2. Methodology

In this chapter, we outline our strategy for identifying and screening articles relevant to the management of bronchiolitis among infants and children. We describe the process of abstracting relevant information from the eligible articles and generating the summary evidence tables and cost analysis.

Literature Review Methods

Inclusion and Exclusion Criteria

Based on the final key questions specified in Chapter 1, we generated a list of inclusion and exclusion criteria for each key question (Table 1). We excluded studies that (1) did not pertain to infants and children; (2) were published in languages other than English; (3) did not report information pertinent to the key clinical questions; and (4) were not original studies.

Based on consultation with the TEAG, the RTI-UNC team revised the specification of the patient population of interest for Key Questions 1, 2 and 3 from "infants and children ages 0-5" to "infants and children." We made this revision because the age category 0 to 5 years did not reflect the fact that bronchiolitis is diagnosed primarily in children under 3 years of age. Also, the team wanted to be able to capture studies that looked at the long-term consequences of treatment of bronchiolitis in infancy or early childhood, even if those consequences were recorded at later ages. For Key Question 4 (cost-effectiveness of prophylaxis), the target populations for the cost-effectiveness question are (1) infants born 32 through 35 weeks' gestational age, and (2) infants born 32 through 40 weeks' gestational age with comorbid conditions.

The original geographic areas to which we intended to confine our literature searches and attention were North America, the United Kingdom, Australia, New Zealand, and Europe. Based on the recommendations of the TEAG, we removed this exclusion criterion for two reasons. First, some high-quality studies on this condition may well have been conducted elsewhere in the world, and we needed to be able to capture them. Second, including all areas may facilitate our examining information on different ethnicities and races in the report, as AHRQ and the professional societies had originally requested.

The criteria for study design were different for each key question based on the sufficiency and quality of evidence. Our diagnostic question (Key Question 1) was broad and required a lower admissibility standard. Therefore, we included both RCTs and prospective studies. The treatment and prophylaxis questions (Key Questions 2 and 3) were more specific and required greater strength of evidence; we thus elected to limit searches to RCTs. For the cost-effectiveness of prophylaxis (Key Question 4), we reviewed studies that employed economic analysis.

For all studies, key inclusion criteria included outcomes that were both clinically relevant and able to be abstracted. We set a minimum sample size of 10; small case series and single case

reports were excluded. For Key Question 4 alone, we also excluded article abstracts that did not mention using an analytical method such as cost, cost-effectiveness, cost-utility, or cost-benefit analysis.

To ensure that we were reviewing therapies relevant to current clinical practice, we excluded individual studies before 1980. Our search was last updated on April 1, 2002, and contains all abstracts entered into the MEDLINE® and other databases until that date.

Search Terms

Based on the inclusion/exclusion criteria above, we generated a list of Medical Subject Heading (MeSH) search terms (Table 2). The TEAG also reviewed these terms to ensure that we were not missing any critical areas. This list represents our collective decisions as to the MeSH terms to use for all searches.

Identification of Relevant Data Sources for Review

We used multi-faceted search strategies to include all the current valid research on the key questions. We searched standard electronic databases such as MEDLINE®, Cochrane Collaboration resources, and the Health Economic Evaluations Database (HEED) (Table 3). We conducted hand-searches of the reference lists of relevant articles to ensure that we did not miss any relevant studies. In addition, we consulted with the TEAG about any studies or trials that were under way but not yet published.

Literature Assessment

Using the inclusion/exclusion criteria (Table 1) and resulting search terms (Table 2), we identified a total of 744 abstracts for review; of these we retained 83 articles for all key questions.

For the clinical questions (Key Questions 1, 2 and 3), based on our initial search terms, we judged that 74 articles were possible inclusions, based upon full article review. The Scientific Directors independently evaluated each abstract for inclusion or exclusion, using the abstract review form (see Appendix B). When the Scientific Directors disagreed on an abstract, they reviewed it again together and came to a consensus. During the process of abstraction, we found that one article was a followup to a study not included by our search parameters. The original study was not classified under the MeSH term 'bronchiolitis'. In order to capture any RCTs on bronchiolitic children that we may have missed, we conducted a systematic search titles and abstracts in MEDLINE® of the term 'wheezing infants' and identified 81 studies. After reviewing the abstracts, we included 10 articles for full review. Upon full review of the articles, we retained 4 articles in which the recruitment was conducted specifically during winter months and had children presenting with viral symptoms including wheezing. This suggests that the majority of the subjects had a clinical diagnosis of bronchiolitis rather than asthma.

For the cost-effectiveness of prophylaxis (Key Question 4), we identified 82 unique articles that mention the economic analysis of prophylaxis for the prevention of bronchiolitis in infants.

Upon examination, we found that 21 article abstracts met our inclusion/exclusion criteria, and we obtained the full articles for review. We identified and ordered additional relevant articles based on a review of the reference lists from articles abstracted for any of the key questions. In all, we abstracted 41 articles for the cost-effectiveness questions.

In our review of the literature on prophylaxis and its costs for infants in the target populations, we identified published articles that describe two RCTs for RSVIG IV and one RCT for palivizumab; all met the inclusion criteria. We considered the possibility of pooling results from RCTs for RSVIG IV and palivizumab, but TEAG members discouraged this approach, citing that palivizumab exhibits higher efficacy, better safety, and ease of administration. TEAG members recommended that we consider only palivizumab in an evaluation of the cost-effectiveness of prophylaxis. However, because only one clinical trial has been conducted for palivizumab to date, data on outcomes for children in the intervention branch of the tree would necessarily be derived from this single study.[10]

Outcomes from the IMpact-RSV study are available for the following subpopulations of interest: (1) >32 weeks and = 35 weeks' gestational age and = 6 months at the time of randomization and (2) infants with a diagnosis of BPD and = 24 months upon randomization. The primary study outcome is rate of hospitalization. Although secondary endpoints included hospital length of stay, frequency and length of stay for intensive care unit (ICU), and mechanical ventilation, these results were not reported separately for the subpopulations of interest.

Our primary analysis focuses on the six articles that review the cost-effectiveness of palivizumab.

Data Collection

The data collection process involved abstracting relevant information from the eligible articles and generating summary evidence tables that present the key details and findings for the articles. A trained abstractor completed a detailed data abstraction form. The Study Director used the forms and the original articles to generate summary evidence tables. The Scientific Directors performed quality control assessments by reviewing each of the evidence tables against the original articles.

Abstractors and Trainers

The RTI-UNC EPC used both clinical and methods abstractors. All abstractors attended three training sessions. At the first session, we explained the process and goals of data abstraction, and then sent the abstractors home with an article to review. We then reconvened the group and, through a review of the test article, ensured that the abstractors understood what was expected of them. The reviewers abstracted an additional two test articles, reconvened, and reviewed their work. At this time the Scientific Directors determined that the abstractors were able to abstract the data as required, and we began the data abstraction process. The Research Coordinator monitored progress and routed the data abstractors' questions or issues to the Scientific Directors.

Data Abstraction Forms

For Key Questions 1, 2 and 3, the Study Director and the Scientific Directors created a single data abstraction form (Appendix C). This form was developed through multiple rounds of pretesting on different articles spanning the entire range of interventions to ensure that it would adequately capture all relevant issues. We solicited feedback from the data abstractors during training to refine further the data abstraction form.

For Key Question 4, we used a systematic approach to review and abstract economic data.[15] We first developed and used a standardized abstraction form to identify information from each article about the study design, analytic perspective used, cost components included in the analysis, and value of the economic summary measure (e.g., cost, cost-effectiveness ratio, or cost-utility ratio). This form is an adaptation of the Economic Evaluation Abstraction Form (version 3.0) developed and used to evaluate economic studies for the *Guide to Community Preventive Services*.[16]

We made adjustments to summary measures from the abstracted articles to facilitate comparisons across study findings. For example, to account for cost differences across studies attributable solely to price inflation, we used the medical care price index (MCPI) to adjust all estimated costs to constant 2001 dollars. The MCPI is a subset of the Consumer Price Index compiled by the Bureau of Labor Statistics; it includes medical care items such as prescription drugs and medical supplies, physicians' services, eyeglasses/eye care, and hospital services.

We also focused our comparisons on specific components of cost, such as treatment or hospital costs, rather than on total cost measures, because different studies may have included different resources in their total cost estimates. In some cases, we could not adjust study results because of differences in methods. For example, if costs were not presented separately for each component included in the study, we could not make adjustments to total cost estimates for comparability.

For articles that did not indicate the year for which costs were reported, we assumed that the costs were valued in constant dollars for the year prior to publication.

Development of Evidence Tables

After abstracting the included articles, we developed evidence tables to present the essential information to address Key Questions 2 and 3 relating to treatment and prophylaxis. These tables appear in at the end of this report and cover the following pieces of information:

- Setting of the intervention: country, patient setting;
- Followup: acute (48 hours after intervention), short-term (2-14 days after intervention) and long-term (14 days and more);
- Research design: randomized trials, including placebo-controlled, nonplacebo-controlled (both those comparing active treatment and control groups to nonplacebo), and crossover trials;
- Length of enrollment;
- Masking;
- Objective of the study;
- Inclusion/exclusion criteria;

- Number enrolled in and completed study;
- Sex;
- Mean age at enrollment and mean gestational age;
- Comorbidities;
- Interventions;
- Results and significance tests for primary and secondary outcomes and subgroup analysis;
- Adverse events;
- Quality; and
- Significant differences at baseline and other comments.

Given the wide range of reported outcomes, we assigned results in evidence tables as primary or secondary outcomes based on their clinical relevance to the key questions. In studies with multiple outcomes, we generally listed the more clinically important outcomes such as length of hospitalization or development of long-term sequellae as primary outcomes and the more physiologic measurements such as heart rate or respiratory rate as secondary outcomes. Applying this rule, however, depended on the nature of results presented in the study. When the authors presented pulmonary function tests as their primary outcomes and did not present data on length of hospitalization or development of long-term sequellae, the Scientific Directors may have chosen physiologic measurements as the more clinically relevant outcome from that study and placed them as the primary outcome for the purposes of the evidence table.

For primary outcomes, individual results for each study arm and *P* values were always recorded where possible. For secondary outcomes, *P* values were generally reported when results were positive.

Grading the Strength of Evidence

For Key Question 1 on diagnosis, we initially intended to assign quality scores to the diagnostic studies using standard criteria.[17] However, several factors prevented this. First, no articles specifically assessed diagnostic tests or criteria for bronchiolitis. The literature, the TEAG, and our study team all agreed that bronchiolitis is a clinical diagnosis for which no true or "gold standard" test exists.

Second, the majority of diagnostic information extracted for review came from the 61 treatment studies. As such, the data had not been collected for the purposes of assessing their diagnostic utility. In most studies, viral studies, clinical scores, complete blood counts (CBCs), and chest x-rays were all used as baseline independent variables.

We did use selection criteria that ensured a minimal study validity. We took diagnostic data only from the RCTs in which all patients were tested (i.e., rather than at the discretion of the investigators or treating physicians). Of the non-RCT articles identified that included diagnostic data, all were prospective cohort studies.

For Key Questions 2 and 3, the Scientific Directors developed a quality assessment form for RCTs of treatment or prophylaxis (Appendix D). In prior work for AHRQ, the RTI-UNC EPC had developed an exhaustively peer-reviewed evidence report on systems to rate the strength of scientific evidence.[18] We based our quality assessment tool on this work, with appropriate modifications for the literature on the management of bronchiolitis in infants and children. The

quality assessment tool comprised four individual elements: randomization; masking, statistical analysis, and funding/sponsorship.

We rated each element as excellent, adequate, inadequate, or unable to determine. In addition to these four elements, we considered the appropriateness of the population studied, the clarity and relevance of outcome used, and the appropriateness of the statistical analysis used. Based on the composite of the assigned scores and their individual comments on each study, the Scientific Directors assigned an overall quality score on a four point scale, ranging from 1 (poor) to 4 (excellent). The subjectivity involved in this method of scoring the quality of evidence was reduced by the independent assessment of each article by both Scientific Directors. When they did not agree, they reviewed the article together and arrived at a consensus. Of the 61 articles that were scored for quality for Key Questions 2 and 3, the Scientific Directors had a 98 percent rate of agreement within one point.

For Key Question 4 on the cost-effectiveness of prophylaxis, we adopted the *Guide to Community Preventive Services* convention for the Centers for Disease Control and Prevention (CDC) of not scoring economic studies on quality. As Carande-Kulis et al. explain, differences in economic methods may be attributable to differences in study objectives; even when differences result from variations in quality, they may not have a large impact on study findings.[15] Further, the number of economic studies available for review is quite limited, so we adopted the CDC approach of reviewing all available studies but adjusting results to account for differences in methods.

Analysis Strategy

In developing an approach for synthesizing the literature for the evidence on the management of bronchiolitis in infants and children, our review of the literature and conversations with the TEAG made apparent that each key question would require a different analysis strategy. These are briefly described below.

Key Question 1: Diagnosis

The TEAG agreed that we should retain this question because of its theoretical importance. TEAG members generally agreed that patients with bronchiolitis undergo many tests but that few influence clinical management or outcome; they do affect the costs of care. We identified 16 studies dealing with diagnosis. We also reviewed 61 clinical trials for additional data on diagnostic testing. The data available fell into several natural categories:

- Case definitions and inclusion criteria used in the clinical trials;
- Etiology of cases of bronchiolitis when all subjects were tested;
- Comparison of various virus isolation techniques;
- Predictors of disease severity or complications; and
- Studies in which standardized tests were performed on all patients as part of their evaluation (e.g., chest x-rays, complete blood counts).

Key Questions 2 and 3: Treatment and Prophylactic Therapy

Our assessment of the literature for Key Questions 2 and 3 suggested a range of interventions, with studies choosing to report a widely varying set of outcomes measured at different time intervals. Given the disparity in outcomes, we grouped studies by type of intervention rather than by outcomes for Chapter 3 (Results). This grouping resulted in 15 sets of interventions and evidence tables:

- Nebulized epinephrine versus nebulized saline placebo;
- Subcutaneous epinephrine versus saline placebo;
- Nebulized epinephrine versus nebulized bronchodilators (salbutamol or albuterol);
- Nebulized bronchodilators (salbutamol or albuterol) versus placebo or other treatments;
- Nebulized bronchodilators (salbutamol or albuterol) plus ipratropium bromide versus either nebulized salbutamol or nebulized albuterol alone and/or placebo;
- Oral corticosteroids versus placebo, with or without bronchodilators;
- Parenteral dexamethasone versus placebo;
- Nebulized corticosteroids versus placebo or usual care;
- Ribavirin versus placebo;
- Antibiotics versus no treatment or other antibiotics;
- RSVIG IV as treatment for bronchiolitis
- Other miscellaneous treatments for bronchiolitis;
- RSVIG IV versus placebo or standard care to prevent RSV bronchiolitis;
- Monoclonal antibody for prophylaxis of RSV bronchiolitis; and
- Vaccines to prevent RSV bronchiolitis.

Key Question 4: Cost-Effectiveness of Prophylactic Therapy

To determine whether we could assess the cost-effectiveness of prophylactic therapy using existing data, we used a decision analysis framework to describe the treatment options and the possible costs and outcomes that could result. Based on our initial findings from the literature and on input from the TEAG, we developed a decision tree to show treatment alternatives—administer prophylactic therapy versus no treatment intervention—and the possible outcomes associated with each alternative.

The resulting decision tree is shown in Figure 3. By convention, open squares represent decision nodes, circles represent chance nodes, and each line emanating from a chance node denotes an uncertain outcome associated with the preceding action. Solid black squares represent terminal nodes. This decision tree in Figure 3 depicts only one decision node—the decision to administer prophylactic therapy or not. The possible outcomes associated with either choice are identical—an infant may or may not develop bronchiolitis, may or may not need ambulatory care, may or may not require hospitalization, and so on—but the likelihood of experiencing each outcome and the associated costs may differ depending on whether this infant received prophylactic therapy. Although administering prophylactic therapy will have higher initial costs than not intervening, the potential cost savings associated with prophylaxis, perhaps

through reduced ambulatory care or hospitalization costs, could outweigh the initial cost of intervention.

As shown in Figure 3, an analysis of the cost-effectiveness of prophylactic therapy from the societal perspective would require an extensive amount of data on costs and outcome probabilities. For example, some of the information needed for a cost-effectiveness analysis includes the rates of bronchiolitis infection, ambulatory care for bronchiolitis, hospitalization, and admission to ICU — both for children who receive prophylactic therapy and for those who do not.

In Chapter 3 we summarize results from existing economic analyses of prophylactic therapy for the prevention of bronchiolitis. However, as we discuss in some detail in Chapter 5, the existing literature contains many gaps, and much of the data required for a cost-effectiveness analysis from the societal perspective are not available. Our discussion section in Chapter 4 summarizes these data gaps and offers recommendations about additional data needed to answer the question of whether prophylactic therapy is cost-effective when used in the target population.

Peer Review Process

We requested review of this report from several individual experts in the field and from relevant professional societies and public organizations. They are acknowledged at the beginning of this report. We revised the report in response to suggestions from these outside agents.