	Bachur (2001)[57]	5,279/ 5,279 0 – 90 d	Total: 373 (7.0) UTI: 297 Meningitis: 17 Bacteremia: 40 Bacteremia/meningitis: 8 Bacteremia/UTI: 11	71.0 [66.0, 76.0]	NR	NR	NR	NR
			UTI: 297 (5.6)	81.0 [76.0, 85.0]	NR	NR	NR	NR
Urine – UA ($LE,^+$ nitrite,$^+$ or protein)	Bonsu (2007)[50]	3,765/ 3,765 0 – 89 d	UTI: 307 (8.1) (UTI with sepsis)	84.0 [79.3, 87.8]	63.6 [62.0, 65.2]	17.0 [15.1, 19.0]	97.8 [97.1, 98.3]	LR^+ = 2.31 LR^- = 0.25
Urine - UA: dipstick (LE^+, nitrite, $^+$ or both)	Gomez (2010)[40]	1,125/ 1,018 0 – 90 d	Total: 23 (2.2) Bacteremia: 9 UTI/bacteremia: 8 Meningitis: 4 Sepsis: 2	43.5 [24.1, 64.8]	82.8 [82.3, 83.3]	5.6 [3.1, 8.4]	98.4 [97.9, 99.0]	LR^+ = 2.52 LR^- = 0.68
Urine – UA Microscopy (spun urine; ≥ 5 WBC/hpf, LE^+ or nitrite$^+$)	Reardon (2009)[49]	NR/51 < 90 d	Total: NR (UTI)	40.0 [7.0, 83.0]	85.0 [71.0, 93.0]	NR	NR	NR

Table 5. Test results - Laboratory criteria (Continued)

Criteria	Study ID	N/n Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV (%) [95% CI]	Other
Urine –UA (LE^+) by bag	Schroeder (2005)[52]	3,066/ 1,482 0 – 90 d	UTI: 152 (10.2) UTI/bacteremia: 16	76.0 [NC]	84.0 [NC]	NR	NR	LR^+ = 4.75 LR^- = 0.28
Urine - UA (LE^+) by CATH				86.0 [NC]	94.0 [NC]	NR	NR	LR^+ = 14.33 LR^- = 0.14
Urine – UA (LE^+) combined both methods: bag/CATH				84.0 [NC]	91.0 [NC]	NR	NR	LR^+ = 9.33 LR^- = 0.17
Urine – UA\ (Nitrites $^+$) by bag				25.0 [NC]	98.0 [NC]	NR	NR	LR^+ = 17.50 LR^- = 0.76
Urine - UA (Nitrites $^+$) by CATH				43.0 [NC]	99.0 [NC]	NR	NR	LR^+ = 43.00 LR^- = 0.57
Urine - UA (Nitrites$^+$) combined both methods: bag/CATH				39.0 [NC]	99.0 [NC]	NR	NR	LR^+ = 39.00 LR^- = 0.61
Urine microscopy (0-2, 3-5, 6-10, 11-20, > 20 WBC/hpf) combined both methods: bag/CATH		3,066/ 1,056 0 – 90d		NR	NR	NR	NR	ROC (AUC): 83.0%, 95% CI: 79.0, 87.0
Urine microscopy (0-2, 3-5, 6-10, 11-20, > 20 WBC/hpf) by bag		3,066/273 0 – 90d		NR	NR	NR	NR	ROC (AUC): 71.0%, 95% CI: 61.0, 82.0
Urine microscopy (0-2, 3-5, 6-10, 11-20, > 20 WBC/hpf) by CATH		3,066/716 0 – 90d		NR	NR	NR	NR	ROC (AUC): 86.0%, 95% CI: 82.0, 91.0

Table 5. Test results - Laboratory criteria (Continued)

Criteria	Study ID	N/n Age range	N (%) with SBI	Sensitivity % [95% CI]	Specificity % [95% CI]	PPV % [95% CI]	NPV (%) [95% CI]	Other
d=day(s); UTI=urinary tract infection; NR=not reported; LE=leukocyte esterase; hpf=high-power field; WBC=white blood cell count; NA=not applicable; UA=urinanalysis; CATH=catheterization; NC=not calculable; ROC (AUC)=receiver operating characteristic (area under the curve); LR=likelihood ratio; NA=not applicable; SBI=serious bacterial infection; ESR=erythrocyte sedimentation rate; CRP=C-reactive protein; ABC= absolute band count; SE=standard error; CBC=complete blood count; PMN=polymorphonuclear count; CSF=cerebrospinal fluid; PPV= positive predictive value; NPV= negative predictive value; ANC = absolute neutrophil count; +ve = positive; PCT = Procalcitonin								

* N/n: number of infants enrolled/number of infants with test and culture results

KQ 1B. How do the findings on test characteristics (sensitivity, specificity and predictive values) of individual or combinations of clinical features for identifying serious bacterial illness vary within the age range 0 – 3 months?

The diagnostic test characteristics were compared for selected criteria across age groups (neonates vs. older infants) using the data from 14 studies. [9-12,19,21,23,24,26,31,34,51,53,108] This comparison was possible for only selected number of criteria (Boston, Philadelphia, Rochester, combined laboratory and clinical criteria).

Combined Clinical and Laboratory Criteria

For the Boston criteria,[23] the estimates of sensitivity, specificity, PPV, and NPV for total SBI in neonates were 82.0 percent (95 percent CI: 67.4, 91.5), 68.0 percent (95 percent CI: 62.8, 73.1), 26.0 percent (95 percent CI: 19.4, 34.4), and 97.0 percent (95 percent CI: 93.0, 98.4), respectively. In infants aged 28 - 90 days, these parameters had the following values: 88.5 percent (95 percent CI: 82.8, 92.5), 56.2 percent (95 percent CI: 54.0, 58.4), 16.2 percent (95 percent CI: 14.0, 18.6), and 98.1 percent (95 percent CI: 97.0, 98.7), respectively.[24]

With respect to total SBI, the Philadelphia protocol in neonates,[11,23] sensitivity values were 84.4 percent[11] and 87.9 percent[23] and specificity values were 46.8 percent[11] and 55.0 percent [23]). In infants aged 29 – 60 days,[9,12] higher sensitivity (98.0 percent and 100.0 percent) and lower specificity values (26.6 percent and42.0 percent) were reported. For detecting bacteremia, the Philadelphia protocol demonstrated higher sensitivity (i.e., 100.0 percent) in older infants (age: 29-60 days)[9,12] compared to sensitivity of 75.0 percent and 83.3 percent in neonates (age: 0-28 days).[11,23]

The two studies that tested Rochester criteria for total SBI in infants 28 days or younger,[21,26] showed the following estimates of sensitivity (97.6 percent and 86.4 percent), specificity (62.2 percent and 46.4 percent), PPV (33.6 percent and 26.8 percent), and NPV (99.2 percent and 93.8 percent). In two other studies the application of Rochester criteria in infants aged 28 – 90 days[19] and 28 – 60 days[10] yielded sensitivities of 52.0 percent (95 percent CI: 31.7, 71.6) and 59.0 percent (95 percent CI: 36.6, 78.5), respectively. The corresponding specificity value was reported only for one study (26.3, 95 percent CI: 22.5, 30.3).[10] In identifying bacteremia, the Rochester criteria in neonates demonstrated sensitivity of 86.4 percent[26] as opposed to 55.5 percent in older infants (age: 28-90 days).[19]

The results for combined criteria (clinical and laboratory) for predicting total SBI in neonates were reported for in one study.[31] In another study,[34] the classification of infants aged 0 – 30 days and 30-60 days with respect to risk of bacteremia, using a similar criteria of ill appearance and WBC $\geq$ 15,000/mm^3, resulted in lower sensitivity values of 28.5 percent (95 percent CI: 5.1, 69.7) and 75.0 percent (95 percent CI: 21.9, 98.6), respectively.

Clinical Criteria Alone

One study reported the result for identifying risk of bacteremia using ill appearance as a criterion in neonates with sensitivity of 85.7 percent (95 percent CI: 42.0, 99.2) and specificity of 73.2 percent (95 percent CI: 63.4, 81.3).[34] The value for sensitivity in another study in infants 60 – 90 days using the same criteria for predicting bacteremia was 37.5 percent (95 percent CI: 10.2, 74.1).[108] No specificity was reported for the latter study.

Laboratory Criteria Alone

In one study,[34] the application of WBC ≥ 15,000/mm^3 for identifying bacteremia in neonates was associated with a sensitivity value of 28.6 percent. In the same study, the sensitivity was 75.0 percent when the criterion WBC ≥ 15,000/mm^3 was used in older infants aged 30-60 days.

One study reported sensitivity of 82.0 percent (95 percent CI: 71.0, 90.0) and specificity of 92.0 percent (95 CI: 90.0, 94.0) for urinalysis (dipstick, microscopy) in detecting UTI in neonates.[51] In the same study this test criteria was applied to older infants (29 – 89 days) and yielded similar estimates of sensitivity (82.0 percent, 95 percent CI: 75.0, 87.0) and specificity (94.0 percent, 95 percent CI: 93.0, 95.0).

In one study,[53] nine of 30 infants with SBI were younger than 28 days of age. The overall performance of Procalcitonin (PCT) levels in this study to identify SBI (definite and possible SBI) in ROC curve analysis had an AUC of 0.85 for patients >28 days of age compared with an AUC of 0.73 for patients ≤ 28 days of age.

Table 6. Test characteristic variations within age range 0 – 90 days

Study ID	N/n* Age range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
			Boston Criteria				
Kadish (2000)[23]	394/372 1 – 28 d	SBI: 45 (12.1)	82.0 [67.4, 91.5]	68.0 [62.8, 73.1]	26.0 [19.4, 34.4]	97.0 [93.0, 98.4]	LR^+=2.58 LR-= 0.26
		Bacteremia: 12	75.0 [42.8, 93.3]	63.3 [58.1, 68.3]	6.4 [3.1, 12.1]	98.7 [96.0, 99.6]	LR^+=2.04 LR-= 0.39
Kaplan (2000)[24]	3,166/2,190 28 – 90 d	SBI: 191 (8.7)	88.5 [82.8, 92.5]	56.2 [54.0, 58.4]	16.2 [14.0, 18.6]	98.1 [97.0, 98.7]	LR^+= 2.02 LR-= 0.20
			Philadelphia Protocol				
Baker (1999)[11]	254/254 3 – 28 d	SBI: 32 (12.5)	84.4 [67.0, 95.0]	46.8 [40.0, 53.0]	18.6 [12.0, 25.0]	95.4 [90.0, 99.0]	LR^+=1.58 LR-= 0.33
		Bacteremia: 8	75.0 [35.6, 95.5]	43.5 [37.2, 49.9]	4.1 [1.7, 9.1]	98.1 [92.7, 99.7]	LR^+=1.32 LR-= 0.57
		Meningitis: 4	100.0 [39.6, 100.0]	43.6 [37.4, 49.9]	2.7 [0.9, 7.3]	100.0 [95.7, 100.0]	LR^+=1.77 LR-= 0
Kadish (2000)[23]	394/372 1 – 28 d	SBI: 45 (12.1)	87.0 [72.5, 94.4]	55.0 [49.5, 60.5]	21.0 [15.5, 27.6]	97.0 [92.8, 98.7]	LR+=1.92 LR-= 0.24
		Bacteremia: 12	83.3 [50.8, 97.0]	51.1 [45.8, 56.3]	5.3 [2.7, 9.9]	98.9 [95.6, 99.8]	LR+=1.70 LR-= 0.32
		Meningitis: 5	100.0 [46.3, 100.0]	50.7 [45.5, 55.9]	2.6 [0.9, 6.5]	100.0 [97.4, 100.0]	LR+=2.03 LR-= 0
Baker (1993)[12]	747/747 29 – 56 d	SBI: 65 (8.7)	98.0 [92.0, 100.0]	42.0 [38.0, 46.0]	14.0 [11.0, 17.0]	99.7 [98.0, 100.0]	LR^+=1.69 LR-= 0.03
			100.0‡ [93.0, 100.0]	42.0‡ [38.3, 45.9]	14.1‡ [11.1, 17.7]	100.0‡ [98.3, 100.0]	LR^+=1.72 LR-= 0
		Bacteremia: 19	100.0‡ [79.0, 100.0]	39.4‡ [35.8, 43.0]	4.1‡ [2.5, 6.5]	100.0‡ [98.3, 100.0]	LR^+=1.65 LR-= 0
		Meningitis: 9	100.0‡ [62.8, 100.0]	38.9‡ [35.4, 42.5]	2.0‡ [0.9, 3.8]	100.0‡ [98.3, 100.0]	LR^+=1.63 LR-= 0
Condra	1,672/240	*Data on low risk infants*	NR	NR	NR	96.7	NR

Table 6. Test characteristic variations within age range 0 – 90 days (Continued)

Study ID	N/n* Age range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
(2010) [80]	29 – 60 d	*(n=62)* UTI: 2 (NR)				[NR]	
Baker (1999)[9]	422/422 29 – 60 d	SBI: 43 (10.2)	100.0 [89.7, 100.0]	26.6 [22.3, 31.4]	14.0 [10.0, 17.7]	100.0 [96.0, 100.0]	LR+= 1.36 LR-= 0
		Bacteremia: 9	100.0 [62.9, 100.0]	24.4 [20.4, 28.9]	2.8 [1.4, 5.4]	100.0 [95.4, 100.0]	LR+= 1.32 LR-= 0
		Meningitis: 5	100.0 [46.3, 100.0]	24.2 [20.3, 28.7]	1.5 [0.6, 3.8]	100.0 [95.4, 100.0]	LR+= 1.31 LR-= 0
Rochester Criteria							
Chiu (1997)[21]	250/250 4 – 28 d	SBI: 41 (16.4)	97.6 [92.9, 100.0]	62.2 [55.6, 68.8]	33.6 [25.1, 42.1]	99.2 [97.7, 100.0]	LR+= 2.58 LR-= 0.04
		Bacteremia/Meningitis: 7 Bacteremia/Enteritis: 3 Bacteremia/Osteomyelitis: 1	100.0 [67.8, 100.0]	54.8 [48.2, 61.2]	9.2 [4.9, 21.2]	100.0 [96.4, 100.0]	LR+= 2.21 LR-= 0
Ferrera (1997)[26]	188/134 0 – 28 d	SBI: 22 (16.4)	86.4 [64.0, 96.4]	46.4 [36.3, 56.7]	26.8 [17.2, 38.8]	93.8 [81.8, 98.4]	LR+=1.61 LR-= 0.29
		Bacteremia: 4	100.0 [39.5, 100.0]	41.7 [32.7, 51.3]	5.6 [1.8, 14.3]	100.0 [90.2, 100.0]	LR+=1.71 LR-= 0
Bonadio (1993)[10]	534/532 29 – 60 d	SBI: 22 (4.1)	59.0 [36.6, 78.5]	26.3 [22.5, 30.3]	3.3 [1.9, 5.8]	93.7 [88.0, 96.9]	LR+=0.80 LR-= 1.55
		Bacteremia: 6	33.3 [6.0, 75.9]	26.3 [22.5, 30.3]	0.5 [0.09, 2.1]	97.1 [92.3, 99.0]	LR+=0.45 LR-= 2.53
		Meningitis: 4	50.0 [9.1, 90.8]	26.7 [23.0, 30.7]	0.5 [0.08, 2.1]	98.6 [94.5, 99.7]	LR+=0.68 LR-= 1.87
Baskin (1992)[19]	503/501 28 - 89 d	SBI: 27 (5.4)	52.0 [31.7, 71.6]	NR	NR	NR	NR
		Bacteremia: 8	55.5 [22.6, 84.6]	NC	NC	NC	NC
Clinical Impression of Sepsis/ Appearance of Infant + Laboratory Markers							
Herr (2001)[31]	434/344 < 59 d	SBI: 41 (12.0)	68.3 [51.7, 81.4]	37.6 [32.2, 43.3]	12.9 [8.8, 18.2]	89.7 [82.8, 94.2]	LR^{+}=1.09 LR^{-}=0.84

Table 6. Test characteristic variations within age range 0 – 90 days (Continued)

Study ID	N/n* Age range	N (%) with SBI	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]	Other
	434/42 0 – 14 d	SBI: 3 (7.1)	100.0 [31.0, 100.0]	28.2 [15.5, 45.1]	9.6 [2.5, 26.9]	100.0 [67.8, 100.0]	LR^+=1.39 LR^-=0
	434/104 15 – 28 d	SBI: 9 (8.6)	100.0 [62.8, 100.0]	26.3 [18.0, 36.5]	11.3 [5.6, 21.0]	100.0 [83.0, 100.0]	LR^+=1.35 LR^-=0
	434/138 29 – 45 d	SBI: 19 (13.7)	100.0 [79.0, 100.0]	39.5 [30.7, 48.9]	20.8 [13.3, 30.9]	100.0 [90.5, 100.0]	LR^+=1.65 LR^-=0
	434/113 46 – 59 d	SBI: 10 (8.7)	100.0 [65.5, 100.0]	35.9 [26.8, 46.0]	13.1 [6.8, 23.3]	100.0 [88.2, 100.0]	LR^+=1.56 LR^-=0
Clinical Criteria Alone: Ill Appearance							
Caspe (1983)[34]	305/305 0 – 90 d	Bacteremia: 11 (3.6)	91.0 [57.1, 99.5]	56.6 [49.3, 63.5]	10.4 [5.4, 18.7]	99.1 [94.4, 99.9]	LR^+=2.10 LR^-=0.16
	305/107 0 – 30 d	Bacteremia: 7 (6.5)	85.7 [42.0, 99.2]	73.2 [63.4, 81.3]	18.2 [76.1, 36.0]	98.6 [91.8, 99.9]	LR^+=3.20 LR^-=0.19
	305/198 30 – 60 d	Bacteremia:: 4 (2.0)	100.0 [39.6,100.0]	69.6 [62.5, 75.9]	6.3 [2.0, 16.2]	100.0 [96.5, 100.0]	LR^+=3.28 LR^-=0
	305/305 0 – 90 d	UTI: 7 (2.3)	42.8 [11.8, 79.8]	NR	NR	NR	NR
Bonadio (1994)[108]	367/356 60 – 90 d	SBI: 33 (9.3)	33.3 [18.5, 51.9]	NR	NR	NR	NR
		Bacteremia: 8 (2.2)	37.5 [10.2, 74.1]	NR	NR	NR	NR
Laboratory Criteria Alone: WBC > 15,000/mm^3							
Bonadio (1987)[109]	55/55 0 – 28 d	SBI: 8 (14.5)	0.0 [NA]	NR	NR	NR	NR
Caspe (1983)[34]	305/107 0 – 30 d	Bacteremia: 7 (6.5)	28.6 [5.1, 69.7]	NR	NR	NR	NR
Caspe (1983)[34]	305/107 30 - 60 d	Bacteremia: 4 (2.0)	75 [21.9, 98.7]	NR	NR	NR	NR

d=day(s); UTI=urinary tract infection; NR=not reported; WBC=white blood cell count; mm^3= millimeter; LR=likelihood ratio; PPV= positive predictive value; NPV= negative predictive value

Table 6. Test characteristic variations within age range 0 – 90 days (Continued)

*N/n: number of infants enrolled/ number of infants with test and culture results
‡ Values based on Philadelphia protocol + no immunodeficiency syndrome, band-to-neutrophil ratio < 0.2

KQ 1C. In infants < 3 months old who present with a fever, what is the evidence for the sensitivity, specificity and predictive values of individual or combinations of clinical features (including history, information on the mother's history and previous testing, risk factors, findings on clinical exam and formal scoring instruments based on clinical features) for identifying those with invasive herpes simplex virus infection (HSV)? How do these findings vary within the age range 0 – 3 months?

The reported data on the presence of Herpes Simplex Virus (HSV) in febrile infants 3 months or younger was very scarce. For example, there were only four studies [28,42,54,55] in which the prevalence of Herpes Simplex Virus (HSV) was reported. In total, there were seven infants diagnosed with HSV in these studies and none of them had a concurrent bacterial infection. The prevalence rates of HSV amongst the febrile infants admitted across these studies (period range: 2 years[54]-6 years[28]) were 2.0 percent,[28] 1.7 percent,[54] and 0.3 percent.[42,55] The diagnostic accuracy of any given criteria in predicting the risk of HSV could be calculated only for one study.[55] In this study, CSF pleocytosis (defined as $\geq$ 20 WBCs/mm^3 and > 1 WBC per 500 red blood cells s/mm^3) predicted the risk of HSV in neonates with sensitivity of 66.6 percent (95 percent CI: 12.5, 98.2) and specificity of 74.6 percent (95 percent CI: 71.4, 77.6). The Positive and negative predictive values in this study were 1.0 percent (95 percent CI: 0.2, 3.9) and 99.8 percent (95 percent CI: 98.9, 99.9), respectively. There were insufficient data to compare the findings in neonates and infants in older age groups.

KQ 2A. What is the evidence that clinical features alone, basic laboratory tests (e.g., complete blood count [CBC], urinalysis) alone or the combination are sufficient to identify febrile infants < 3 months who are at low risk of having a serious bacterial illness (i.e., have a high negative predictive value)?

The evidence indicated that the reviewed 23 criteria/protocols were able to correctly classify the majority or all of the infants truly without SBI into low-risk groups (Table 7).[5,9-12,20-29,31,32,40,56,58,60,79,80]

Given the study results, the probability that an infant (< 3 months old) who was classified in 'Low Risk' group was free of SBI (i.e. NPV) ranged from 90.0 percent[31] to 100.0 percent[9]. For the 'Low-Risk' criteria, the values of sensitivity ranged from 82.0 percent[23] to 100.0 percent for identifying SBI (Table 7).[20] The corresponding values of specificity in the same studies ranged from 26.6 percent[9] to 68.8 percent.[20] In two studies,[10,31] the sensitivity was below 70.0 percent and specificity below 40.0 percent. In one study,[10] the Rochester criteria showed a lower discriminatory power (sensitivity: 59.0 percent and specificity: 26.3 percent) compared to that in other studies or other criteria across the studies.[9-12,20-29,32,56,60]

Table 7. Reported negative predictive values and other accuracy indices (Low-risk criteria/protocols)

Criteria	Author (year)	Age of Infants	n/N with Diagnosis	NPV (%) [95% CI]
Boston Criteria	Kadish (2000)[23]	1 – 28 d	SBI: 45/372 (12.1)	97.0 [93.0, 98.4]
			Bacteremia: 12	98.7 [96.0, 99.6]
	Kaplan (2000)[24]	28 – 90 d	SBI: 191/2,190 (8.7)	98.1 [97.0, 98.7]
Milwaukee Protocol	Bonadio (1993)[10]	29 – 60 d	SBI: 24/534 (4.5)	99.3 [98.0, 100.0]
Philadelphia Protocol	Kadish (2000)[23]	1 – 28 d	SBI: 45/372 (12.1)	97.0 [92.8, 98.7]
			Bacteremia: 12	98.9 [95.6, 99.8]
			Meningitis: 5	100.0 [97.4, 100.0]
	Baker (1999)[11]	3 – 28 d	SBI: 32/254 (12.5)	95.4 [90.0, 99.0]
			Bacteremia: 8	98.1 [92.7, 99.7]
			Meningitis: 4	100.0 [95.7, 100.0]
	Baker (1999)[9]	29 – 60 d	SBI: 43/422 (10.2)	100.0 [96.0, 100.0]
			Bacteremia: 9	100.0 [95.4, 100.0]
			Meningitis: 5	100.0 [95.4, 100.0]
	Baker (1993)[12]	29 – 56 d	SBI: 65/747 (8.7)	99.7 [98.0, 100.0]
			Bacteremia: 19	100.0‡ [98.3, 100.0]
			Meningitis: 9	100.0‡ [98.3, 100.0]

Table 7. Reported negative predictive values and other accuracy indices (Low-risk criteria/protocols) (Continued)

Criteria	Author (year)	Age of Infants	n/N with Diagnosis	NPV (%) [95% CI]
	Condra (2010) [80]	29 – 60 d	Data on only low risk infants (n=62)/ UTI: 2/NR	96.7 [NR]
	Garra (2005)[27]	0 – 56 d	SBI: 65/259 (25.1)	99.7 [98.0, 100.0]
			Bacteremia: 8	97.0 [82.9, 99.8]
	Brik (1997)(	0 – 90 d	SBI: 60/492 (12.3)	97.3 [94.5, 98.7]
			Bacteremia: 10	99.6 [97.8, 99.9]
Rochester Protocol	Jaskiewicz (1994)[25]	0 – 60 d	SBI: 66/931 (7.0)	98.9 [97.2, 99.6]
			Bacteremia: 16 (1.7)	99.5 [98.2, 99.9]
	Bonadio (1993)[10]	29 – 60 d	SBI: 22/532 (4.1)	93.7 [88.0, 96.9]
			Bacteremia: 6	97.1 [92.3, 99.0]
			Meningitis: 4	98.6 [94.5, 99.7]
	Chiu (1997)[21]	0– 28 d	SBI: 41/250 (16.4)	99.2 [97.7, 100.0]
			Bacteremia/Meningitis: 7 Bacteremia/Enteritis: 3 Bacteremia/ Osteomyelitis:1	100.0 [96.4, 100.0]
	Ferrara (1997)[26]	0 – 28 d	SBI: 22/134 (16.4)	93.8 [81.8, 98.4]
			Bacteremia: 4	100.0 [90.2, 100.0]
	Garra (2005)[27]	0 – 56 d	SBI: 65/259 (25.1)	98.9 [97.0, 100.0]
			Bacteremia: 8	97.3 [89.6, 99.5]
			Bacteremia/UTI: 5	100.0 [93.6, 100.0]

Table 7. Reported negative predictive values and other accuracy indices (Low-risk criteria/protocols) (Continued)

Criteria	Author (year)	Age of Infants	n/N with Diagnosis	NPV (%) [95% CI]
	Dagan (1988)[20]	< 60 d	SBI: 22/236 (9.3)	100.0 [96.8, 100.0]
	Byington(2004)[28]	1 – 90 d	SBI: 109/888 (12.3)	96.9 [94.0, 98.5]
			Bacteremia: 8	100.0 [96.8, 100.0]
	Dagan (1985)[29]	< 90 d	SBI: 23/233 (9.8)	99.3 [95.6, 99.9]
			Bacteremia: 9	100.0 [96.7, 100.0]
Clinical + Laboratory (ESR, WBC, UA)	Marom (2007)[32]	0 – 90 d	SBI: 108/386 (28.0)	99.4 [99.3, 99.5]
Clinical + Laboratory (WBC, ABC, UA-WBC, stool-WBC)	McCarthy (1990)[58]	0 – 60 d	SBI: 1/NR (all infants were at low risk)	98.8 [92.7, 99.9]
Clinical without any history of GBS + Laboratory (WBC, ABC, UA- stool, CSF) Criteria	Herr (2001)[31]	< 59 d	SBI: 41/344 (12.0)	89.7 [82.8, 94.2]
Clinical + Laboratory (WBC, ESR, CRP, ABC, UA)	Chiu (1994)[56]	4 – 31 d	SBI: 45/254 (17.7)	94.0 [88.2, 97.2]
			Bacteremia/meningitis: 13	99.2 [95.3, 99.9]
Clinical + Laboratory (Urine dipstick: LE+, nitrite+ or both vs. normal)	Gomez (2010)[40]	0 – 90 d	Bacteremia: 23/1,018 (2.2)	99.4 [98.2, 99.8]
Clinical + Laboratory (WBC, CSF, Urine dipstick test)	Schwartz (2009)[79]	0 – 28 d	Total: 14 (6.2) Bacteremia & meningitis: 1/226 (0.4) UTI: 13/226 (5.8)	93.8 [90.1, 96.4]
Clinical judgment (appearance/history)	Wasserman (1990)[60]	< 90 d	SBI: 53/443 (12.0)	97.7 [94.5, 99.1]
Clinical judgment (minimally ill, T < 38.6°C, age ≥ 25 d)	Pantell (2004)[5]	0 – 90 d	Bacteremia/bacterial meningitis: 14/3,066 (0.5)	99.6 [98.9, 99.8]

d=day(s); SBI=serious bacterial infection; LE=leukocyte esterase; hpf=high-power field; WBC=white blood cell count; UA=urinanalysis; ESR=erythrocyte sedimentation rate; CRP=C-reactive protein; ABC= absolute band count; CSF=cerebrospinal fluid; GBS=group B streptococcal disease; PPV= positive predictive value; NPV= negative predictive value; LE=leukocyte esterase

KQ 2B. What is the evidence for the potential risks resulting from a delay in the diagnosis and treatment of patients who appear low risk but have serious bacterial illness?

There were 15 studies relevant to this question. [5,9,10,12,20-22,24,25,32,58-61,77]One study,[5] had multiple publications.[52,67,104]

In the study by McCarthy, [58] 86 low risk (well appearing with WBC: 5,000-15,000/mm^3, ABC ≤ 1,500/mm^3, UA ≤ 10 WBC/hpf, and stool ≤ 5 WBC/hpf) for SBI infants younger than 2 months were enrolled and treated as outpatients with cefriaxone (50 mg/kg). All infants returned at day 2 (24 hours for follow up). There were no serious complications. Twelve (14.0 percent) infants developed transient problems possibly related to intramuscular cefriaxone therapy. Six infants were hospitalized, one for SBI (*Neisseria meningitidis* bacteremia) and five others for medical and social reasons. The infant with SBI was a 4 week-old female who received ceftriaxone for 7 days. No further data were reported.

In the study by Wasserman, [60] 49.9 percent (221/443) of included infants were classified as low risk for SBI and were not given antibiotic therapy. Of these, 2.3 percent (5/221) were later diagnosed with SBI. One infant had bacteremia and received 10 days of parenteral antibiotics upon positive culture. The other four infants had UTI (n=3) and one was diagnosed with *Salmonella enteritis* (n=1) who were later treated with antibiotics. All five infants recovered uneventfully, without any harms related to delayed diagnosis and treatment.

In the study by Bonadio, [10] 26.8 percent (143/534) of the included infants were considered low risk.[10] Eight of them were hospitalized within 72 hours after being discharged due to bacteremia (n=1), gastroenteritis (n=4), and paediatrician's preference (n=3). Only 0.7 percent (1/143) of the infants were diagnosed as having SBI (Moraxella catarrhalis bacteremia with a negative repeat blood culture) and were treated with parenteral antibiotics for 72 hours. No complications occurred in these infants.

In the study by Jaskiewicz, [25] 50.5 percent (511/1005) of the included infants were classified as being low risk. Only 1.0 percent (5/511) of these infants were diagnosed with SBI; three infants had UTI due to Group B *streptococcus* (n=1) and E. coli (n=2), one infant had Yersinia enterocolitica bacteremia, and one had *Neisseria meningitidis* bacteremia. The three infants with UTI experienced delayed diagnosis and treatment with antimicrobial therapy which did not begin until the cultures were positive, yet all recovered without complications after the treatment. The infant with Yersinia enterocolitica bacteremia was treated after being hospitalized for two days with antimicrobial therapy. The last infant received outpatient intramuscular ceftriaxone and then was diagnosed with Neisseria meningitides bacteremia. Inpatient treatment of once daily intramuscular ceftriaxone was administered and the infant fully recovered.

In the study by Birk,[22] 60.0 percent (296/492) of the included infants were considered low risk for SBI. Of these, 3.0 percent (8/296) were found to have SBI; one had bacteremia and 7 had UTI. Details regarding the management of the infants later diagnosed with SBI were not reported, including any potential harm associated with delayed diagnosis and/or treatment. However, it was reported that 24.0 percent (71/296) of the low risk infants had a lumbar puncture but a decreasing trend in frequency was observed over the two-year study period.

In the study by Chiu, [21] 52.4 percent (131/250) of the included infants were considered low risk for SBI. However, 58 of the low-risk infants were later reclassified as being high risk. Of the low risk infants, only 0.8 percent (1/131) were later diagnosed with SBI. The type of SBI was UTI caused by E. coli diagnosed by a bag specimen culture with normal urinalysis. The patient

was given a 7-day course of antibiotics after being hospitalized for more than 48 hours. Renal sonogram indicated mild dilation of the left renal pelvis, yet retrograde voiding cystourethrogram was normal. No other details related to the harms of delayed diagnosis and treatment was reported.

In the study by Kaplan,[24] 52.0 percent (1146/2190) of the included infants were at low risk for SBI. Of these, 1.9 percent (22/1146) were diagnosed with SBI. Delayed diagnosis and treatment was reported for 0.3 percent (3/1146) of the low risk infants. All infants with SBI were treated with parenteral antibiotics. The study authors reported that all infants recovered without any untoward clinical outcomes.

In the PROS study by Pantell,[5,52,104] 3,066 febrile infants were included of whom 1,056 were classified in low risk group if they had minimally ill appearance, were older than 25 days, and had a temperature < 38.6° C. Using the 'current guidelines' model, four infants classified as low risk were later diagnosed with bacteremia/bacterial meningitis. Outcomes associated with delayed diagnosis for these three infants were not reported. Employing the PROS practitioner model, one low risk infant developed GBS bacteremia and one low risk infant developed *Streptococcus pneumoniae* meningitis. Both experienced delayed treatment, yet recovered uneventfully. Of the 3,066 included infants, 807 (26.3 percent) were classified as being at low risk for UTI.[104] It was estimated that 7.6 percent (61/807) would have had a positive culture, yet only 0.3 percent (2/807) were subsequently diagnosed with UTI. These two children experienced delayed diagnosis and treatment, yet recovered uneventfully.

In the study by Marom,[32] 43.0 percent (166/386) of the febrile neonates were classified into low risk for SBI. A delayed diagnosis for SBI occurred in 0.6 percent (1/166) of the low risk infants; UTI was discovered 36 hours after the infant's admission. The patient was treated after the confirmation of positive culture and had an uneventful hospitalization.

In the study by Dore-Bergeron,[61] the feasibility of outpatient management for 67 'low risk' (nontoxic, normal renal function, normal CSF findings, no underlying medical problem, normal creatinine levels) febrile infants 30-90 days of age admitted to an emergency department of a tertiary hospital was examined. Before referring these infants to the outpatient day treatment center (DTC), they were treated with intravenous antibiotics (2.5-5 mg/kg per dose gentamicin and ampicillin, each single dose) and two-three doses of oral amoxicillin. In the DTC, after 24 hours of initial visit to ED the infants were administered intravenous gentamicin (5 mg/kg/day) until the infant was afebrile or urine culture results were available. Infants who had UTI (n=58) were additionally treated with oral antibiotics for 10 days. The remaining nine infants who did not have UTI were not treated with oral antibiotics. Febrile resolution occurred in 98.3 percent of 58 infants with UTI after antibiotic treatment initiation. Seven (12.0 percent) of the 58 infants with UTI treated in the DTC were hospitalized (i.e., treatment failures) due to severe concomitant gastroesophageal reflux (n=1), hydronephrosis (n=1), concomitant bacteremia (n=5). These 7 infants had no serious events during their hospitalization. The success rate of treatment amongst the 58 infants with UTI treated in the DTC was 86.2 percent. The success rate of treatment for younger (≤ 60 days old) infants tended to be lower (RR=0.2, 95 percent CI: 0.1, 1.1) compared to that for older (> 60 days old) infants.

In the study by Baker,[12] 139 (18.6 percent) of 747 febrile infants 29 to 60 days of age admitted to an emergency department were classified as 'low risk' (Infant Observational Score≤ 10, normal physical appearance) and were assigned to outpatient-observation group. All 139 infants had a viral illness (viral syndrome, nonbacterial gastroenteritis, bronchiolitis, nonbacterial

cystitis, and varicella infection) and none of them had SBI. One of the infants was hospitalized due to increasing severity of viral illness. No further data were reported for this cohort of infants.

In the study by Baker,[9] 101 (24.0 percent) of 422 febrile infants 29 to 60 days of age admitted to an emergency department were classified as 'low risk' (according to the Philadelphia protocol) and were assigned to outpatient management without antibiotics. Of these, 94 infants were managed without antibiotics as in accordance with the protocol and seven infants were managed with antibiotics as inpatients (i.e., out of accordance with the protocol). None of the 101 low risk infants had SBI.

In the study by Dagan,[20] 148 (63.0 percent) of 237 febrile infants 2 months of age or younger admitted to an emergency department were classified as 'low risk' (no physical findings consistent with a soft tissue or skeletal infection, no purulent otitis media, normal WBC and differential counts, normal urine, and < 25 WBC/high-power field x 40 in microscopic stool examination when diarrhea was present) and were observed for < 24 hours (n=75) or discharged to home (n=62) with no antibiotic therapy. Of the 75 infants who were initially observed, 72 were later discharged to home. In total, 134 infants were discharged to home. None of the 148 infants considered at low risk for having SBI actually had SBI (one infant was too ill to be included in this evaluation). Of the 148 infants, 17 (11.0 percent) were redefined as high risk and were hospitalized due to dehydration (n=3), study physician was not located (n=5), respiratory distress (n=1), no vacant bed in observation unit (n=1), cyanosis during crying (n=1), and persistent fever/repeat blood cell counts indicating high risk (n=6). Eleven of the 17 hospitalized infants (for 5 infants no study physician could be located and 6 infants were redefined as high risk) were treated with antibiotics. The cohort of 137 untreated infants was contacted > 10 days after. Two of the infants developed otitis but without fever and were treated with amoxicillin successfully. The remaining 135 infants became afebrile without relapse. Twelve percent of the 148 infants developed generalized rash and 4 percent developed mild diarrhea.

In one study by Bressan,[59] all well appearing neonates (58 of original sample of 99) with initial negative screening tests (WBC < 5,000/ mm^3, or > 15,000/ mm^3; CRP > 20 mg/L; ANC > 10, 000/ mm^3) were hospitalized for observation without receiving antibiotics. Laboratory tests were repeated at 6 – 12 hours after admission before making a decision to treat. Five of these infants were diagnosed with SBI. There were no clinical deteriorations reported for the period of admission to repeated blood testing. No other outcomes were reported.

In a study by Mintegi,[77] a total of 685 consecutive well appearing infants were included. Lumbar puncture (LP) was performed in 198 infants including all infants under the age of 15 days. LP was not performed in remaining 487 infants, and 69 of these infants were admitted to ward (46 with UTI) while 418 were discharged without antibiotics. Thirty eight unscheduled visits were reported including four with aseptic meningitis in the later group (n=418). No complications were reported for the seven infants with aseptic meningitis. The study concludes that the decision to perform the LP in previously healthy febrile well appearing infants can be individualized with no subsequent adverse outcomes.

KQ 3A. What is the evidence that clinical features alone, basic laboratory tests (e.g., complete blood count [CBC], urinalysis) alone or the combination are sufficient to identify febrile infants < 3 months who are at high risk of having a serious bacterial illness (i.e., have a high positive predictive value)?

We identified 10 studies that reported diagnostic accuracy data for 'high risk' and 'not low risk' criteria (e.g., ill appearance, WBC < 5,000/mm^3 or WBC > 15,000/mm^3 and WBC ≥ 5/high powered field) (Table 8).[30,34-37,40,49,57,62,63] Seven studies reported criteria representing different combinations of clinical and laboratory characteristics,[30,34-37,57,62] two studies - clinical only criteria,[40,63] and one study reported laboratory only criteria.[49] These criteria were associated with low PPVs. For example, in two studies reporting combined clinical and laboratory criteria for identifying SBI in infants 0 – 90 days, reported PPVs were 21.0 percent (95 percent CI: 19.0, 23.0)[57] and 60.0 percent (95 percent CI not reported).[30] Similarly, the PPVs for predicting bacteremia across 4 studies[34-36,40] ranged from 4.5 percent[36] to 27.3 percent[34] In one study,[40] infants not meeting the high risk criteria were classified as not low risk.

The values of sensitivity for predicting SBI reported for the two studies (see above) were 61.0 percent (95 percent CI not reported)[30] and 82.0 percent (95 percent CI: 78.0, 86.0).[57] The corresponding values for specificity were 90.0 percent (95 percent CI not reported)[30] and 76.0 percent (95 percent CI: 75.0, 77.0).[57]

Table 8. Reported positive predictive values and other accuracy indices (High risk and not low-risk criteria/protocols)

Criteria	Author (year)	Age of Infants	n/N with Diagnosis	NPV (%) [95% CI]
Combined Clinical + Laboratory Criteria				
Clinical Impression of sepsis + Laboratory (WBC, ESR)	Crain (1988)[37]	0 – 15 d	Sepsis/meningitis: 3/35 (8.5)	75.0 [56.2, 87.9]
Clinical Impression of sepsis + Laboratory tests (WBC, ESR)	Crain (1990)[62]	8 – 57d	UTI: 33/442 (7.4)	64.0 [42.6, 81.3]
Impression of sepsis + Laboratory tests (WBC, ESR)	Crain (1982)[36]	0 – 60 d	Bacteremia: 5/134 (3.7)	4.5 [1.6, 10.6]
Clinical Impression of sepsis + Laboratory (WBC, ABC)	Broner (1990)[35]	0 – 56 d	Bacteremia: 5/52 (9.6)	17.2 [6.5, 36.5]
Clinical Impression of sepsis + Laboratory tests (WBC)	Caspe (1983)[34]	30 – 60 d	Bacteremia: 4/198 (2.0)	27.3 [7.3, 60.6]
Age < 13, T > 39.6°C + Laboratoire tests (WBC, UA)	Bachur (2001)[57]	0 – 90 d	SBI: 373/5,279 (7.0)	21.0 [19.0, 23.0]
			Bacteremia or meningitis: 48 (0.9)	NR
Clinical (no respiratory tract infection in infant or siblings) + Laboratory (CRP)	Shin (2009)[30]	0 – 90 d	SBI: 51 (23.0)	60.0 [NR]
Clinical Criteria Alone				
Not well appearing	Chen (2008/ 2009)[63,103]	0 – 90 d	SBI: 23 (NR) (n=44 high risk)	52.3 [36.8, 67.3]
Not well appearing	Gomez (2010)[40]	0 – 90 d	Bacteremia: 23/1,018 (2.2)	12.5 [5.4, 22.6]
Temperature (≥ 39.5° vs. 38°–39.4°C)	Gomez (2010)[40]	0 – 90 d	Bacteremia: 23/1,018 (2.2)	6.1 [2.6, 11.3]
Laboratory Criteria Alone				
Laboratory (WBC, UA)	Reardon (2009)[49]	< 90 d	UTI: NR/51	NR

d=day(s); SBI=serious bacterial infection; WBC=white blood cell count; UA=urinanalysis; ESR=erythrocyte sedimentation rate; CRP=C-reactive protein; ABC= absolute band count; PPV= positive predictive value

KQ 3B. What is the evidence on the benefits and harms of immediate antibiotic (antibacterial and antiviral) therapy and or hospitalization (vs. delaying until diagnostic workup is complete) in patients at high risk of serious bacterial illness?

There was no evidence directly comparing outcomes in the immediate vs. delayed treatment groups. We identified 10 studies reporting on immediate antibiotic (or antiviral) therapy administered to infants at high risk of SBI (or HSV).[9,10,12,19,35,59,61,73,76,114] No treatment outcomes was reported for three studies.[10,19,59] Overall, the benefits and harms of immediate antibiotic/antiviral therapy (vs. delaying until diagnostic workup is complete) in patients at high risk of SBI (or HSV) were poorly reported.

In the study by Broner (1990),[35] reported treatment related results for immediate antibiotic treatment. In this study, immediate intravenous antibiotic therapy administered to 13 (25 percent) toxic appearing infants younger than 8 weeks was reported to be without any complications. These infants were discharged on fourth or eleventh day.

In the study by Baskin (1992),[19] 13 of 25 infants with SBI were identified as high risk using Rochester criteria. The number of infants without SBI meeting the high risk criteria was not reported. All of the included children (i.e., low and high risk infants) were managed with intramuscularly administered ceftriaxone (50 mg/kg) and were followed-up 2 to 7 days posttreatment. Specific details regarding the benefits and harms of antibiotic treatment for the high-risk infants were not reported. All infants except one with SBI were reported to stay healthy at followup. The one child had occult bacteremia and was treated with intramuscular ceftriaxone was diagnosed with *Staphylococcus aureus* osteomyelitis one week after initial presentation.

In the study by Baker (1993),[12] 460 (61.6 percent) of 747 infants were classified as being high risk and were hospitalized receiving unspecified antibiotic treatment for 72 hours. Of the 460 high risk infants, 64 were diagnosed with an SBI. Complications among the high-risk infants included infiltration of intravenous line (87/460, 18.9 percent), contaminated urine culture (31/460, 6.7 percent), contaminated blood culture (12/460, 2.6 percent), and contaminated cerebrospinal fluid culture (5/460, 1.1 percent). Specifically related to treatment, 0.4 percent (2/460) experienced a suspected drug-related rash.

In the study by Bonadio (1993),[10] 391 (73.2 percent) of 534 infants were classified as having a compromised presentation (i.e., high risk for SBI) according to the Milwaukee criteria. They were all hospitalized receiving 46 to 72 hours of parenteral antibiotic treatment with ampicillin 50 mg/kg/day or cefotaxime 50 mg/kg/day. The criteria correctly classified 13 of 22 infants with SBI as being high risk yet misclassified 9/22 as being low risk even though they were diagnosed with an SBI. The benefits and harms of immediate antibiotic therapy were not reported.

In the study by Baker (1999),[9] 321 (76.1 percent) of 422 febrile infants were classified as being high risk according to the Philadelphia protocol and were treated with unspecified antibiotics as inpatients. All 43 febrile infants with SBI were identified as being high risk. Overall, there were 21 high risk infants who were mismanaged according to the study protocol; 10 were managed without antibiotics as outpatients and 11 were managed without antibiotics as inpatients. Three of the 21 high risk infants were diagnosed with SBI, yet they experienced delayed antibiotic treatment. All patients with SBI eventually completed their antibiotic therapy and recovered uneventfully.

In the study by Dore-Bergeron (2009),[61] 51 febrile infants 30-90 days of age admitted to an emergency department of a tertiary hospital, presumed at 'high risk' (age < 30 days, toxic

appearance, dehydration, abnormal renal function/CSF findings, underlying serious medical problem, abnormal creatinine levels, and dubious parental compliance), were hospitalized and treated with intravenous antibiotics for the mean of 3.8 days (standard deviation: 4.0 days). Of these 51 febrile infants, 45 (88.2 percent) were diagnosed with UTI based on urine culture results. Minor intravenous access problems occurred in 7 infants (15.6 percent) and 30 infants (66.7 percent) were transferred to an outpatient day treatment center (DTC) to complete their intravenous antibiotic therapy course.

In the study by Jordan (2009),[76] the immediate antibiotic treatment was administered to 6 infants aged 28 days or younger, of whom 3 infants had enterovirus and 3 infants had sepsis/meningitis. Two of the 6 infants died and both of them had enterovirus. None of the two infants who died had SBI.

The study by Bressan (2010),[59] reported immediate antibiotic therapy for 37 neonates (7 – 28 days) who were hospitalized upon admission. Twenty (54.0 percent) of these neonates were diagnosed with SBI. No treatment outcomes were reported.

The study by Kneen (2010),[114] reported data on nine febrile infants aged 0-28 days, suspected of having viral encephalitis (high risk of being HSV positive), who had been treated with intravenous acyclovir. None of the infants died after the end of treatment. No additional data were reported.

In a study by Watt (2010),[73] ampicillin treatment was administered to 562 febrile infants 0 – 90 days of age. In this study, the antibiotic resistance rate for the period of 1997-2006 was 41.7 percent. After antibiotic sensitivities were identified, the antibiotic treatment was changed for 30 percent of SBI cases. Six infants with ampicillin resistance gram-negative rod bacteremia had longer antibiotic courses compared to nonbacteremia infants. Four of these infants (66.6 percent) had prolonged hospital stays (≥ 2 days), and in the two others, indwelling venous catheters were kept for at least two extra days.

KQ 4. What is the evidence that the presence of an identified viral infection predicts against a serious bacterial infection?

This review identified and included 11 studies in which the association between the status of viral infection and the risk of SBI in febrile infants was explored (Table 9).[28,29,64-71,81] One study was reported in two publications.[68,72] Two studies were reported in multiple publications. The PROS study by Pantell et al. were reported in four publications,[5,52,67,104] and the study by Levine et al. was reported in three publications.[68,72,101]

There was no evidence to assess the probability of having SBI with respect to the presence of HSV infection in febrile infants. We identified four studies reporting prevalence of HSV in febrile infants, however, none of these studies reported concurrent SBI.[28,42,54,55]

The most frequent types of SBI across the reviewed studies were UTI (range: 5.6 percent[64] - 11.3 percent[65]) and bacteremia (range: 1.4 percent[64] – 3.8 percent[29]). The types of virus studied were: influenza A/B,[28,65,72,81] RSV,[28,29,67-72] nonpolio EV,[29,66] and EV.[28,64] In these studies, the rates (e.g., prevalence, risk, odds) of SBI were compared between the two groups of virus-positive and virus-negative infants. For two studies,[64,81] the number of infants with SBI was not reported for one or two groups, and therefore the prevalence ratios (or risk ratios) could not be calculated. The authors of one study, however, provided the estimates of odds ratio by age groups (Table 9).[81]

Overall, based on the study results, there was an inverse statistically significant association between the status of viral infection and the rates of SBI. Specifically, there were higher prevalence rates (or risk) of SBI in infants without viral infection or clinically diagnosed bronchiolitis compared to infants with viral infection or clinically diagnosed bronchiolitis. The observed differences were either statistically significant,[28,29,65,68-70,81] or marginally statistically nonsignificant,[66] regardless of relatively smaller samples and event counts for some of these studies. For example in the study by Levine (2009),[72] in infants 60 days of age or younger the prevalence rates of both SBI (RR=0.19, 95 percent CI: 0.06, 0.59) and UTI (RR=0.23, 95 percent CI: 0.07, 0.70) were significantly lower amongst infants with influenza-positive test as compared to those with negative test result.

The prevalence rate of SBI in virus-positive infants across the studies ranged from 0 percent[71] to 7.0 percent.[64,68] The corresponding rate in virus-negative infants ranged from 9.6 percent[69] to 19.8 percent.[29] The estimate of odds ratio ranged from 0.08[70] to 0.41.[66](Table 9) For infants with RSV,[28,29,68,70] the odds ratios for having an SBI ranged from 0.08[70] to 0.58.[68] The odds ratios for those with influenza A/B,[28,65,81] were similar: 0.28 (95 percent CI: 0.16, 0.48),[81] 0.32 (95 percent CI: 0.19, 0.52),[28] and 0.13 (95 percent CI: 0.03, 0.44).[65] In two studies[29,66] of infants with nonpolio EV, the odds of having an SBI relative to those without this virus were 0.41 (95 percent CI: 0.15, 1.07)[66] and 0.12 (95 percent CI: 0.03, 0.40).[29]

Results from two studies indicated that infants with bronchiolitis (some infants RSV-positive) were less likely to have SBI than infants without bronchiolitis.[67,69] Similarly, in one study there was a higher prevalence rate of bacteremia and UTI in infants without bronchiolitis (2.0 percent and 12.0 percent respectively) compared to infants without bronchiolitis (0 percent). Although this study showed similar findings to the two other bronchiolitis studies, the numbers were very small.[71]

The rates of SBI in low and high risk groups were compared in febrile infants with and without viral infections.[28] The Rochester criteria was used to determine low vs. high groups and viral testing was performed on all infants. The lowest rate of SBI was in the low risk group with

a documented viral infection (1.8 percent). In the high risk group the rate of SBI was 5.5 percent when a viral infection was present compared to 16.7 percent when there was negative viral testing. High risk infants were 3.5 times more likely to have an SBI than the high risk infants where no virus was identified.

The majority of the articles were retrospective cohort studies that have their inherent limitations of incomplete testing and other potential biases. Of the prospective studies that looked at the targeted population, three provide meaningful results.[68,69] Levine and colleagues reported on a prospective 3 year, eight centre study on the SBI rate in infants 0 – 60 days of life who presented to the emergency department with fever. Based on rapid Respiratory Syncytial Virus (RSV) testing they were able to assess the impact of RSV status on SBI rates. Consistent with all the viral studies, there was a significant overall decrease in SBI rates when RSV was identified (7.0 percent vs. 12.5 percent; risk difference 5.5 percent: 1.7, 9.4). Although the majority of the SBI were UTI, bacteremia did occur in the RSV positive group. Only 38 percent of RSV positive infants had clinical bronchiolitis. The most important observation from this study was the fact that in the young infant subpopulation (<or equal to 28 days) the SBI rate did not differ between RSV positive or negative groups (10.1 percent vs. 14.2 percent; RR: 0.71; 95 percent CI: 0.35, 1.5).[68] In the same study (analyzed data from 5 centers),[72] the prevalence rates of both SBI (RR=0.19, 95 percent CI: 0.06, 0.59) and UTI (RR=0.23, 95 percent CI: 0.07, 0.70) were significantly lower amongst infants with influenza- or RSV-positive test as compared to those with negative test result. There were no significant differences between the two groups of infants with regards to bacteremia (0 percent vs. 2.2 percent, p=0.15) and meningitis (0 percent vs. 0.9 percent, p=0.6).

In a prospective study in two pediatric departments from 2005-2007, infants less than 90 days of age who had clinical bronchiolitis vs. no clinical bronchiolitis had a significantly decreased chance of SBI 3/136 (2.2 percent) vs. 30/312 (9.6 percent) (p = 0.005).[69]The three cases of SBI in the clinical bronchiolitis group were UTI that clinically resolved with antimicrobial therapy. Clinical bronchiolitis was also found to significant predictor against SBI in the PROS research network with 0/125 cases in infants less than 3 months with bronchiolitis vs. 212/1933 in patients without bronchiolitis. This study did not provide specific data for the various age groupings within the 0-90 day study population so we are unsure of whether the prediction against SBI was as strong in the neonatal age group.

Table 9. The rates of concurrent viral and bacterial infection

Study ID	Type of Virus [Condition]	Viral infection +			Viral infection -			Prevalence ratio (%) [95% CI]	OR* [95% CI]
		SBI+ n	Total N	Prevalence (%) [95% CI]	SBI+ n	Total N	Prevalence (%) [95% CI]		
Neonates 0 – 28 days									
Smitherman (2005)[81]	Influenza A	NR	13	NA	NR	49	NA	NA	NR
Infants 0 – 60 days									
Kuppermann (1997)[71]	RSV, other: NR [Bronchiolitis] *Blood culture* Bacteremia	0	36	0	1	50	2.00 [1.88, 5.88]	-	-
	RSV, other: NR [Bronchiolitis] *Urine culture* UTI	0	33	0	6	50	12.0 [3.00, 21.00]	-	-
Krief (2009)[72]	RSV, influenza [SBI]	3	119	2.5 [0.5, 7.2]	92	690	13.3 [10.9, 16.1]	0.19 [0.06, 0.59]	0.16 [0.04, 0.56]
	RSV, influenza [UTI]	3	123	2.4 [0.5, 6.9]	77	712	10.8 [8.6, 13.3]	0.23 [0.07, 0.70]	0.20 [0.05, 0.69]
	RSV, influenza [bacteremia]	0	123	0	16	715	2.2 [1.3, 3.6]	-	p=0.15
	RSV, influenza [meningitis]	0	119	0	6	698	0.9 [0.3, 1.9]	-	p=0.6
Levine (2004)[68]	RSV [SBI]	17	244	7.00 [4.10, 10.90]	116	925	12.50 [10.50, 14.80]	0.60 [0.30, 0.90]	0.58 [0.33, 0.99] ζ δ
	RSV [UTI]	14	261	5.4 [3.0, 8.8]	98	966	10.1 [8.3, 12.2]	0.50 [0.30, 0.90]	-
	RSV [bacteremia]	3	267	1.1 [0.2, 3.2]	22	968	2.3 [1.4, 3.4]	0.5 [0.1, 1.6]	-
	RSV [meningitis]	0	251	0	8	938	0.9 [0.4, 1.7]	-	-
Titus (2003)[70]	RSV	2	174	1.15 [0.43, 2.73]	22	174	12.60 [7.70, 17.60]	0.09 [0.02, 0.38]	0.08 [0.01, 0.36]
Infants 29 – 90 days									
Smitherman	Influenza A	NR	45	NA	NR	185	NA	NA	0.21

Table 9. The rates of concurrent viral and bacterial infection (Continued)

Study ID	Type of Virus [Condition]	Viral infection +			Viral infection -			Prevalence ratio (%) [95% CI]	OR* [95% CI]
		SBI+ n	Total N	Prevalence (%) [95% CI]	SBI+ n	Total N	Prevalence (%) [95% CI]		
(2005)[81]									[0.05, 0.93] ψ 0.19 [0.03, 1.44] ζ
				Infants 0 – 90 days					
Bilavsky (2008)[69]	RSV, other: NR [Bronchiolitis]	3	136	2.20 [0.60, 6.00]	30	312	9.62 [6.35, 12.89]	0.23 [0.05, 0.76] θ	0.21 [0.05, 0.74]
Byington (1999)[66]	Nonpolio EV	6	89	6.70 [2.8, 13.3]	38	256	14.84 [10.5, 19.20]	0.45 [0.17, 1.06]	0.41 [0.15, 1.07]
Byington (2004)[28]	EV, RSV, Influenza A/B, parainfluenza, rotavirus	21	491	4.30 [2.80, 6.20]	110	894	12.30 [10.15, 14.45]	0.34 [0.21, 0.55]	0.32 [0.19, 0.52]
Dagan (1985)[29]	Nonpolio EV RSV, influenza	4	137	2.92 [0.10, 5.34]	19	96	19.79 [11.82, 27.76]	0.14 [0.04, 0.44]	0.12 [0.03, 0.40]
Luginbuhl (2008)[67]	RSV, other: NR [Bronchiolitis]	0	125	0	212	1933	10.96 [9.62, 12.46]	-	-
Mintegi (2009)[65]	[Influenza A/B]	3	113	2.65 [0.0, 5.6]	47	268	17.5 [13.0, 22.0]	0.15 [0.04, 0.48]	0.13 [0.03, 0.44]
Rittichier (2005)[64]	EV	15	214	7.00 [3.59, 10.43]	NR	847	NA	NA	NA
Smitherman (2005)[81]	Influenza A	NR	58	NA	NR	234	NA	NA	0.28 [0.16, 0.48] ψ 0.14 [0.04, 0.46] ζ

D=day(s); NA=not applicable; NR=not reported; RSV=respiratory syncytial virus; YOS=Yale Observation Score; WBC=white blood cell; SBI=serious bacterial infection' EV=enterovirus; UTI=urinary tract infection

*The odds of SBI in viral infection-positive infants divided by the odds of SBI in viral infection-negative infants
ψ including pneumonia
ζ excluding pneumonia

Table 9. The rates of concurrent viral and bacterial infection (Continued)

δ adjusted for age, temperature, YOS, and WBC count
θ relative risk (i.e., rate ratio)

KQ 5. What is the evidence that the prevalence of SBI varies among febrile infants presenting to primary care and emergency practice? What is the evidence that prevalence affects the predictive value of clinical and laboratory findings?

In order to assess whether the crude prevalence rates of total SBI (and/or HSV) varied depending on the setting (i.e., emergency department vs. primary care) of the study, the included studies reporting the prevalence rates of total SBI (and/or HSV) were divided by the setting and were matched by the country of conduct. Overall, there were 69 studies included in this section.[5,9-13,19,21,23-27,31,35,38,39,43,45,50,51,54,56,57,60,62,66,68,70,74,75,84,105,10628,29,33,34,36,37,40-42,44,46,47,53,55,59,64,65,71,73,76,77,79,107-112,115-121]

Although in one study conducted in the US, nine SBI cases had been identified amongst infants 90 days or younger, the prevalence of SBI could not be calculated due to lack of the appropriate denominator (i.e., the number of infants with culture results).[121]

For the studies conducted in North America (Table 10), the prevalence rate of total SBI in the emergency departments ranged from 4.1 percent[10] to 25.1 percent.[27] More than half of the studies conducted in emergency departments of North America reported the prevalence rate of total SBI ≥10.0 percent. One US study,[73] reported an increase in the rate of SBI for the period of 2002 – 2006 compared to 1997 – 2001 (14.4 percent vs. 6.5 percent, p = 0.001). This increase was reported to be due to an increase in *E. coli* UTI particularly in infants 31 – 90 days of age. Of the 3 primary care setting study reports,[5,29,34] two reported the prevalence rates of total SBI of 9.9 percent[29] and 10.3 percent.[5]

For Taiwanese studies (Table 11), the prevalence rate of total SBI was numerically similar in emergency departments vs. primary care setting (17.7 percent-25.2 percent vs. 16.4 percent).[21,56]

The prevalence rates of total SBI in the two Spanish studies (both emergency departments) were 13.1 percent[65] and 18.9 percent (Table 11).[76] In the third Spanish study, the prevalence of SBI was significantly higher in infants younger than 29 days than in those older than 29 days (20.1 percent vs. 12.6 percent, p=0.04).[77] This study did not report the crude prevalence rate of SBI based on the total sample.

In two prospective studies conducted at a hospital emergency department in Israel, the prevalence rates of total SBI were 10.8 percent (infant age: 0 - 60 d)[78] and 11.3 percent (infant age: 0 – 90 days).[47] In one of these studies,[78] the prevalence rates of UTI, bacteremia, and pneumonia amongst febrile infants 60 days or younger were 10.8 percent (90/833), 8.1 percent (68/833), 1.3 percent (11/833), and 1.2 percent (10/833), respectively (Table 11). Another Israeli study,[79] reported an estimate of the prevalence of SBI in neonates (0 – 28 days) of 19.4 percent The prevalence rate of SBI in this study did not differ for infants aged 3 – 7 days (21.6 percent), 8 – 18 days (26.1 percent), 15 – 21 days (17.9 percent), and 22 – 28 days (12.1 percent).[79]

In one Italian study,[59] the prevalence of SBI amongst neonates (0 – 28 days of age) was 25.3 percent.

Across all studies, the prevalence rate of total SBI was higher in the neonates (age: 0 – 28 days) ranging from 11.5 percent[74] to 25.3 percent[59] compared to the older infants (age: > 28 days) in whom it ranged from 4.1 percent[10] to 13.0 percent.[121]

The effect of prevalence rate of total SBI on the PPVs was possible to be examined only for the Philadelphia protocol[9,11,12,23,27] and the Rochester criteria[19,21,25,26,28,29] regardless whether a study was conducted in an emergency department or primary care setting in North America or Taiwan (Tables 10-11). For the Philadelphia protocol, the prevalence of total SBI did not appear

to contribute to the difference observed in the PPVs. For the Rochester criteria, higher prevalence of total SBI corresponded to higher PPVs. The enrollment rate (n analyzed/N enrolled) in the 11 studies of Philadelphia protocol [9,11,12,23,27] and Rochester criteria [19,21,25,26,28,29] was uniformly high (> 70.0 percent). For example, the enrollment rate in six studies was 100.0 percent,[9,11,12,19,21,29] and in four studies > 80.0 percent.[23,25,27,28] The enrollment rate was less likely to affect the differences in prevalence of SBI across studies.

Table 10. Prevalence of serious bacterial infection by setting for studies across North America

Author (year)	Study period	Age range	Prevalence rate n/ N (%) SBI (or SBI type)	PPV (%) [95% CI]
Emergency Setting				
Baker (1993)[12]	1987 – 1992	29 – 56 d	65/747 (8.7) SBI	14.0 [11.0, 17.0]
Baker (1999)[11]	1994- – 1996	3 – 28 d	32/254 (12.5) SBI	18.6 [12.0, 25.0]
Baker (1999)[9]	1994- – 1996	29 – 60 d	43/422 (10.2) SBI	14.0 [10.0, 17.7]
Garra (2005)[27]	1998 – 2004	0 – 56 d	65/259 (25.1) SBI	13.9 [11.0, 17.0]
Kadish (2000)[23]	1993 – 1996	1 – 28 d	45/372 (12.1) SBI	21.0 [15.5, 27.6]
Baskin (1992)[19]	1987 – 1990	28 - 89 d	27/501 (5.4) SBI	NR
Byington (2004)[28]	1996-2002	1- 90 d	109/888 (12.3) SBI	16.6 [13.8, 20.0]
Ferrera (1997)[26]	1990 – 1994	0 – 28 d	22/134 (16.4) SBI	26.8 [17.2, 38.8]
Jaskiewicz (1994)[25]	1984 – 1992	0 – 60 d	66/931 (7.0) SBI	12.3 [9.6, 15.6]
Kaplan (2000)[24]	1993 – 1997	28 – 90 d	191/2,190 (8.7) SBI	16.2 [14.0, 18.6]
Stanley (2005)[38]	1993 – 2000	0 – 90 d	480/5,279 (9.1) SBI	NR
Bonadio (1993)[10]	1991 – 1992	29 – 60 d	22/532 (4.1) SBI	5.9 [3.6, 8.2]
Bonadio (1993)[106]	1991 – 1992	0- 29 d	29/233 (12.4) SBI	37.3 [25.3, 50.8]
Zorc (2005)[101]	1999 – 2001	1 – 60 d	91/995 (9.0) UTI	5.6 [1.8, 14.5]
Baker (1990)[110]	1987 – 1988	29 – 56 d	12/126 (9.5) SBI	11.4 [3.7, 27.6]
Bonadio (1994)[108]	1989-1993	60-90 d	33/356 (9.3) SBI	NR
Wasserman (1990)[60]	NR	< 60 d	22/236 (9.3) SBI	21.6 [16.5, 27.7]

Table 10. Prevalence of serious bacterial infection by setting for studies across North America (Continued)

Author (year)	Study period	Age range	Prevalence rate n/ N (%) SBI (or SBI type)	PPV (%) [95% CI]
Crain (1988)[37]	NR	0- 15 d	3/35 (8.5) sepsis/meningitis	27.3 [7.3, 60.7]
Crain (1990)[62]	1982 – 1987	8- 57 d	33/442 (7.4) UTI	64.0 [42.6, 81.3]
Crain (1982)[36]	1979 – 1981	0 – 60 d	5/134 (3.7) bacteremia	4.5 [1.6, 10.6]
Herr (2001)[31]	1999 – 2000	< 59 d	41/344 (12.0) SBI	12.9 [8.8, 18.2]
Bachur (2001)[57]	1993 – 1999	0 – 90 d	373/5,279 (7.0) SBI	21.0 [19.0, 23.0]
Bonadio (1991)[39]	1986-1990	30- 60 d	34/683 (5.0) SBI	26.0 [11.8, 46.6]
Bachur (2001)[51]	1993 – 1999	0 – 29 d	73/868 (8.4) UTI	48.4 [39.4, 57.5]
Bonsu (2007)[50]	1993 – 1999	0 – 89 d	307/3,765 (8.1) UTI/sepsis	17.0 [15.1, 19.0]
Dayan (2002)[13]	1998 – 2000	1 - 60 d	27/193 (14.0) UTI	56.6 [37.6, 74.0]
Hoberman (1993)[84]	1990-1991	0- 59 d	306/14 (4.6) UTI	NR
Berkowitz (1985)[107]	1978 – 1979	< 60 d	10/239 (4.2) sepsis/meningitis	NR
Bonsu (2003)[43]	1992 – 1999	0 – 89 d	38/3,810 (1.0) bacteremia	2.0 [1.2, 3.2]
Broner (1990)[35]	NR	4- 56 d	5/52 (9.6) Bacteremia	10.0 [0.5, 45.8]
Brown (2005)[44]	1999 – 2002	< 28 d	8/66 (12.0) SBI	21.0 [7.8, 50.2]
Bonadio (1987)[109]	1986 – 1987	0- 28 d	8/55 (14.5) SBI	NR
Rosenberg (1985)[41]	1981 – 1982	0- 60 d	5/122 (4.1) bacteremia	NR
Bonadio (1992)[45]	1985-1991	4- 60 d	81/1,009 (8.0) SBI	NR
King (1987)[42]	1978-1982	< 60 d	4/97 (5.4) bacteremia or meningitis	5.5 [0.2, 29.3]
Caviness (2008)[55]	2001 – 2005	0 – 28 d	119/800 (14.8) SBI	18.1 [13.2, 24.2]

Table 10. Prevalence of serious bacterial infection by setting for studies across North America (Continued)

Author (year)	Study period	Age range	Prevalence rate n/ N (%) SBI (or SBI type)	PPV (%) [95% CI]
Meehan (2008)[111]	NR (4 Years study)	0 – 90 d	192/2003 (9.6%) SBI	4.9 [2.5, 9.1]
Bonadio (1987)[120]	1984 – 1985	0- 60 d	12/159 (7.5) UTI	NR
Bonadio (1991)[75]	January-November 1990	28- 60 d	18/161 (11.2) SBI	NR
DeAngelis (1983)[115]	1978 – 1981	0- 60 d	39 /290 (13.4) SBI	NR
Ferguson (2008)[117]	2004-2005	30-60 d	9/90 (10.0) SBI	NR
		60- 90 d	10/100 (10.0) SBI	NR
Filippine (2001)[54]	1995 – 1997	0-30 d	27/113 (23.8) SBI	NR
Grover (1999)[116]	1992 – 1993	0- 60 d	7/48 (14.6) SBI	NR
Hsiao (2006)[118]	2003-2004	57- 90 d	NR (8.8) SBI	NR
Kuppermann (1997)[71]	1993 – 1995	0- 60 d	6/86 (7.0) UTI	NR
Kuppermann (1999)[119]	1994 – 1995	0- 60 d	7/30 (23.3) SBI	NR
Levine (2004)[68]	1998 – 2001	0 – 60 d	133/1,169 (11.3) SBI	NR
Rittichier (2005)[64]	1996-2002	0- 90 d	15/214 (7.0) SBI	NR
Titus (2003)[70]	1997- 2001	0 - 60 d	24/348 (6.9) SBI	NR
Byington (1999)[66]	1996-1997	0 – 90 d	44/345 (12.8) SBI	NR
Andreola (2007)[74]	2004- 2005	< 30 d	6/52 (11.5) SBI	NR
		< 90 d	20/175 (11.4) SBI	NR
Levine (2004)[68] Krief (2009) [72]	1998- - 2001	0 – 60 d	123/1,169 (11.4) SBI	NR
Gomez (2010) [40]	2003-2008	0 – 90 d	198/1,018 (19.4) SBI	NR
		0 – 90 d	23/1,018 (2.2) bacteremia	12.5 [5.4, 22.6]
Watt (2010)[73]	2002 - 2006	0 – 90 d	52/361 (14.4) SBI [UTI: 45/52 (86.0%); 38 cases in infants 31-90 d]	NR
	1997 - 2001	0 – 90 d	20/307 (6.5) SBI [UTI: 13/20 (65%), 9 cases in infants 31 – 90 d]	NR

Table 10. Prevalence of serious bacterial infection by setting for studies across North America (Continued)

Author (year)	Study period	Age range	Prevalence rate n/ N (%) SBI (or SBI type)	PPV (%) [95% CI]
Wolff (2009) [112]	2000-2007	45 – 90 d	130/1,950 (6.6) SBI	7.1 [6.7, 7.3]
Maniaci (2008)[53]	2005 – 2007	0 – 90 d	30/234 (12.8)	NR
Primary Care Setting				
Caspe (1983)[34]	1974 – 1979	0 – 30 d	7/107 (6.5) bacteremia	NR
		30 – 60 d	4/198 (2.0) bacteremia	27.3 [7.3, 60.6]
Dagan (1985)[29]	1982 – 1984	0 – 90 d	23/233 (9.9) SBI	24.7 [16.4, 35.2]
Pantell (2004)[5,52,67,104]	PROS Study: 1995 – 1998	0 – 90 d	63/3066 (3.6) bacteremia/meningitis	NR
			212/2058 (10.3) SBI (excluding Gastroenteritis)	NR

d=days; PPV = positive predictive value; SBI = Serious Bacterial Infection; UTI= urinary tract infection; PROS = Pediatric Research in Office Setting

Table 11. Prevalence of serious bacterial infection by setting for studies conducted in other countries (Taiwan, Israel, Spain)

Study ID	Study period	Age range	Prevalence rate n/ N (%) SBI (or SBI type)	PPV(%) [95% CI]
Emergency Setting In Taiwan				
Chiu (1994)[56]	1992 – 1993	4 – 31 d	45/254 (17.7) SBI	30.8 [22.9, 40.0]
Lin (2000)[105]	1997 – 1998	< 60 d	22/162 (13.5) UTI	34.0 [21.3, 49.4]
Chen (2009)[33]	2003-2004	0 – 90 d	34/135 (25.2) SBI	NR
Emergency Setting In Israel				
Mintegi (2009)[65]	2003-2008	0 – 90 d	50/381 (13.1) SBI	2.7 [0.7, 7.5]
Jordan (2008)[76]	2003-2004	0 - 29 d	62/328 (18.9) SBI	NA
Mintegi (2010)[77]	2003-2007	0 - 29 d	26/124 (20.1) SBI (UTI, bacteremia, pneumonia)	NA
		30 d – 90 d	71/561 (12.6) SBI	NA
Emergency Setting In Spain				
Yarden-Bilavsky (2009/2010) [46,78]	2006-2008	0 – 60 d	134/1257 (10.7) SBI	NA
			68/833 (8.1) UTI	NA
			11/833 (1.3) bacteremia	NA
			10/833 (1.2) pneumonia	NA
Bilavsky (2009) [47]	2005 – 2008	0 – 90	102/892 (11.3) SBI	NR
Shwartz (2008) [79]	1997 – 2006	< 28 d	87/449 (19.4) SBI	32.7 [29.5, 35.1]
Primary Care Setting (only for Taiwan)				
Chiu (1997)[21]	1994 – 1995	4 – 28 d	41/250 (16.4) SBI	33.6 [25.1, 42.1]
d=days; SBI = Serious Bacterial Infection; UTI= urinary tract infection; PPV = positive predictive value				

KQ 6A. How likely are parents of infants six months of age or younger with fever other potentially serious medical condition to comply with a provider's recommendation that the parent bring the infant back (to that provider or another) for a return appointment to reassess the condition(s) of concern?

KQ 6B. What is the evidence that identifiable parental factors (e.g. education, insurance status, living situation, history of previous visits with the provider, time/distance required to travel to an appointment, etc.) or clinical setting in which care is sought (community practice vs. emergency department and/or hospital outpatient clinic) independently influence the likelihood that a parent will adhere to provider's recommendation for a return appointment to reassess the condition(s) of concern?

Four studies were included in this section.[19,61,72,80] The study by Krief et al. was reported in 3 publications.[68,72,101] Three studies were conducted in the United States (1987 – 2001),[19,72,80] and one study was conducted in Canada (2005).[61](Table 12) All studies were prospective in design and included 4,593 children aged of 0 – 3 months.[19,61,72,80]

None of the studies reported any evidence regarding the influence of parental factors (e.g., age, education, distance/time to travel to an appointment, living situation) or clinical settings (emergency department vs. primary care office) on rates of parental compliance to telephone or return visit followups.

Results

In the study by Baskin (1992) conducted in the US,[19] outpatient treatment of febrile infants (28 – 89 days) and adherence to strict follow up protocol was investigated as an alternative to hospital admission during the period of 39 months (1987 – 1988). The included 503 infants were febrile well appearing (≥ 38° C) with peripheral leukocyte count < 20 x 109 cells/L, cerebrospinal fluid leukocyte count < 10 x106/L, and without any urinary leukocyte esterase. All infants required to have a caretaker available by telephone. Follow up was obtained for all except for one infant (99.8 percent). Infants were initially treated with intramuscular injection of ceftriaxone (50 mg/kg) and then discharged from the emergency department. A second injection of cefriaxone was administered on return visit in 24 hours. Follow up calls were conducted at 12 hours, 2 days, and 7 days later after first entry to ED. When culture results became available, patients with bacterial growth in cultures of blood, CSF, urine, or stool were immediately recalled to the emergency department for appropriate antimicrobial therapy.

Twenty seven of 503 (5.4 percent) infants were identified with SBI. A 24 hour visit and administration of 2nd dose of ceftriaxone was documented for 494 (98 percent) of infants. A 48 hour telephone call was made for 475 (94 percent) and a 7 day call for 482 (96 percent). Overall some follow up was obtained for all but one infant. All infants without SBI 453 (95.2 percent) were treated successfully as outpatient. Twenty three infants without SBI (4.8 percent) were hospitalized due to concerns documented during follow ups. Two of these infants were hospitalized more than 24 hours due to concerns about parental supervision.

In a prospective multicenter US study by Krief et al (2009) [68,72] during the period of 1998 - 2001, the risk of SBI in infants with or without influenza virus infections in 1091 infants ≤ 60 days of age was compared. The Yale observation scale (YOS) score was determined by the

examining physician upon admission to ED (prior to laboratory evaluations). Eighty five percent (n=712) of infants tested for influenza virus were admitted to the hospital. Telephone follow ups on patients discharged from the ED (n=132) within 4 – 7 days were performed and were successfully completed for 103 (78.0 percent) infants. No other information about noncompliant infants was reported.

In one Canadian study by Dore-Bergeron (2008),[61] the feasibility of ambulatory treatment of 67 febrile infants (aged 33-85 days) with presumed UTI presented to ED of a tertiary hospital was investigated. The diagnosis of UTI was confirmed for 86.6 percent of infants treated in a Day Treatment Center (DTC). Seven infants were subsequently admitted to hospital due to confirmed bacteremia or other complications. The treatment protocol for ambulatory patients included a single dose of intravenous gentamicin, a single dose of ampicillin and 2 or 3 doses of oral amoxicillin until the next visit to DTC in 24 hours. Parents were instructed to monitor the fever every 4 hours during 24 hours after initial visit to ED. Daily administration of intravenous antibiotics was continued at DTC until the infant was afebrile or diagnosed with SBI (UTI) in which case full course of antibiotic treatment would follow. Four infants were hospitalized because of parents' refusal to follow up with the DTC protocol. Parental compliance with DTC visits and with antibiotic treatment at home was 98.3 percent and 80.4 percent, respectively. There were no differences in rate of compliance with DTC treatment between parents of younger infants (≤ 60 days) and those of older infants (61-90 days).

Adherence of ED physicians to patient referral to the appropriate setting (DTC or hospital ward) was somewhat lower for younger infants, but this association was not statistically significant (comparing <60-day-old children with older children: crude OR: 0.5; 95 percent CI: 0.2–1.5). The authors conclude that ambulatory treatment of infants 30-90 days of age with febrile UTI is a feasible option.

One US study by Condra (2010),[80] investigated the costs and complications involved in the inpatient treatment with antibiotic therapy for 62 febrile infants aged 29 – 60 days. This study included infants meeting Philadelphia criteria for low risk for SBIs during a 16 months study period. Six (9.7 percent) of the 62 low risk subjects were discharged from the ED by the physician after a full evaluation for sepsis. Five (83.3 percent) discharged infants required reevaluation, and 2 (33.3 percent) required reevaluation and hospitalization within 24 hours of discharge (one for an erroneous positive blood culture and one for continued fever and newly documented pneumonia). Despite meeting low-risk criteria, all remaining 56 febrile infants were hospitalized and received intravenous antibiotics.

Follow up calls were scheduled and were successful on days 2 (77.4 percent), 7 (85.4 percent), and 14 (83.9 percent) after discharge. All six subjects (100 percent) discharged directly from the ED did have medical followups within 48 hours. Medical follow up with primary care provider was not made for one third (27.4 percent) of infants discharged after hospitalization. This study also reported that most parents preferred discharge to admission after the experience of hospitalization

Table 12. KQ6 Included studies reporting on relevant outcomes for infants 0-6 months of age

Author, (year)RefID Country	Study Design/objective Setting Study period	Population characteristics	Treatment characteristics	Followup details	Results
Baskin, MN (1992)[19] US	-Prospective -ED -1987 – 1997	N=503 infants 28 – 89 d (67% 28-60 d, 33% 61-89 d); with fever without a source – 476 were treated as outpatients and were followed Age: mean 55 (SD 17) d No other characteristic reported	IMI of Cefriaxone (2 doses within 24 hrs) pending culture results	3 phone calls (1 – 12 hrs; 2 – 48 hrs; 3 – 7 d post discharge) and 1 return visit to the ED in 24 hrs post initial visit	Infants with fu at 24 hrs: 494 (98%) who had a 2nd dose of cefriaxone Infants with fu at 48 hrs: 482 (96%) There was concern about 2/476 (0.42%) parents of infants without SBI about parental supervision — These infants were hospitalized > 24 hrs of initial entry
Krief (2008)[68,72,101] US	Prospective cross sectional/ to determine the risk of SBIs in FI with or without influenza virus infections 5 pediatric ED clinics (original report of this trial include 8 ED hospitals) 3 consecutive influenza seasons 1998-2001	N=844 FI ≤ 60 d, n=844 FI +ve for influenza virus (original report included 1025 infants) Age: mean 35.8 d, 55% male, median YOS score (IQR 6-8)	Yale Observation Scale (YOS) was used as a tool to determine infants' status. Antibiotic therapy and/or hospitalization, were at the discretion of the responsible physician & not determined by study protocol	One telephone fu on patients discharged from the ED within 4 to 7 d	Compliance with phone fu: 103/132 (78.0%) of discharged infants. 7 (1%) (patients without CSF cultures were determined not to have bacterial meningitis by telephone fu) No information about characteristics of compliant or noncompliant parents/infants was reported.
Dore-Bergeron, MJ (2009)[61] (10351 commentary) Canada	Prospective cohort/ to investigate feasibility of ambulatory tx at day treatment centre (DTC) One tertiary-care pediatric ED Period: 2005	N=118 FI 30 – 90 d with presumed UTI Age: median age for 67 FI admitted to DTC = 66 d (range: 33– 85 d)	Inpatient tx (protocol not described) if any: abnormal CSF, toxic appearance, underlying medical problems, abnormal creatinine levels, parental refusal to fu in DTC, or outpatients tx Ambulatory tx protocol:	In outpatient tx, monitoring the fever every 4 hrs + return the child after 24 hrs	67/118 (56.8%) of FI were admitted to DTC. Rate of parental compliance with DTC visits: 98.3%. Successful tx in the DTC (attendance at all visits, normalization of temperature within 48 hrs, -ve control urine & BC results, & absence of hospitalization): 86.2% of pts with

Table 12. KQ6 Included studies reporting on relevant outcomes for infants 0-6 months of age (Continued)

Author, (year)RefID Country	Study Design/objective Setting Study period	Population characteristics	Treatment characteristics	Followup details	Results
			single IVI gentamicin (5 or 2.5 mg/kg)+ 1 dose IVI ampicillin, & 2 or 3 doses oral amoxicillin, to be taken until the 1st visit to DTC in 24 hrs. At DCT IVI gentamicin daily until the child was afebrile. If UTI was confirmed tx with antibiotics were started.		confirmed UTI Compliance with guidelines of antibiotic tx: 80.4%; hospitalization during the course of tx in DTC: 12.1% Adherence of ED physicians to patient referral to the appropriate setting (DTC or hospital ward): lower but not statistically-significant for younger infants, [crude OR, comparing < 60-day-old children with older children: 0.5 (95% CI: 0.2, 1.5)]
Condra SC (2010)[80] US	Prospective observation/ evaluation of cost and complications in inpatient treatment of febrile infants 29-60 d of age Period: NR – total length of study was 16 months	N = 62 infants 29 – 60 d; fever without a source; met a criteria derived from Philadelphia for Low Risk for SBI 55% male median age: 44 d 39 (63%) White; 18 (29%) African American, 5 (8%) Hispanic (range 29 -60 d) White (63%), African American (29%), Hispanic (8%). 8 (12.9%) Group B Streptococcus +ve or unknown (the mothers treated with peripartum	Despite meeting LR criteria, 56/62 (90.3%) infants were admitted and received IVI antibiotics 6/62 (9.7%) were LRI and discharged from the ED after a full sepsis workup.	3 phone followups with parent and primary care provider (PCP) within the 2 wks after discharge + contact with PCP at 14 d post discharge Questionnaire on 1-Intants' health status 2-compliance 3-hospital charges	Compliance with phone calls after initial discharge (reported for FI who were managed as inpatients 56 (90.32%)]: d 2: 77.4%; d 7: 85.4%; d 14: 83.9% All 6 subjects (100%) discharged directly from the ED did have medical followup within 48 hours with PCP Parents preferred discharge to admission (66%-70%) 5/6 (83.3%) discharged infants required reevaluation and 2/6 (33.3%) were hospitalization within 24 hrs of discharge-one for a +ve blood culture (later determined to be a contaminant) and one for continued fever & newly documented pneumonia.

Table 12. KQ6 Included studies reporting on relevant outcomes for infants 0-6 months of age (Continued)

Author, (year)RefID Country	Study Design/objective Setting Study period	Population characteristics	Treatment characteristics	Followup details	Results
		antibiotics)			Complications in outpatients:

RefID=Reference Identification; US = United States; N = number of participants; yrs = years; mo/s= month/s; wks = weeks; d=day/s; hr/s = hour/s; IMI = intramuscular injection; IVI=intravenous injection; SBI= serious bacterial infection; LRI=low risk infants; FI=febrile infant; tx=treatment; fu=follow up; #, n, N=number; LR= low risk for SBI; HR= high risk for SBI; SBI=serious bacterial infection; LP=lumbar puncture; BC= blood culture; YOS= Yale Observational Scale; IQR=inter-quartile range; NR= not reported; CSF=cerebrospinal fluid; UTI= urinary tract infection; ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification; CPT-4=Current Procedural Terminology, Forth Revision

Excluded Studies- Qualitative Description

Nine studies reported somewhat relevant outcomes in pediatric population (age 0 – 6 months) but data was not stratified by age.[127-135] A brief summary of these studies is provided in this section.

In a US quasi-experimental study by O'Neill-Murphy (2001),[131] education (interactive fever education program and the standard written fever pamphlet) on fever and its effect on parental anxiety in parents of febrile (> 38.4° C) children 3 months to 5 years of age was investigated. Outcomes included correct use of a thermometer, fever home management skills, and appropriate fever telephone follow up. Both intervention programs were equally effective in improving all outcomes. This information was not reported for parents of children less than 6 months of age.

In another study by Sarrell (2003),[130] impact of a single session education program on parental knowledge and approach to low grade childhood fever (< 38.5° C) was investigated. This study included parents of children with a broad age range (mean age of youngest child 53.5 months). This study indicates that parental knowledge of fever management in children can be improved by reinforced educational session. The outcomes were not stratified by age groups.

One study by Hemphill (1998),[132] reported compliance rates in 423 febrile children aged 3 months - 10 years. In this study, the follow up rates during the period of 1993-1994 were compared between two medical systems in US with preset appointments after ED release and free medical care (WHMC); or one in which parents must arrange follow up appointments after ED release (FFX). One to 7 days telephone follow ups were conducted. Variables associated with poor followup compliance for the entire study population were: Hispanic children (OR: 2.5, 95 percent CI 1.3-4.8), children within the FFX system of follow ups (OR: 2.5, 95 percent CI: 1.1-5.3), children whose parents did not speak English (OR: 2.8, 95 percent CI 1.2-6.6), and children who were told to follow up in 2 – 3 days after the ED visit rather than in 1 day (OR 1.7, 95 percent CI 1.3-2.2). Compliance to follow up in the WHMC system was better compared with that in the FFX system (92 percent vs. 67 percent, $p < 0.001$). For FFX alone the following factors were associated with poor follow up: Hispanic ethnicity, self-payer status, lack of a primary physician for follow up, the diagnosis of otitis media, and follow up in > 24 hours.

In one study by Crane (2000)[128] parents' compliance to after-hours telephone advice given by pediatric residents in a continuity clinic in US was investigated. Study population consisted of 412 consecutive patients enrolled in the resident-staffed pediatric continuity clinic with access to a telephone triage system. Only 21 percent of chief complaint of children was fever. No specific outcomes for the febrile children were reported. Overall 412 (87 percent) of caregivers complied with the advice given over the telephone by resident. The study reports no discrepancy in caregiver compliance based on the child's age. Most of the 474 calls were about children younger than 1 year. Only slightly higher levels of compliance were noted among parents of children younger than 3 months, whereas lower levels of compliance were found in parents of children aged 1 – 3 years.

In one US study by Baker (2009),[129] the impact of a brief educational video shown to parents during an emergency department visit for minor febrile illness was investigated. 280 caregivers of febrile children 3 – 36 months were enrolled into two intervention groups (either an 11 minutes fever education video or a control child safety video). There was no difference between the rates of return visit to ED for fever for intervention or control groups. The consensus among the 3 blinded independent ED physician reviewers was that 30/81 visits (37 percent) were medically necessary in the intervention group compared with 21/81 (25.9 percent) in the control

group (statistically not significant, p = 0.07). The overall rate of medical necessity was found to be 31.5 percent.

In a prospective cohort study by Gauthier (2004),[133] feasibility and complications of outpatient management with IV antibiotics among 212/291 episodes of UTI (72.9 percent) in 275 febrile infants and children (3 months to 5 years) treated at a day treatment center of a tertiary care pediatric hospital was investigated. This study was conducted in US within the period of 2002-2003. In this study nontoxic apparent children were treated with IV ampicillin and three doses of oral amoxicillin to be taken until the visit at the day treatment centre within the next 24 hrs. Parents were asked to measure the child's temperature every 4-6 hrs during IV treatment. In total there were 202 children treated at the DTC, 65 children treated as inpatient, and eight who were discharged from the ED with oral treatment. In 9/71 hospital admissions, the child was admitted due to parents refusal or inability to comply with day treatment center treatment protocol. Overall, the adherence to protocol for both physicians and parents were described as excellent. The data for infants and children under 6 months of age was not presented.

Baker (1999),[134] in a US survey of three private practices, and one urban hospital based nonprivate practice during a 2 week period in 1996 compared compliance with recommended ED or office visit referrals in the two settings. Pediatric telephone triage and advice system (developed by Barton D. Schmitt) was used to evaluate medical complaints and suggest appropriate management including referral for physician evaluation (immediate, 4 hours, 24 hours, 48 hours, 72 hours, 2 weeks) and/or advice for caregiver for management in the home. In total 663 calls were received from 377 nonprivate practice patients (age range 1 – 192 months; mean 39 months) and 286 for private practice patients (age range 1 – 242 months; mean age 58 months). Only 6 percent of all calls were based on a primary complaint of fever. Other complaints included respiratory complaints (21 percent), trauma (14 percent), rash (10 percent) and miscellaneous (36 percent). Significantly more nonprivate practice patients were referred to their primary care physician for an office visit (p = 0.005) or were referred to an ED or urgent care facility for immediate evaluation (p=0.01). There were no differences between compliance rates of the two settings. Data was not stratified for infants with fever.

In one retrospective study by Vidwan, G (2010),[135] conducted in US at an urban academic tertiary care pediatric hospital ED during the period of 2000-2005, management and outcome of focal bacterial infections in nontoxic infants under 60 days of age was investigated. In this study febrile (39) and afebrile infants (158) were included. Twenty-three (59 percent) of the febrile infants were discharged home from the ED. Two (8.7 percent) of these infants were returned to the ED within 72 hours; both were initially diagnosed with acute otitis (AOM) media and had planned followups as no primary care was available. No other information regarding the follow up visits or mode of contact was provided.

Chapter 4. Discussion

The synthesis of the literature on the diagnosis of serious bacterial illnesses (SBI) and invasive herpes simplex virus infection in infants less than 90 days of life has been challenging. In general, there is a lack of standard definitions in this field. Even simple issues such as what constitutes a fever or what should be included in the definition of SBI vary widely. The increase in precision of testing over time (i.e. aseptic meningitis vs. enteroviral meningitis), and emergence of different types of testing make it difficult to standardize the above mentioned definitions.

The majority of the serious bacterial illnesses cases reviewed in this systematic review were due to urinary tract infections from *Escherichia coli*. A significant percentage of the cases of bacteremia and bacterial meningitis were due to *Streptococcus agalactiae* (group B streptococcus). This likely reflects the inclusion in many studies of neonates 0 – 6 days of age and studies done before the implementation of current screening and intrapartum antibiotic strategies that have significantly decreased the incidence of early on group B S*treptococcus* disease.

Although many studies had high negative predictive values, these should be interpreted with caution as predictive values vary based on prevalence. A rare event such as bacterial meningitis as the cause of fever in an infant will reflect a high negative predictive value. Sensitivity, specificity and likelihood ratios are independent of prevalence and thus better to compare between studies.

The evaluation of a patient is not always a one-time event and experienced clinicians value the ability to followup a patient over time for serial reassessment. Only the minority of studies report on reassessment and reassignment of the clinical status [20,21] and variable or no followup durations are reported. Additionally, only a fraction of studies reported to have employed lumbar puncture to diagnose bacterial meningitis. Similarly, majority of studies reporting the use of lumbar puncture did not employ this test on all included infants, thereby raising the possibility of incorrect test interpretations. Also, the vast majority of the studies did not report on long-term followup where partially treated meningitis might have been identified.

The heterogeneity of studies has precluded meta-analysis; therefore, simple summary statistics were not available except for the Rochester criteria and Philadelphia protocol. There was no clear difference in the study quality (QUADAS scores) between the studies reporting combined clinical and laboratory criteria such as Rochester, Boston, Philadelphia criteria/protocol and those reporting clinical or laboratory criteria alone. Moreover, the diagnostic test accuracy results for infants older than 90 days of age reported in some studies were not considered in this review (KQ1a). Such studies were included in the review only if they reported other relevant data (e.g., prevalence of SBI, outcomes related to management of febrile infants).

The clinical conundrum is how to balance the risk of missing an SBI (with potentially a devastating outcome) with the risks associated with diagnostic and management strategies. To date, a tremendous amount of resources and effort has been focused on developing tests, protocols, and criteria to attempt to minimize the first while almost ignoring the latter. The literature has revealed that the field of febrile infants less than 90 days is not homogenous and there are factors that either increase (i.e., neonatal age group) or decrease (i.e., viral syndrome) the risk and also the testing strategy accuracy. Equally heterogeneous are the risks associated with the specific types of SBI (e.g. urinary tract infections, bacteremia, and meningitis). A

clinician fears the consequences of missing a case of meningitis much greater than missing a urinary tract infection; however the data are lacking to determine the accuracy of detecting the rarer and more devastating meningitis.

This systematic review has several strengths. We were able to calculate the test accuracy characteristics from raw data when possible; we provided prevalence rates and test accuracy characteristics on the different types of SBI (UTI, bacteremia, meningitis) for the whole 0 – 90 day age group and for the neonatal group. We also provided data on prevalence rates of specific bacterial organisms causing various types of SBI. To our knowledge, this is the first systematic review to seek the evidence on harms in the evaluation and management of febrile infants 0 – 3 months of age, to evaluate the role of viral infections or clinical bronchiolitis in the rates of SBI, and to identify the factors that influence compliance in febrile infants or other infants with serious medical problems in infants 0 – 6 months of age.

KQ 1A/B In infants < 3 months old who present with a fever, what is the evidence for the sensitivity, specificity and predictive values of individual or combinations of clinical features (including history including information on the mother's history and previous testing, risk factors, findings on clinical exam and formal scoring instruments based on clinical features) for identifying those with serious bacterial illness (SBI)? How do these findings vary within the age range 0 to 3 months?

The formal scoring instruments were the most evaluated standard approach used across multiple sites, with the Rochester criteria being tested the most. These criteria reported a higher sensitivity and negative predictive value compared with clinical criteria or only laboratory criteria. The use of combined clinical and laboratory criteria also yielded high sensitivity and negative predictive values. Specificity and positive predictive value were fairly uniformly poor across the different groupings of test strategies. There was a consistent trend of similar test characteristics between total SBI and bacteremia and meningitis across the criteria and various other tests, however reflecting the small numbers, the confidence intervals were large.

The studies evaluating clinical criteria revealed test characteristics that were not appreciably different from laboratory testing. Although they were similar to laboratory testing, it can be difficult to standardize clinical impression with varying experience across different settings and volume. There was not one laboratory test or clinical criteria that had sufficient sensitivity for a serious bacterial illness.

The pooled sensitivity, specificity, and the area under the SROC curve were similar for the Rochester criteria and Philadelphia protocol. Given the similar test accuracy between the two criteria, attention should be paid to the differences. Where the Philadelphia criteria requires the evaluation of the cerebrospinal fluid by lumbar puncture and a chest x-ray in the 29-60 day old group to define the low risk group, the Rochester criteria identifies the low risk group in the 0 60 day old infants without using LP and CXR.

The neonatal period (0 – 28 days of life) was shown to have a higher prevalence compared with older children. When separately evaluated, neonates did not have the same test characteristics as the older children or whole group of less than 3 months of age. In only one study evaluating the Rochester criteria in neonates the testing in the neonatal age group showed

better numerical accuracy than in the older age group. The rest of the combined, laboratory or clinical criteria demonstrated lower sensitivity in the neonate as compared to older groups.

There remains controversy about the need for lumbar puncture in infants with fever. In our review, six studies reported to have misclassified 8 cases of meningitis into low-risk for SBI using the Rochester criteria (4 missed cases), a data-derived model of combined clinical and laboratory (1 missed case), clinical only (one missed case), and a laboratory test (2 missed cases). None of these criteria included a lumbar puncture and CSF analysis.

KQ1C. In infants < 3 months old who present with a fever, what is the evidence for the sensitivity, specificity and predictive values of individual or combinations of clinical features (including history including information on the mother's history and previous testing, risk factors, findings on clinical exam and formal scoring instruments based on clinical features) for identifying those with invasive herpes simplex virus infection (HSV)? How do these findings vary within the age range 0 to 3 months?

Little evidence on invasive herpes simplex virus infection in febrile infants included in this systematic review does not indicate the lack of clinical cases. The literature mainly focused on the end diagnosis of HSV,[136] rather than the clinical syndrome of a febrile infant. When invasive herpes simplex virus infection is reported in large series of febrile infants, the numbers are very small. In a recent study, Caviness et al. reported that during the season, enterovirus infection was 20 times more likely and a serious bacterial illness was 23 times more likely to occur in hospitalized febrile neonates as compared with HSV in febrile infants[55] This lack of evidence is likely due to the fact that HSV does not routinely present with fever (3/10 in Caviness 2008 study[55]) and the fact that herpes simplex infection due to skin eyes and mouth infection were likely excluded from other studies as they represent a focus of infection. Given the lack of evidence of diagnostic accuracy and the inability to target and adequately screen mothers,[137,138] we are left only with expert opinion.[139]

KQ 2A. What is the evidence that clinical features alone, basic laboratory tests (e.g., complete blood count [CBC], urine culture) alone or the combination are sufficient to identify febrile infants < 3 months who are at low risk of having a serious bacterial illness HSV (i.e., have a high negative predictive value)?

There were several studies that used clinical and laboratory criteria to identify infants at low risk for SBI. The first study to use this approach used the Rochester criteria and showed a high negative predictive value of 99.3 percent in infants < 90 days of age.[29] Other studies that used the Rochester criteria showed similar negative predictive values (93.7 – 99.2 percent). The other low risk criteria (Philadelphia, Boston, and Milwaukee) also had high negative predictive values for SBI. The low risk criteria used in these studies had high sensitivity (86 – 100 percent) but low specificity (26 – 66 percent).

The rate of SBI in the low risk group is about 1 – 2 percent compared to a rate of ~10 percent overall. Low risk criteria can identify infants unlikely to have SBI and who can be managed less aggressively.

Infants < 1 month of age have been treated differently based on a higher baseline risk of SBI and the difficulty of clinical assessment. Several studies have shown that although the overall risk of SBI is higher, the Rochester criteria may be able to identify low risk infants in this age group. The negative predictive values for the Rochester criteria in this younger age group were 93 – 97 percent. The rate of SBI in the low risk group of neonates is 3 – 5 percent. The low risk criteria can identify infants < 1 month old who are unlikely to have SBI but a small number of infants with SBI will be missed.

KQ 2B. What is the evidence for the potential risks resulting from a delay in the diagnosis and treatment of patients who appear low risk but have a serious bacterial illness?

There is very little evidence on the risks of delay in diagnosis and management in low risk infants who were later found to have SBI. Several studies reported the outcomes of infants in which the diagnosis of SBI was initially missed. Most infants were subsequently hospitalized and treated with antibiotics. Although somewhat reassuring, the fact that there were no adverse outcomes in these infants can also be related to the significant underreporting and lack of followup in these studies. Of note, several of the studies reported on contaminated urine, blood and cerebrospinal fluid cultures. The added management and harms associated with these false positive results were not reported.

Indirect evidence comes from the PROS research network febrile infant study. In the office based study by Pantell,[5] many practitioners were not following the guidelines for the management of febrile infants. In this study, only 54 percent of the infants had a urinalysis and 24 percent had no testing of blood, urine or cerebrospinal fluid. The guidelines were not being followed even for febrile infants < 1 month of age. The rate of UTI was 5.4 percent and of bacteremia was 1.8 percent in the overall group, but in the infants that actually had testing the rates of UTI and bacteremia were 9.7 percent and 2.4 percent respectively. It is possible that cases of SBI were missed because many infants had no investigations. Despite this, there were no adverse outcomes reported. It should be noted that many infants had either office or telephone follow up which may enable the practitioner to have a less aggressive management approach. Additionally, Newman reports from the same study on UTIs.[104] It was modeled that in the 807 infants not initially tested or treated with antibiotics there should have been 61 UTIs, based on predictors of UTIs whereas only 2 cases were diagnosed on followup. No adverse outcomes were reported with office and telephone followup suggesting that some acute UTIs spontaneously resolve. The study was not designed to look at the long-term renal damage of these patients, but the findings do not support the concern that all untreated UTIs lead to bacteremia.

The low risk criteria have been used in practice for many years and yet there is minimal data on the morbidity and mortality of infants with SBI who are missed by the low risk criteria. To truly balance the risks and benefits of management strategies, the long term morbidity of missed diagnoses need to be fully determined.

KQ 3A. What is the evidence that clinical features alone, basic laboratory tests (e.g., complete blood count [CBC], urine culture) alone or the combination are sufficient to identify febrile infants < 3 months who are at

high risk of having a serious bacterial illness (i.e., have a high positive predictive value)?

A confusing aspect of the literature on SBI in febrile infants is the focus on either identifying high risk patients or identifying low risk patients. It is important that studies reporting on indentifying low risk infants emphasize that that infants not meeting the low risk criteria are not necessarily high risk, and therefore are more appropriate to be labeled as not low risk.

Contrary to the approach of ruling out a SBI, studies attempting to rule in an infection have not been as successful. Positive predictive values of the tests/protocols/clinical impression range from only 4.5 percent to 64 percent. One study also looked at a small group of patients that had a 'toxic' appearance or a band count of >5000/uL. It is difficult to determine what this report adds to clinical practice, as most clinicians would automatically consider 'toxic appearing infants' at high risk and not apply protocols or testing, as the result would not sway them from potential empiric management with antibiotics or admission to hospital. Interestingly, given such a concerning clinical picture, the PPV was only 17.2 percent however the NPV was 100 percent.

In absence of better data on harms and the costs of diagnostics and therapeutics or improved positive predictive values, clinicians will continue to opt to identify low risk infants and over treat a large group of SBI negative patients.

KQ 3B. What is the evidence on the benefits and harms of immediate antibiotic (antibacterial and antiviral) therapy and / or hospitalization (vs. delaying until diagnostic workup is complete) in patients at high risk of serious bacterial illness or HSV?

Overall, the reporting of harms for this area has been very poor. The realm of this question should encompass medical harms as well as cost associated with immediate hospitalization and treatment with antibiotics. Cost effectiveness modeling has been performed for febrile infants 28 – 90 days of age.[140] The cost-effectiveness was greatest for infants who had a total sepsis evaluation followed by IV or IM antibiotics. Additionally, the psychological harms of the testing have not been explicitly stated in the studies. Unnecessary testing may have had the unexpected consequence of the parents viewing the infant as more fragile or have more anxiety around the chance of a serious bacterial infection although the literature has not delineated the presence or absence of such factors.

Byington and Paxton reported on a survey of parents of infants undergoing a 'rule-out sepsis' (ROS) evaluation months after admission. The majority of the sixty parents who interviewed reported finding the ROS evaluation very stressful with 28 percent believing their infant was to die. Additionally, 36 percent of mothers reported breastfeeding problems with 18 percent stopping breastfeeding, 35 percent perceived their child to be less healthy on followup, 43 percent reported financial stress, and 33 percent reported perceived iatrogenic problems.[141]

KQ 4. What is the evidence that the presence of an identified viral infection predicts against a serious bacterial infection?

There seems to be some confusion surrounding SBI evaluation in a child with a recognized viral syndrome. [142-144] Advent of rapid testing for viral pathogens has given many clinicians the ability to diagnose viral infections in children less than 3 months of age. This review has shown a

consistent statistically significant inverse relationship between viral testing positive or clinical bronchiolitis and the presence of SBI. Most of the SBI were UTI, although there were some cases of bacteremia, but no meningitis.

For the clinician in an office or with no access to rapid viral testing a clinical diagnosis is more applicable. Some of the studies enrolled patients with viral culture positive results due to their retrospective nature. As rapid antigen testing is not 100 percent sensitive (87 percent),[81] some patients with rapid testing negative, culture positive would not benefit from this information. More concerning is the issue of false positives, where 3/135 were rapid testing positive, but viral culture negative.[81]

However, even in the absence of rapid testing, the clinician is able to obtain significant information that decreases the chance of SBI. The three studies by Lubinghl, Bilavsky and Kuppermann demonstrate a similar inverse relationship between clinically diagnosed bronchiolitis and SBI.

The sample sizes of the studies did not answer the clinical dilemma of the need for lumbar puncture in infants with clinical bronchiolitis or a positive viral test. The study by Levine et al. reported 0 cases of meningitis in the RSV positive group. Although bacteremia and meningitis were lower in the RSV positive group it did not reach statistical significance. Luginbuhl et al's PROS study also cannot answer this question due to the sample size (only 35 patients [16 percent] of the bronchiolitis group had a lumbar puncture). No cases of SBI were found in the patients with clinically diagnosed bronchiolitis which had statistical significance compared with the nonbronchiolitis group in total SBI and the sub-group of bacteremia plus bacterial meningitis. Bilavsky et al. reported no cases of meningitis or bacteremia in the bronchiolitis group compared with 1 and 4 in the no-bronchiolitis group respectively. The rarity of the entity of bacterial meningitis in RSV or bronchiolitis positive patients likely means that this question will not be answered without an enormous effort. Indeed, only a few cases of meningitis have been described in the literature in febrile infants with a viral infection.[144,145]

The lack of reporting of the age-specific sub-groups does not provide information on whether the group of infants 0-3 months of age is homogenous in terms of risk of SBI in the bronchiolitis or virus positive patient. However, given our understanding that the prevalence of SBI is significantly higher in the 0-28 day group and that the diagnostic tests differ in their accuracy in this age group compared with the entire 0-3 month group, it seems logical that the neonatal time period should be viewed differently. This is supported by the only study by Levine et al. that provided neonatal specific SBI rates and demonstrated no significant difference in SBI rates between patients with and without proven RSV.

Overall, evidence in this review indicates that bronchiolitis or a positive result for a virus significantly predicts against SBI. The majority of cases of SBI were UTI. Caution should be used when evaluating neonates with these findings as the presence of bronchiolitis or virus in this sub-population may not be as predictive against an SBI as in older groups of infants.

KQ 5. What is the evidence that the prevalence of serious bacterial illness varies among febrile infants presenting to primary care and emergency practice? What is the evidence that prevalence affects the predictive value of clinical and laboratory findings?

The majority of studies were conducted in an emergency department setting. The reported prevalence rates of SBI in North American emergency department settings varied from 4.0

percent to 25.0 percent. The prevalence rates in the primary care studies varied about 9.0 percent-10 percent. There appears to be a somewhat higher prevalence of SBI in the emergency department population. The difference in prevalence rates may reflect a difference in the patient population that seeks care in the emergency department. The patients seen in the emergency department may be a sicker group than those who those who wait to see their primary care provider.

There is considerable practice variation between emergency department and office settings. These differences bring up the following questions: in the emergency department, are infants being over-investigated or does this reflect a difference in their level of acuity? In office practice, are infants with bacterial infections being missed and is there any associated morbidity and long-term consequences?

Given the low prevalence of serious bacterial illness and very low prevalence of bacteremia and meningitis, many clinicians, especially physicians who evaluate low volumes of febrile infants less than 3 months of age may never see a significant adverse outcome regardless of what their practice of diagnostics and management. Unfortunately, this may provide a false sense of security that the clinician is correctly managing these infants. The small numbers of bacteremia and meningitis in all the cited studies do not allow an accurate understanding of the accuracy of current testing strategies for these more serious outcomes.

KQ 6A. How likely are parents of infants six months of age or younger with fever or other potentially serious medical condition to comply with a provider's recommendation that the parent bring the infant back (to that provider or another) for a return appointment to reassess the condition(s) of concern?

The dearth of studies in this area led us to expand our inclusion criteria to up to six months of age and to include infants with fever or other potentially serious medical condition. The lack of focus in this area is evidenced by the identification of only four studies with this expanded inclusion criteria. Although the followup was reported in these studies, they were not the primary focus. The high rate of success for outpatient therapy and telephone followup in these studies could in part be explained by the increased motivation of parents whose infants were enrolled in the studies.

KQ 6B. What is the evidence that identifiable parental factors (e.g. education, insurance status, living situation, history of previous visits with the provider, time/distance required to travel to an appointment, etc.) or clinical setting in which care is sought (community practice vs. emergency department and/or hospital outpatient clinic) independently influence the likelihood that a parent will adhere to provider's recommendation for a return appointment to reassess the condition(s) of concern?

Follow up and reassessment of the febrile infant is an important component of their care. A clinician's decision making can be highly influenced by his/her assessment that the patient's caregivers are likely to comply with followup or further testing. A patient's clinical status can fluctuate from moment to moment making the development of testing strategies difficult to apply

to a rapidly changing situation. Additionally, clinicians may over-investigate an infant when they suspect lack of parental adherence to followup visits that might be required. If a clinician is convinced that a patient will be adherent to suggestions for followup or other management strategies, it would allow other less conservative options to be considered such as a multistep management strategy. Very little is known about the factors that affect compliance for follow up in this population and it is an area where more research is needed.

There was a lack of evidence regarding the influence of parental factors (e.g., age, education, distance/time to travel to an appointment, living situation) or clinical settings (emergency department vs. primary care office) on rates of parental compliance to telephone or return visit followups.

Although there were no included studies in this review on parental factors or clinical setting influencing followup, a review of the broader literature reveals some potential factors that need to be further studied in the 0-3 month febrile infant population. In some studies Hispanic patients were less likely to comply with followup. The other identified parental factors such as lack of parental ability to speak English, having to make their own appointment, self-pay, lack of a primary care provider and followup greater than 24 hours seem self-evident but require further study.

Conclusion

Overall, the focus of the literature has been on ruling out SBI. Harms associated with testing or management strategies have been poorly reported. Attempts to identify high risk groups, as described in the minority of reports, were not accurate. The Boston, Philadelphia, Rochester, and Milwaukee were fairly accurate in identifying a low risk group for SBI in infants younger than 3 months of age. The diagnosis of a viral infection or clinical bronchiolitis significantly decreased the chances of a serious bacterial illness. Invasive herpes simplex virus infection is a significant differential diagnosis in the febrile infant, yet the relevant literature is presented from the diagnosis rather than from the syndrome point of view, making it difficult to draw conclusions of test accuracy or management efficacy in an undifferentiated febrile infant. Although crucial to the management strategies in the low risk group, there is sparse literature on factors associated with compliance in this population. Future studies should focus on identifying the risks associated with testing and observation strategies and on factors that influence adherence to followup care.

Research needs and future directions

Many studies have been performed that accurately define a low-risk group. To move the field further, there is a need to further delineate the risks associated with testing and also observation of this group. Rigorous studies need to be done and reported (see QUADAS in Appendix G) with separate reporting of 0-28, 29-60, 61-90 days.

Consideration should be given to not include the 0-6 day old group as these infants likely represent another clinical syndrome of early onset sepsis related to perinatal factors. Group B *Streptococcus* has been identified as a major pathogen in this age group and has been the focus of many clinical guidelines for testing and intrapartum management. Most clinicians when faced with a febrile infant of 0 – 6 days of age would perform a full evaluation including lumbar puncture and admit the infant for intravenous antibiotics. The focus should be on the clinical conundrum of febrile infants with no apparent source of infection - UTI, bacteremia, and meningitis.

The group of low-risk patients needs to be defined incorporating risks associated with age group and viral or clinical syndrome status and observed. Detailed reporting of the harms associated with the diagnosis and in and outpatient observation of this low-risk group would be crucial. This should include management changes associated with contaminated specimens, parental anxiety, breastfeeding cessation, a long-term concern over 'vulnerable child syndrome', and financial costs. The outcomes should not only be numbers of SBI, but followup should be done to determine the long-term consequences of 'missed' or 'delayed' diagnosis of SBI such as decreased renal function with urinary tract infection, progression from UTI to bacteremia, and complications of meningitis.

Integrated into these studies should be evaluations on the factors or interventions that increase parental compliance with return assessments in febrile infants. Optimally, these studies should be multi-centered and evaluate both outpatient and emergency department settings. Once there are better data on harms of diagnostic and observation protocols a consensus expert panel should be struck to define the risk balance.

Furthermore, a registry or surveillance network should be developed to describe the changing pathogens and resistance over time as there is increasing concern over these shifts and their potential clinical significance.[73,86,146] Effects of vaccination and other interventions protocols utilizing IV/IM Ceftriaxone may be appropriately studied on a population basis. The majority of the SBI cases were UTIs and most frequent organism isolated for UTI cases was *E. Coli*. Most cases of bacteremia and meningitis were caused by Group B *Streptococcus* and *Streptococcus pneumonia*. These pathogens have changed significantly over time due to vaccinations or interventions. There is some evidence of resistance of different pathogens to antibiotic treatments in more recent studies.[86,146,147]

Other questions that were not in the scope of this review but are related are: the need for immediate IV antibiotics and the need for lumbar puncture at presentation to manage well appearing infants (0 – 1 month, 1 – 3 months) with a confirmed urinary tract infection or other focus of infection (cellulitis, acute otitis media)

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Acronyms/Abbreviations

CLINICAL

ABC	absolute band count
CATH	catheterization
CBC	Complete blood cell
CI	confidence interval
CRP	C-reactive protein
CSF	cerebrospinal fluid
CT	computer tomography
CXR	Chest x-ray
DAS	Diagnostic accuracy study
ESR	Erythrocyte sedimentation rate
EV	enteroviral
GBS	group B streptococcal disease
hpf	high power field
HR	high risk (+: positive or -: negative)
HSV	Herpes Simplex Virus
IV/I	Intravenous/ injection
HSV	rare invasive herpes simplex virus infection
LE	leukocyte esterase
LR	low risk (+: positive or -: negative)
PCMC	primary children's medical center
PCR	polymerase chin reaction
PCT	procalcitonin
PMN	polymorphonuclear count
RSV	respiratory syncytial virus
SBI	serious bacterial infection/ illness
T	temperature
UA	urinalysis
UTI	urinary tract infection
WBC	White blood cell
YIOS	Young Infant Observation Scale
YOS	Yale Observation Score

UNITS

µg	micrograms
µg /L	micrograms per liter
µg /mL	micrograms per milliliter
µg/dL	micrograms per deciliter
µm	micromolar
µmol/L	micromoles per liter
cm	centimeters
cm/s	centimeters/second

Ibs	pounds
IU/L	international units per liter
IU/L	international units per liter
kg	kilograms
kg/m^2	kilograms per meter squared
m	meters
mg	milligrams
mg/d	milligrams per day
mL	millilitre
mmol/L	millimoles per liter
N	sample size
ng/dL	nanogram per deciliter
ng/L	nanogram per liter
ng/mL	nanograms per milliliter
nmol/L	nanomoles per liter
pg/mL	picograms per milliliter
pmol/L	picomoles per liter
° F	degrees in Fahrenheit
° C	degrees in Celsius

STATISTICS

ARD	absolute risk difference
CCT	controlled clinical trial
CI	confidence interval
IQR	interquartile range
LS	Least square
NS	not significant
RCT	randomized controlled trial
S/sign.	significant
SD	standard deviation
SE/SEM	standard error
WMD	weighted mean difference
ROC (AUC)	receiver operating characteristic (area under the curve)
LR	likelihood ratio
PPV	Positive predictive value
NPV	Negative predictive value

COMMONLY USED ABBREVIATIONS

#	number
%	percent
<	greater than
< or </=+	less than or equal to and
>	less than
> or >/=	greater than or equal to
▲/↑ or ▼/↓	increased, or decreased,
CG	control group

grp	group/s
ctrls	controls
d	day
Deg or °	degrees
Dept.	department
F	female
f/u	followup
FHx	family history
hr	hour
Hx	history
IG	intervention group
M	male
max	maximum
min	minimum
mo	month
NA	not applicable
NIH	National Institute of Health
NR	not reported
Q	question
Tx	treatment
vs.	versus
wks	weeks
y	year