3. Results

We included a total of 83 articles in our analysis. Of these, 16 are primary articles on diagnosis of bronchiolitis, 52 pertain to the treatment of bronchiolitis, and nine are on prophylactic therapies. Finally, although we found several articles that are relevant to the cost-effectiveness of prophylaxis, our primary analysis is limited to six articles that reviewed cost-effectiveness for palivizumab. Our results are organized by key questions, with tables at the end of the chapter and Evidence Tables.

Key Question 1: Effectiveness of Diagnostic Tools for Diagnosing Bronchiolitis in Infants and Children

Our retrieval and review of abstracts based on the inclusion/exclusion criteria in Table 1 resulted in the final inclusion of 16 articles that addressed some aspects of Key Question 1. In addition, we examined the case definitions and inclusion criteria used in 61 clinical trials to see how bronchiolitis had been defined or diagnosed.

The studies reviewed that dealt with diagnosis, in the most general sense, fell into the following 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, complications, or both; and
- Studies in which standardized tests were performed on all patients as part of their evaluation (e.g., chest x-rays, complete blood counts).

The challenge with this literature is the fact that bronchiolitis is a clinical diagnosis based on a typical history and findings on physical examination. Specifically, it is a disease of infants and young children characterized by initial signs and symptoms of upper respiratory infection followed by cough, tachypnea, and wheezing. Additional signs can include fever, hypoxia, and retractions. No diagnostic test or "gold standard" confirms the disease. Various tests exist that are used to diagnosis the specific etiology of bronchiolitis.

The TEAG twice reviewed this issue. All TEAG members agreed that bronchiolitis is a clinical diagnosis. However, the TEAG advised U.S. to examine the effectiveness of numerous ancillary studies that are commonly performed on infants with bronchiolitis, such as chest x-rays and CBCs.

Case Definition and Inclusion Criteria

We reviewed the case definition and inclusion criteria from the clinical trials. Case definitions were quite similar: (a) 38 used tachypnea in either the case definition or inclusion criteria; (b) 39 used wheezing; (c) 30 used oxygen saturation; and (d) 28 used retractions.

However, many studies simply stated that infants with signs and symptoms consistent with bronchiolitis were cases eligible for inclusion. Many authors referred to the historical definition of bronchiolitis published by Court.[19]

Eligibility criteria in the clinical trials varied to a greater extent, especially with respect to variables such as age, duration of symptoms, comorbidities (e.g., prematurity, chronic lung disease), history of previous wheezing, and severity of disease. This variation was determined by the specific objectives of the studies (e.g., numerous studies included only infants who were positive for RSV disease).

Most trials measured disease severity both as a baseline independent variable and as a dependent outcome (i.e., change in disease severity resulting from treatment). Disease severity was most commonly measured using clinical scales (43 of the 52 treatment trials). The variety of scales used made comparisons between studies difficult. Appendix A describes the numerous clinical scales used.

Some studies used clinical scales that had been validated in previous studies such as the Respiratory Distress Assessment Instrument (RDAI).[20-23] Others were created or modified by authors for their particular trial.[24,25] Despite this variation, the clinical scales all incorporated measures of respiratory rate, respiratory effort, severity of wheezing, and oxygenation.

Identification of Etiology of Bronchiolitis

Many, but not all, of the included studies attempted to identify the etiology of the enrolled cases. As mentioned above, a subset of the treatment trials enrolled only infants who were RSV positive.

Of the 52 treatment studies, 42 performed RSV testing on all subjects. In the studies that tested all and included all regardless of RSV status, the range in the prevalence of cases caused by RSV was 26 percent to 95 percent. Twelve studies tested patients for other viral etiologies (e.g., parainfluenza viruses) in addition to RSV. It is recognized that RSV testing of patients with bronchiolitis is justified in several situations. First, isolation of RSV as the etiology of fever in an infant under 3 months may support a clinician's decision to forego additional testing in the traditional "rule out sepsis" work-up. Second, RSV testing may be helpful in clinical situations where the diagnosis of bronchiolitis is not clear. Third, RSV testing will be essential in research settings where RSV-specific therapies are being evaluated for effectiveness. Finally, RSV testing is an important tool to epidemiologists and public health officials responsible for surveillance of lower respiratory tract infections in infants. However, most reported results as percentage positive for RSV versus "other viruses."

Various techniques for identifying RSV as the causative agent of bronchiolitis were used, including viral cultures, rapid antigen detection tests (e.g., direct immunofluorescence assay [IFA], enzyme immuno-assays [EIA]), polymerase chain reaction (PCR), and measurements of acute and convalescent antibody titers. Rapid antigen detection tests for RSV were used most frequently. In many of these, viral cultures were performed on cases that were negative for RSV.

Comparison of Virologic Tests

Five studies examined the accuracy of various virologic tests for RSV and other causative viruses (Table 4).[26-30] Table 4 demonstrates (1) that numerous tests for RSV exist and (2) that their test characteristics vary. The *AAP Red Book* reports the overall sensitivity of the rapid antigen detection tests to be in the 80 percent to 90 percent range.[6] The data in Table 4 are consistent with this estimate. It is likely that individual test manufacturers have additional, unpublished data on their own assays, as they generally report test characteristics in the package insert materials that come with these test kits. Our search strategy would not have identified this unpublished data. In addition to looking at test agreement, Ahluwalia et al. compared two methods of specimen collection and demonstrated that viral culture, EIA, and IFA all yielded positive results more often when performed on nasopharyngeal aspirates than when performed on nasopharyngeal swabs.[26]

Of interest from both the clinical and utilization points of view is the question of whether RSV testing is necessary in all patients with bronchiolitis. Although such testing is commonly used to document the etiology of bronchiolitis, the etiology rarely changes clinical management. Many institutions require testing all infants being admitted to the hospital; the rational involves assisting with identifying cohorts (i.e., to decrease nosocomial RSV infections). However, no good quality RCTs examine the effects of cohort segregation in preventing nosocomial transmission of bronchiolitis.[31] As a result, many infection control policies recommend that all infants with acute lower respiratory infection (ALRI) be isolated, regardless of etiology. No study we reviewed addressed the issue of utility of RSV testing.

Predictors of Severe Disease or Complications

Several studies measured various predictors of disease severity; these are summarized in Table 5. Our search strategy did not specifically set out to capture all studies that examine disease severity. Shaw et al. directly use five types of clinically important data to predict clinically important outcomes denoted “mild” or “severe” disease.[32] The Mulholland study, focused on oximetry and arterial blood gases, is useful as well, although most clinicians check arterial blood gases only on patients who appear to be in respiratory failure.[33]

In contrast, Cherian et al. focused on determining the reliability of easily observed physical findings in diagnosing ALRI in developing countries, as used in current World Health Organization (WHO) algorithms.[34] The Saijo et al. study focused on using laboratory studies to predict three categories of RSV disease defined radiographically rather than clinically.[35] As such, these findings have limited usefulness to clinicians.

Most textbooks cite young age, history of prematurity or other comorbidities, toxic appearance at presentation, and rapid progression of symptoms as risk factors for severe disease. Two studies support these assertions.[32,33] Additional prospective studies of disease severity or clinical prediction models are lacking.

Utility of Chest Radiographs in Bronchiolitis

In 14 studies of bronchiolitis investigators performed chest x-rays on all patients (Table 6).[24,25,32,36-45] Large numbers of infants with bronchiolitis have abnormalities on chest x-rays. However, data are insufficient to demonstrate that these chest x-rays correlate well with disease severity.

Two studies set out to examine the relationship between x-ray abnormalities and disease severity. Shaw et al.'s data show that the patients with atelectasis were 2.7 times more likely (95% CI: 1.97-3.70) to have severe disease than those without this x-ray finding.[32] This association persisted when it was included in a multivariable analysis. In contrast, Dawson's data demonstrated no correlation between chest x-ray findings and baseline disease severity as measured by a clinical severity scoring system.[36]

The Roosevelt et al. study showed that the presence of chest x-rays abnormalities was strongly correlated with the use of antibiotics.[43] The effectiveness of antibiotic treatment in these patients was not examined. The fact that bronchiolitis is usually a viral illness calls in to question this course of disease management.

These data suggest that in mild disease, chest x-rays offer no information that is likely to affect treatment and that, therefore, they should not be routinely performed. In fact, the Roosevelt et al. data suggest that such x-rays may lead to inappropriate use of antibiotics, although this was not the focus of their study.[43] Chest x-rays may be useful in predicting which patients are likely to have more severe disease in cases in which this assessment is not otherwise clear.

Utility of Complete Blood Counts in Bronchiolitis

The research teams in 10 studies did CBCs on all patients (Table 7).[24,35,42,45-51] Although investigators in many of the clinical trials included CBCs, results were often not reported or were used only to demonstrate that the treatment and control groups were similar at baseline. Only the Saijo et al. study attempted to correlate white blood counts with category of lung disease defined radiographically (i.e., lobar pneumonia vs. bronchopneumonia vs. bronchiolitis).[35] None of these studies demonstrated that CBCs were useful in either diagnosing bronchiolitis or guiding therapy.

Key Question 2: Efficacy and Effectiveness of Pharmaceutical Therapies for Treatment of Bronchiolitis

Overall, we found 52 studies meeting our inclusion criteria that dealt with treatment of bronchiolitis in infants and young children. Treatments studied included nebulized epinephrine, nebulized bronchodilators, nebulized ipratropium bromide, oral inhaled or parenteral corticosteroids, aerosolized ribavirin, oral antibiotics, and a variety of other treatments. These interventions were studied against either placebo or each other. These studies are summarized in

Evidence Tables 1 through 12 at the end of this report. Key features of selected studies are presented below.

In addition, we reviewed nine articles on prophylactic interventions for bronchiolitis among high-risk infants and children. These studies are summarized in Evidence Tables 13, 14 and 15 and are discussed at the end of this section.

Nebulized Epinephrine versus Nebulized Saline Placebo

Detailed Results

We found one small double-blind, placebo-controlled RCT of nebulized racemic adrenaline for bronchiolitis in infants and toddlers without comorbidities, presented in Evidence Table 1.[52] The dose of racemic adrenaline varied by weight of the subject and ranged from 2.0 mg for infants under 5 kg to 5.0 mg for those greater than 10 kg. This was a small trial (29 children completing the study). The primary outcomes were mean symptom score and mean change in oxygen saturation recorded at 15-minute intervals after treatment for 1 hour. Immediately post-treatment, the adrenaline group improved significantly in mean change in oxygen saturation. Clinical scores were significantly improved in the adrenaline group at all time intervals. Outcomes were tracked out to only 1 hour after treatment.

The group randomized to racemic adrenaline had significantly lower baseline oxygen saturation. A subgroup analysis indicated that, compared with less severely affected infants, more severely affected infants (those with baseline oxygen saturation levels of <93 percent) had significantly elevated oxygen saturation in the hour post-treatment. This raises some concern that baseline maldistribution of subjects could, in part, account for the positive finding of improved oxygen saturation in the adrenaline group. However, the concurrent findings of improved overall clinical scores may argue for a true positive effect of the treatment.

Conclusions

The Kristjansson et al. study is one of the few to demonstrate a statistically significant outcome, i.e., increased oxygen saturation, after the administration of nebulized epinephrine and improvement in clinical scores.[52] However, outcomes were evaluated for only the first hour after treatment and may not translate into longer term benefits. Moreover, this study is too small to make conclusions regarding the efficacy of nebulized epinephrine as a treatment for bronchiolitis, particularly for longer term outcomes and outcomes that are more clinically relevant such as length of hospitalization.

Finally, definitive evidence about the effects of nebulized epinephrine should be subjected to investigation using an appropriately designed and sized RCT. A primary outcome should be meaningful to parents and clinicians, such as the need for hospitalization after emergency room treatment or the development of persistent wheezing. Secondary outcomes might include a standardized respiratory symptom score or total costs of the episode of care.

Subcutaneous Epinephrine versus Saline Placebo

Detailed Results

We located one study that employed subcutaneous epinephrine for the treatment of wheezing in infants under 24 months of age presented in Evidence Table 2. Infants with previous bronchodilator therapy were excluded in an attempt to limit the population to non-asthmatic infants. However, 47% of the epinephrine group and 43% of the placebo group had a prior history of wheezing, but had never been on bronchodilators. Thirty infants were randomized to either two does of 0.1mg/kg of subcutaneous epinephrine administered 15 minutes apart versus subcutaneous saline placebo. The primary outcomes studied were absolute change in the RACS clinical score and a four or more point improvement in the RACS score. Both primary outcomes significantly favored the subcutaneous epinephrine group. Fifty-six percent of the epinephrine group had four or greater point improvement on the RACS compared with 7% of the placebo group. Ten children had laboratory proven RSV infections and seven of these 10 responded to epinephrine with a four or more point improvement on the RACS scale. However, the paper is not clear about whether RSV testing was done in the placebo group. There were no significant differences noted when subgroup analysis of the infants by 6 month age groups was done. Adverse events were not reported by the authors.

Conclusions

This is the only study we located on the use of subcutaneous use of epinephrine to treat acutely wheezing infants. Prior to the availability of newer treatments subcutaneous epinephrine was a standard treatment for asthma in children. Although the results of this study certainly favor the epinephrine group, it is small and important outcomes such as need for hospitalization or length of hospitalization are not reported. We also had concerns that the patients in this study represented a mixed population. This was one of the four papers identified using the search terms for “wheezing infant.” A substantial proportion of the population had a prior history of wheezing despite the fact that none had been on bronchodilators and over 70% had a family history of atopy. A subsequent bout of wheezing, even in the context of a virally mediated illness, may indicate that these children have a reactive airway disease that may respond better to agents like epinephrine than would children without such a disease component. The heterogeneous population in this small study raises concerns about generalizing from this study and we do not believe that this single study provides any evidence of effectiveness for this intervention. If investigators are interested in studying this drug as a treatment modality for bronchiolitis then a carefully designed trial would be needed.

Nebulized Epinephrine versus Nebulized Bronchodilators (Salbutamol or Albuterol)

Detailed Results

Evidence Table 3 presents a group of four studies that compared nebulized epinephrine to nebulized salbutamol (three studies) or albuterol (one study).[22,53-55] All four studies were double blinded. Three of the four studies were conducted in children ages 4 years or younger;[22,53,55] one study admitted those under 2 years of age.[54] None of the studies included children with serious comorbidities, but one study did include a small percentage of children who had had previous episodes of wheezing.[54] The studies were small, ranging from 33 to 100 subjects (the latter divided among four study arms). The doses of epinephrine and bronchodilators were not uniform and were not always dosed on a per-kilogram (kg) basis. Epinephrine doses varied from 0.5 mg to 3 mg as standing doses and 0.1 mg/kg to 0.9 mg/kg by weight. Salbutamol and albuterol doses ranged from 1.5 mg to 2.5 mg standing doses and 0.15 mg/kg to 0.30 mg/kg on a weight basis. Primary outcomes included duration of hospitalization, changes in various clinical scores, respiratory rates, heart rates, need for oxygen therapy, and oxygen saturation.

Virtually no outcome measure differed significantly between study groups. The Menon et al. study was a notable exception; at 60 minutes post-treatment, oxygen saturation was statistically significantly higher in the epinephrine group than in the salbutamol group.[22] This team also found statistically significant differences in several secondary outcomes including fewer infants requiring hospitalization in the epinephrine group (33 percent vs. 81 percent in the salbutamol group). Children in this study were defined as admitted to hospital if they were formally admitted or if they received care in the emergency department for more than 6 hours. No post-epinephrine symptom rebound was reported

In terms of adverse events, the Bertrand et al. study found statistically significantly increased heart rates in the epinephrine group compared to the salbutamol group on the second day.[53] Another study found a higher incidence of pallor in the epinephrine group at 30 and 60 minutes post-treatment; however, the 90-minute post-treatment heart rate in the epinephrine group was actually lower than in the salbutamol group.[22]

Of note, the Sanchez et al. study in Canada in the early 1990s sedated infants with chloral hydrate before administration of each drug in a cross-over design trial; the aim was to facilitate gathering clinical measurements, including pulmonary mechanical parameters.[55] The sedation may not only have influenced the physiologic measures for the infants but also masked any adverse effects. Whether this type of trial (requiring sedating infants) would be approved today is open to question.

Conclusions

Overall, these studies were likely too small to detect a clinically meaningful difference in their primary outcomes. The primary outcomes in these studies were, for the most part, not of substantial relevance to parents or clinicians. None of these studies, with the exceptions noted in the Menon et al. study,[22] demonstrated important differences among the outcomes that were examined. We did not conduct a formal meta-analysis of these four small studies because of the lack of uniformity in both the drug doses and outcomes studied. Finally, the results of the

Menon et al. study[22] combined with the findings of the Kristjansson et al. study[52] (Evidence Table 1) may argue for further investigation of nebulized epinephrine as a treatment for bronchiolitis.

Nebulized Bronchodilators (Salbutamol or Albuterol) versus Oral Bronchodilators, Nebulized Ipratropium Bromide, or Saline Placebo or No Treatment

Detailed Results

Evidence Table 4 shows the 11 studies comparing nebulized bronchodilators to placebo (e.g., nebulized saline), no treatment, or another intervention that met our inclusion criteria.[21,24,37,44,56-62] As to the last, the active arms in Goh et al.'s study compared nebulized salbutamol to nebulized ipratropium bromide.[61] The studies were of moderate size for this literature; the largest had 158 participants.[24] Nearly all the studies included children up to 24 months of age; three included infants of up to 6,[62] 15,[59] and 18 months[60] of age.

Five of the 11 studies compared more than two treatment groups against each other.[24,58-61] The doses of drugs varied substantially. For example, the lowest dose of salbutamol employed was 0.1 mg/kg and the highest standing dose was 2.5 mg/dose, which would be appropriate for only a 25-kg (55-lb.) child. Although the primary route of delivery was via nebulizer, Cengizlier et al. studied the use of salbutamol administered with a metered dose inhaler (MDI) to the oral preparation,[58] and and Hickey et al. examined the use of albuterol via an MDI compared to placebo.[57] Gadomski et al. compared nebulized albuterol to oral albuterol to placebo groups for each of the active arms of the study.[59] The primary outcomes studied included hospitalization, respiratory rate, heart rates, oxygen saturation, and various clinical scores. Virtually all the outcomes studied were short-term surrogate measures. All statistically significant outcomes occurred within the first hour after treatment was given.

Can and colleagues compared nebulized salbutamol to nebulized saline to mist in a tent.[24] They found that the Respiratory Distress Score (RDS) was significantly better for the salbutamol group against both other arms at both 30 and 60 minutes post treatment. The Klassen et al. study of nebulized salbutamol versus saline placebo found that the Respiratory Distress Assessment Instrument (RDAI) score was significantly better in the salbutamol group at 30 minutes post treatment.[21] There was a trend toward improved RDAI scores at 60 minutes as well ($P = 0.12$). Schweich and colleagues found that there was a significant improvement in the mean clinical score in the nebulized albuterol group compared with the saline placebo group at one hour after the start of the intervention.[56] Infants in this study received two doses of nebulized albuterol 30 minutes apart. There was a trend toward improved RDAI scores at 60 minutes as well ($P = 0.12$). The only other significant difference among primary outcomes was found in Gadomski et al.'s US-based study comparing nebulized albuterol to saline placebo to oral albuterol to oral placebo; the heart rates of infants who had been randomly assigned to the oral albuterol group were higher at 60 minutes after treatment was begun.[59]

Cengizlier et al. found that both the oral and inhaled salbutamol groups had improved clinical scores compared to the baseline at admission, but both groups' scores were virtually identical to those for the control group who received no bronchodilator therapy.[58] However, the time frame

for obtaining these clinical scores in this hospitalized population is not clear. Bronchiolitis is largely a self-limited illness; if sufficient time in hospital had passed, the groups might well have had similar scores at discharge as an alternate explanation to the no-treatment-effect explanation. This was also a small study (31 patients randomized into three groups).

Dobson et al. reported that all three patients withdrawn from the study by their physicians for worsening hypoxia and respiratory distress were in the albuterol group.[37] This finding was of borderline statistical significance ($P = 0.10$) and raises concern that repetitive doses of albuterol may be of harm to some infants. Ho and colleagues also noted that nearly all infants given salbutamol experienced oxygen desaturation from baseline values.[62]

The study by Klassen and colleagues (described above) was one of the better studies in our review of this literature.[21] The report is clearly written and the methods are transparent. It is one of the few studies to include a sample size calculation in the paper.

Conclusions

Like the studies in Evidence Table 1, the studies in this group are largely underpowered to detect meaningful differences among study groups. The Schweich and Hickey studies both included infants with wheezing who may have had asthma given that a substantial proportion of the enrollees had a prior history of wheezing in both studies.[56,57] The Schweich study even defined bronchiolitis as "wheezing in infants." In addition, the differences in agents, doses, delivery systems, settings and outcomes chosen limit comparisons and may make meta-analytic pooling of results from these nine studies of dubious validity.

The Can et al. and Klassen et al. research teams both demonstrated short-term benefit in clinical scores in the 30- to 60-minute time frame after treatment. However, these studies do not provide evidence to suggest that these interventions are effective in improving longer-term and more clinically relevant outcomes.[21,24] If future investigators are interested in refining studies of bronchodilators, then they should select appropriate long-term outcomes such as need for and duration of hospitalization and strive to reach some consensus on specific drugs and doses to be studied. Moreover, ensuring that future investigations of these agents have adequate power (sample sizes) is especially critical.

Not all studies reported adverse effects of treatment. However, several studies did report events that would warrant observation in any future investigations. Gadomski et al.[59] found elevated heart rates among children who received oral albuterol; both the Klassen et al. and Schuh et al. studies demonstrated significantly higher heart rates among those randomized to nebulized salbutamol and albuterol, respectively.[21,44] Ho et al. found that the majority of children who received salbutamol had oxygen desaturation compared with their baseline measurements, although mean maximum falls in oxygen saturation were not significantly different.[62] Schweich found "a small decrease" (magnitude not specified and statistical comparison not provided) in oxygen saturation after the first of two nebulized albuterol treatments that resolved after the second treatment.[56]

Nebulized Salbutamol or Albuterol plus Nebulized Ipratropium Bromide versus Bronchodilators or Ipratropium Bromide Alone and/or Saline Placebo

Three studies that compared nebulized bronchodilators in combination with ipratropium bromide to other treatments met our inclusion criteria (Evidence Table 5).[63-65] Two of these studies randomized patients into four groups: salbutamol plus ipratropium bromide, each agent individually, and a placebo group. Salbutamol doses were identical at 0.15 mg/kg in all three; the Chowdhury et al. study used a standing dose of ipratropium bromide for all infants,[63] and the Wang et al. study used a choice of two dose levels depending on age.[65] The third study in this group compared albuterol plus ipratropium bromide to albuterol plus a saline placebo.[64]

These studies included between 62 and 102 participants, but two studies divided subjects among four groups, resulting in small group sizes.[63,65] Chowdhury et al.'s study excluded significant numbers of children after randomization (13 of 102) primarily for subsequent findings of lung consolidation. All three studies included children up to 2 years of age.

Primary outcomes included duration of hospitalization, respiratory rate, and clinical score. Primary outcomes did not differ significantly for any of the treatment groups. Wang et al. demonstrated a statistically significant improvement in the mean change in oxygen saturation. A secondary outcome, considering salbutamol plus ipratropium bromide versus salbutamol alone and ipratropium bromide alone, showed no difference when compared to the placebo group.[65] Schuh et al. did not report any benefit of nebulized ipratropium bromide in addition to nebulized albuterol for vital signs, oxygen saturation, or clinical scores.[64]

Chowdhury et al. did not report any adverse events;[63] Wang et al. noted that one infant in the salbutamol group was withdrawn for tremulousness.[65] As expected with use of these agents, Schuh et al. found a heart rate increase with use of albuterol.[64]

Conclusions

This group of studies suffered from lack of sufficient power to demonstrate meaningful differences in outcomes. The differences seen in oxygen saturation in the Wang et al. study may warrant further investigation of salbutamol plus ipratropium bromide and ipratropium bromide alone.[65] However, the largest arm of the Wang et al. study included only 17 children, so clinically meaningful differences would not likely be able to be detected. There was also a trend toward decreased length of hospitalization in the treatment groups that included ipratropium bromide. Including clinically relevant outcomes such as the need for and duration of hospitalization and duration of symptoms, in future research is a reasonable lesson to draw from these studies.

Oral Corticosteriods versus Placebo, With or Without Bronchodilators

The five studies in Evidence Table 6 met our inclusion criteria.[66] We found two articles on one study; the second reported 5-year outcomes.[23,67-69]

All studies compared oral corticosteroids (i.e., prednisolone, prednisone, or dexamethasone) to placebo. Except for Van Woensel et al., all employed bronchodilators as a cointervention in

all arms of the study.[23,66,69,70] Val Woensel et al. allowed the use of bronchodilators as needed and reported no difference in use between study groups.[67,68] The studies by Goebel et al., Berger et al. and Schuh et al. used albuterol (Berger et al. allowed the use of either oral or nebulized albuterol); the Klassen et al. study used salbutamol as the bronchodilator of choice. The studies were small (51 and 72 subjects). Most of the studies enrolled children up to 2 years of age, although Berger et al. admitted infants up to 18 months and Klassen et al. included infants up to 15 months of age. Van Woensel et al. admitted infants with severe disease and comorbidities, including those on ventilators and with BPD. All studies used some type of symptom score as an outcome. Other primary outcomes included hospitalization, readmission, persistent symptoms, and need for other treatments. Adverse events, largely unreported, were limited to the expected side effects of bronchodilator use.

These research teams found few differences between study groups overall. Goebel et al. reported a statistically significant difference in clinical scores between days 0 and 2; the group that received both prednisolone and albuterol improved more than the placebo and albuterol groups.[66] Berger et al. demonstrated no difference in clinical scores, respiratory rate, or oxygen saturation between the prednisone and placebo groups.[70] They also were able to contact approximately three-quarters of the parents at 2 years after the initial study; for this group, they determined that infants who had received oral prednisone experienced more respiratory symptoms (35.7 percent in the prednisone group versus 28.6 percent in the control group, *P*-value not reported). Overall, about one-third of the followup population had persistent respiratory symptoms at 2 years. Schuh et al. found significantly lower rates of hospitalization (19 percent vs 44 percent), improved clinical scores at 240 minutes post-treatment, and less need for corticosteriods after discharge in the dexamethasone plus nebulized albuterol group compared with the placebo plus albuterol group.[23]

The initial Van Woensel et al. study found a significantly greater mean decline in symptom score among the 39 nonventilated patients and a shorter duration of hospitalization among the 14 ventilated patients.[68] Five-year followup did not demonstrate any significant differences in long-term outcomes such as wheezing in the first year of life or persistent or late-onset wheezing.[67]

Conclusions

As noted for other clinical issues, these studies were likely underpowered to detect many outcomes. Primary outcomes included many surrogate outcomes such as clinical scores, but this group of studies also measured several outcomes of interest to parents and clinicians such as hospitalization and development of asthma. Differences in agents, doses, duration of treatment, and outcomes measured limit comparison and pooling of results in this group of studies. The majority of these studies did not report adverse events; no outcomes specific to the side effects of corticosteroids were reported.

Three studies measured hospitalization or hospital duration as a primary outcome.[23,66,68] Only Schuh et al. found a statistically significant difference between groups.[23] Two studies, those by Berger et al. and Van Woensel et al., examined longer-term respiratory symptoms; both found that the group assigned to oral corticosteroids had increased symptoms on followup.[67,68,70] Two other studies, Schuh et al. and Klassen et al., used dexamethasone, although the Schuh et al. team used a substantially higher dose.[23,69] Because Schuh et al. was the only one to demonstrate a difference in hospitalization of nonventilated patients, a future study may want to compare dexamethasone to placebo and higher versus lower doses of dexamethasone. Finally, several other significant differences appeared between treatment groups. Although many of these

outcomes were of less clinical significance than measures such as hospitalization, the results of this group of studies warrant at least one adequately powered study with clinically relevant outcomes to determine whether corticosteroids are a helpful adjunct to or a primary treatment for bronchiolitis.

Parenteral Dexamethasone versus Placebo

Detailed Results

Two studies in Evidence Table 7 employed parenteral dexamethasone to treat patients with bronchiolitis.[43,48] Roosevelt et al. used 1 mg/kg of dexamethasone administered intramuscularly (IM) each day for 3 days in 122 hospitalized infants under 1 year of age.[43] De Boeck et al. studied 32 hospitalized children younger than 24 months of age.[48] The active treatment group was given a loading dose of 1.2 mg/kg of dexamethasone administered IV with the dose divided and given twice per day on day one. Infants were given "0.015 mg/kg on days 2 and 3", but it is unclear whether this dose was given every day or twice per day. If it is a total dose, then clinically it appears low for maintenance therapy, we would then question whether there might be a typographical error in the article. Children in this study by DeBoeck and colleagues also received salbutamol plus ipratropium bromide aerosolized every 6 hours while hospitalized.

Primary outcomes measured were duration of oxygen therapy and time to normalization of clinical score for the Roosevelt et al. study and duration of hospitalization for the DeBoeck et al. study. Neither study demonstrated significant differences between study groups for either these primary outcomes or their particular secondary outcomes. However, the Roosevelt et al. study may have had an allocation imbalance; significantly more infants with low oxygen saturation had been allocated to the dexamethasone group.

The Roosevelt group reported two episodes of occult stool blood in the dexamethasone group and one in the placebo group. The DeBoeck et al. team did not report adverse events. Neither study examined longer term outcomes such as persistent or recurrent wheezing.

Conclusions

We found no evidence that parenteral corticosteroids represent an effective treatment for bronchiolitis. Although neither of these studies reported sample size calculations, together they included a total of 154 subjects. This is likely a large enough group to safely conclude that the negative results of these studies cannot be attributed simply to low power. Both studies were conducted among hospitalized patients, although only the DeBoeck et al. study measured duration of hospitalization as an outcome (finding no significant differences). Baseline oxygen saturation imbalance in the Roosevelt et al. study may have created a situation in which detecting a significant difference in the primary outcomes would have been impossible. Finally, given that oral corticosteroids achieve blood levels equivalent to those for parenteral dosing, we advise that subsequent studies of corticosteroids for bronchiolitis concentrate on oral preparations.

Nebulized Corticosteroids versus Placebo or Usual Care

Detailed Results

We included seven studies of inhaled corticosteroid (Evidence Table 8).[71-77] Six of the studies used budesonide;[71-76] while Wong et al. used fluticasone.[77] Fox et al. and Wong et al. used a metered dose inhaler (MDI) for medication administration; the remaining studies employed nebulized budesonide.[73,77] Four studies compared inhaled corticosteroids to placebo;[71,73,73,75,76,76,77,77] one used a usual-treatment control group. Usual treatment in this case could include bronchodilators, oxygen, and/or racemic epinephrine. Reijonen et al. compared inhaled budesonide to usual treatment and included a group randomized to inhaled cromolyn sodium in a 3-arm study. Daugbjerg and colleagues compared combinations of nebulized budesonide, nebulized terbutaline, oral prednisolone, and placebo controls in a four arm study.

For the most part, this set of studies enrolled a population younger than those described in earlier evidence tables. Of these six studies, four enrolled infants up to a year of age; the Kajosaari et al. study enrolled children up to 9 months of age and the Reijonen et al. study accepted children up through 23 months of age. These studies measured a diverse range of primary outcomes, including duration of hospitalization, rehospitalization, oxygen requirement, clinical scores, need for other treatments, withdrawal from study because of clinical deterioration and asthma symptoms at time periods up to 2 years after treatment.

Fox et al. found a statistically significant increase in symptoms scores and the median number of symptomatic episodes at 12 months in the group treated with budesonide for 8 weeks after the acute episode of bronchiolitis compared to the placebo group.[73] A subgroup analysis was performed to control for differences by sex among the followup group at 12 months. Although the trial entry groups did not differ significantly by sex, more males had persistent symptoms and had been enrolled in the budesonide group. The authors concluded that there were no differences after controlling for sex, but the *P*-value on this analysis was 0.051, raising concerns that budesonide might unexpectedly have contributed to the increased symptoms in the group that received it. This study violated principles of an intention-to-treat analysis, 11 of 60 subjects were excluded from the final analysis because of loss to followup, partial followup, or noncompliance with treatment. This loss of nearly 20 percent of the original group may have contributed to these findings.

In the Kajosaari et al. study, one budesonide arm received 0.5 mg three times a day for 7 days and the other arm received 0.5 mg twice a day for 2 months. Both arms were compared to infants receiving symptomatic treatment alone. Fewer budesonide infants required asthma inhalation therapy at 2 years after study entry.[74] The Reijonen et al. study found statistically significant decreases in the number of infants who had greater than or equal to one episode of wheezing at the 9 to 16 week followup interval for both the cromolyn sodium and the budesonide groups compared with a group that received no treatment.[75] They also found fewer infants who had at least two episodes of wheezing at the 1-16 week follow up period, but in the budesonide group alone compared with both the cromolyn sodium and no treatment groups. In the Richter et al. work, of 21 infants who received budesonide, 10 were readmitted for respiratory problems. By contrast, of the 19 infants who received placebo, two were readmitted. This group reported no other significant differences in any other outcomes.[76]

Daugbjerg et al. studied 114 children from 6 weeks to 18 months of age who had acute wheezing.[72] This study made no attempt to distinguish between bronchiolitis and asthma and infants with recurrent wheezing were admitted to the study. Infants were randomized into four groups. Group A received a three day oral prednisolone course, nebulized terbutaline every four hours for up to five days and a second nebulized placebo. Group B received the nebulized terbutaline along with nebulized budesonide every four hours for up to five days, and an oral placebo for three days. Group C was given nebulized terbutaline with a placebo nebulized agent and an oral placebo while Group D received all three agents as placebo. All groups who received active treatment versus placebo showed significant improvement as measured by fewer withdrawals for treatment failure, but differences between active treatment groups were not found. There were statistically significant differences between the groups for mean days of hospitalization with Groups A and B having the shortest duration of hospitalization. No adverse events were observed.

Although most of the outcomes measured by this series of studies were intermediate in nature, several significant differences were found. That worsened outcomes in the budesonide group occurred in two of the six studies is of concern, but these differences may be simply a matter of chance.

Wong et al. found no significant differences in audio-recorded episodes of night cough or lung function tests except for a small but statistically significant decrease in these measures at the 36-week followup period in the fluticasone group.[77] Symptom scores were low in both the fluticasone and the placebo groups and showed no statistical differences after correction for multiple comparisons. Two infants on fluticasone developed oral candidiasis.

Of interest, all these studies examined longer-term respiratory symptoms such as persistent wheezing, at 4 to 24 months after study entry. Only the Fox et al. and Kajosaari et al. studies demonstrated improvements in these outcomes in the more clinically relevant followup period of 12 to 24 months.[73,74] Duration of inhaled corticosteroid use was relatively brief in all these studies; both the Fox et al. and Kajosaari et al. studies continued corticosteroids for 8 weeks; only the Wong et al. continued treatment for a longer time (3 months).

Conclusions

Six of these seven studies of inhaled corticosteroids employed budesonide, but at total initial daily doses that ranged from 0.4 mg to 2 mg per day. Duration of treatment with budesonide ranged from 1 to 8 weeks. The variety of dosing regimens and the wide array of outcomes makes comparison across these studies problematic.

Although the number of outcome events in these studies are small, three studies demonstrated longer-term symptom improvement such as fewer episodes of wheezing and less need for asthma therapy. An adequately powered definitive study of inhaled budesonide is needed to determine whether inhaled budesonide is an effective treatment for bronchiolitis or results in improved long-term outcomes such as less development of persistent wheezing and cough. It appears from this review that studies that continued inhaled corticosteroids for longer periods of time after the episode of bronchiolitis (e.g., 8 weeks) were more likely to show this effect. Studies examining the effectiveness of both the dose and duration of inhaled corticosteroid therapy are needed.

Two of the five studies using inhaled budesonide for 6 and 8 weeks after an episode of bronchiolitis compared to placebo found worse outcomes in the budesonide group.[73,76] These adverse outcomes warrant clinical caution in use of inhaled budesonide for bronchiolitis at this

time; a trial with adequate power to detect adverse events will help to clarify these issues in the future.

Ribavirin versus Placebo

Detailed Results

Ribavirin is an antiviral medication that is administered as a continuous aerosol for a number of hours per day. It has been studied as a specific treatment for bronchiolitis caused by respiratory syncytial virus. We located seven articles that met our inclusion criteria (Evidence Table 9).[42,45,46,78-81] Details of the randomization protocol in the Barry study were confusing, although the abstract of the article did state that it was a "randomized double blind placebo controlled trial" (p. 593).[46] However, the article states (p. 593) that "Infants were allocated to active treatment or placebo by a process of minimization of the differences in the pretreatment distribution of age, arterialised capillary carbon dioxide tension, respiratory rate and interval since onset of chest symptoms, and in the incidence of a random factor". In addition, the abstract of the Taber et al. study calls it a "double-blind study," and the paper states (p. 613) that "assignment to treatment or control groups was prepared from a table of random numbers".[45]

As a group these were small studies; the largest enrolled 42 patients.[79] Most of the enrolled infants were younger than 6 months of age; only one study enrolled infants with serious comorbidities. All six studies compared aerosolised ribavirin to saline placebo. Three of the studies used a 20 mg/ml concentration of ribavirin administered 18 hours per day.[46,79,80] Primary outcomes assessed included various symptoms, clinical scores, duration of hospitalization or ventilation, time to clinical improvement, respiratory rate, pulmonary function tests, need for other treatments, readmission to hospital, and development of persistent symptoms such as wheezing.

Barry et al. found that the mean time to sustained improvement in both cough and crepitations was significantly better in the ribavirin group.[46] However, they detected no significant differences in nasal discharge or flaring, feeding, wheezing, rhonchi, and chest retractions. They also reported significant differences in changes in respiratory rate at 24 and 30 hours after enrollment. Heart rate tended to fall more rapidly in the ribavirin group, but the decrease was not significantly different in the treatment compared to the control group at any point during treatment.

Rodriguez and colleagues conducted two studies.[42,81] The initial study involved 30 children randomized in a 2 to 1 ratio to ribavirin or distilled water.[42] The rate of change in the symptom severity score was significantly higher in the ribavirin group at days 2 and 3 compared with day zero. However, the symptom scores in the ribavirin group were nonsignificantly greater at day zero as well. The second concerned longer-term followup of the infants who had been enrolled in their 1987 study and information on an additional 10 infants who had been enrolled in the later study.[81] They state that the same study protocol was used. Over these two seasons 42 patients were randomized (25 to ribavirin and 17 to placebo) and 35 (24 from the ribavirin group and 11 from the placebo group) participated in the followup study. Followup data were collected for up to 6 years of age. Fewer children (four of 24 in the ribavirin group versus six of 11 in the placebo group) had two or more episodes of wheezing at ages 1 to 6 years. Of the 35 patients enrolled in the followup study, 19 completed pulmonary function testing. Significantly more

children in the placebo group had moderate to severe scores (6 of 13 versus 6 of 6, $P = 0.04$). However, the followup participation rate for the ribavirin group was higher (96 percent vs. 65 percent, $P < 0.02$) than in the placebo group. Children with more severe disease might be more likely to followup in both groups; that is, the differentially higher losses to followup in the placebo group raises concern that the less affected individuals did not participate in the followup study.

In the Taber et al. trial, the mean symptom score was lower on day 3 in the ribavirin group than in the placebo group ($P = 0.044$).[45] However, they reported no significant differences in mean symptom scores on Days 1 and 2. Infants in the control group were more likely to experience a four-fold rise in RSV-neutralizing antibody than were infants in the ribavirin group ($P = 0.045$), but no other significant differences occurred in more clinically relevant secondary outcomes such as length of treatment or time to discharge.

Three articles reported adverse events.[46,78,79] These included one episode of transient eyelid erythema thought secondary to ribavirin exposure and one episode of acute respiratory distress leading to discontinuation of ribavirin.

Conclusions

The studies of ribavirin are all very small and likely underpowered to detect significant differences in outcomes. Studies did not account for multiple comparisons in design. Most reported a myriad of outcomes, and most of these were intermediate or surrogate in nature. No significant differences in clinical meaningful outcomes were found in this set of studies. A previously published meta-analysis of ribavirin studies supports this conclusion.[20]

Antibiotics versus No Treatment or Other Antibiotics

Detailed Results

Although our literature search did not locate any primary studies of the effect of antibiotics for treatment of bronchiolitis, we did find two RCTs evaluating the effectiveness of antibiotics for lower respiratory infection in which subsets of enrolled patients had bronchiolitis.[49,82] Evidence Table 10 summarizes the bronchiolitis subgroup analyses of these studies.

Friis et al. studied 61 children with an average age at enrollment of approximately one and a half years who were RSV positive.[49] The active treatment group received oral ampicillin if under 2 years of age and oral penicillin if over 2 years of age. Penicillin-allergic children were treated with erythromycin. The control group did not receive antibiotic therapy on a routine basis, although seven of 27 children ultimately did receive antibiotics for other reasons such as cyanosis or persistent fever. Primary outcomes included duration of hospitalization and whether the child was considered "pulmonarily healthy" on day 3, at discharge, and at 3 weeks after treatment. The study groups did not differ significantly on any of these outcomes.

A large open-label study by Klein enrolled 348 children with acute community-acquired lower respiratory tract infections of whom 19 had bronchiolitis.[82] Children in this study were randomized in a 2:1 ratio to oral cefpodoxime proxetil or oral amoxicillin/clavanulate. In the overall study the group randomized to amoxicillin/clavanulate was significantly older than the cefpodoxime porxetil group (3.1 vs. 1.8 years), but data are not presented individually for the

bronchiolitis subgroup. The primary outcome was clinical cure or improvement. Significance testing was not performed, but Klein reports that nine of 10 children in the cefpodoxime proxetil group versus four of four children in the amoxicillin/clavanulate group experienced a clinical cure or improvement. The time frame for this outcome is not stated. Four patients in each group in the overall study discontinued their treatment medication because of side effects such as vomiting, diarrhea, and rash. Adverse events for the bronchiolitis subgroup are not presented separately.

Conclusions

These two studies were not primarily designed to answer the question of whether antibiotic therapy is useful in the treatment of bronchiolitis. Rather, they had subgroups of children with bronchiolitis who had been randomized into larger studies of the effect of antibiotic therapy on lower respiratory illnesses. These subgroup analyses likely lacked power to detect potentially important outcome differences. Subgroup allocation imbalances and treatment cross-overs may have imposed substantial biases into the bronchiolitis-specific analyses.

No evidence suggests that antibacterial antibiotic therapy is an effective treatment for bronchiolitis. Bronchiolitis in infants and children is caused by viruses, primarily RSV. Therefore, no a priori reason exists to assume that antimicrobial agents effective against bacteria would be appropriate treatment for a viral illness. Antibiotic treatment should be reserved for children who develop complications related to subsequent bacterial infection.

It should be noted, however, that a substantial proportion of infants with bronchiolitis may have acute otitis media (AOM) and thus may have a primary indication for antibiotic therapy. Andrade and colleagues enrolled 42 children with bronchiolitis, age 2 months to 2 years, in a prospective study.[83] They found that 62 percent had or developed AOM within 10 days. While automatic treatment of AOM with antibiotics is controversial, at least some of these infants will likely have a warranted indication for treatment.

RSVIG IV as Treatment for Bronchiolitis

Detailed Results

Rodriguez and colleagues studied the use of RSVIG administered intravenously for treatment of RSV bronchiolitis in two studies (Evidence Table 11). The first study was done with a group of previously healthy infants and the second was conducted among infants at high risk for complications from RSV bronchiolitis. The first studied a group of 101 previously healthy infants under 2 years of age who were hospitalized with moderate to severe RSV-positive bronchiolitis and/or pneumonia and followed them for 1 year after the intervention.[25] This medication is generally used for prophylaxis against RSV bronchiolitis among high-risk infants during RSV season. (The studies detailing its use in this manner appear in the results section for Key Question 3.) However, in these studies by Rodriguez and colleagues the drug was used as a treatment for infants who already had bronchiolitis rather than as a prophylactic agent. The intervention group in the first Rodriguez study received a single dose of 1500 mg/kg IV RSVIG or 0.5 percent albumin placebo. Mean days of hospitalization (4.58 vs. 5.52, $P = 0.24$) and mean days of mechanical ventilation (4.31 vs. 5.54, $P = 0.45$) were not statistically different between

the treatment and placebo groups. However, there was a trend toward a decrease in the mean number of days of ICU admission (3.92 vs. 6.60, $P = 0.06$). There were no adverse events related to RSVIG therapy. The study was designed with 90 percent power to detect a 20 percent decrease in duration of hospitalization assuming that the control group had a mean stay of 3.5 days. Although the study achieved its target enrollment, hospital stays among the control group averaged 5.52 days. Thus, the study was underpowered to detect less than a 35 percent difference in duration of hospitalization.

Rodriguez et al. also studied 107 high-risk infants under 2 years of age who had severe BPD, other serious chronic lung disease, or congenital heart disease or who had been premature at under 32 weeks' gestation with a chronological age of less than 6 months.[41] Infants were randomized to 1500 mg/kg IV RSVIG or albumin placebo and were followed into the next RSV season to assess possible harms, including whether there was any increased risk of enhanced RSV disease in children who did develop the disease in the second season. No meaningful difference was noted between the groups in the primary outcome of duration of hospitalization (8.41 days vs, 8.89 days, $P = 0.73$). No significant differences were reported for secondary outcomes such as duration of ICU admission, duration of mechanical ventilation, need for supplemental oxygen, change in respiratory scores after infusions, need for additional medications (bronchodilators, ribavirin, or steroids), development of RSV in the subsequent season, or readmission during the subsequent season. Some differences between the study groups could have contributed to the negative findings of this study. The RSVIG group had higher entry respiratory scores and more severe disease episodes than did the placebo group. Forty-seven percent and 28 percent, respectively required ICU admission, and 31 percent and 18 percent needed mechanical ventilation.

Conclusions

The Rodriguez et al. studies of the use of RSVIG IV as a treatment modality among normal infants with more severe disease did show a trend toward lowered duration of ICU hospitalization, but it was underpowered to detect a difference in total length of hospitalization.[25] Similarly, the study conducted among high-risk infants failed to demonstrate the effectiveness of RSVIG IV as a treatment modality although this study was relatively small and baseline differences between groups could have accounted, at least in part, for the negative results. In either case, a larger study would be required to detect meaningful clinical differences.

Other Miscellaneous Treatments for Bronchiolitis

Detailed Results

Evidence Table 12 groups six heterogeneous studies that each examined a novel treatment for bronchiolitis: Alpha-2 interferon,[47] helium-oxygen therapy,[84] Chinese herbs,[51] porcine-derived surfactant,[39] aerosolized furosemide,[85] and recombinant human deoxyribonuclease.[40] We consider the results of these studies individually although for convenience we grouped them in this single evidence table.

Chipps et al. enrolled 22 infants with acute bronchiolitis under 2 years of age to receive intramuscular injections of alpha-2 interferon or placebo for five days.[47] Six of these infants

were on ventilators: four in the interferon group and two in the placebo group. The primary outcomes were a clinical symptom score and the number of days on oxygen therapy. The researchers found no significant differences between study groups for either these outcomes or for any secondary outcomes. They also noted no adverse events. However, the study was halted after other reports of interferon (IFN) cardiotoxicity were published.

Hollman and colleagues studied 13 infants with RSV-positive bronchiolitis in a randomized cross-over trial of inhaled helium-oxygen versus inhaled air-oxygen mixtures.[84] Virtually all the patients also received nebulized albuterol, and most had some comorbidity such as cardiac disease and clinical asthma. The primary outcome was change in clinical asthma scores. The authors reported a significant improvement in clinical score for infants on the helium-oxygen mixture compared to baseline ($P < 0.05$). Analysis of trial results is difficult not only because of the small numbers involved, but also because five nonrandomized patients were included in the report of many outcomes.

Kong et al. studied 96 previously well children up to 4 years of age admitted to hospital with lower respiratory tract disease and serologic evidence of RSV. Subjects were randomized to three groups.[51] The first group received a traditional Chinese herbal treatment, Shuang Huang Lian, intravenously for 7 days. The second group received the herbal preparation plus either lincomycin or cephazolin, also for 7 days. The third group received only the antibiotics as for group two. The authors provided no rationale for the seemingly interchangeable use of these two antibiotics. Primary outcomes studies included mean days of wheezing, mean days of any sign or symptom, and mean duration of hospital stay. The analyses tested the first two groups, those that received Shuang Huang Lian with or without antibiotics, against the third group that received only antibiotics. The authors report statistically significant improvements in the mean days with any sign or symptom and mean duration of hospital stay for groups one and two compared to group three. The fact that these patients were hospitalized for extended periods makes generalizability to other populations questionable.

The Luchetti et al. study was designed to assess the effect of porcine-derived surfactant therapy for children with severe bronchiolitis requiring continuous positive pressure ventilation for at least 24 hours without clinical improvement prior to study entry.[39] One group received two to three doses of surfactant instilled into the trachea via an endotracheal tube along with continuous positive pressure ventilation; the other group had continuous positive pressure ventilation. Children were sedated and paralyzed prior to administration of surfactant. A careful reading of the paper does not find any indication that the control group was sedated or paralyzed or received any placebo. Both groups received other standard care as needed. The primary outcome measures were mean duration of ICU stay and of continuous positive pressure ventilation. The authors reported that the surfactant group showed statistically significant improvements in both outcome measures. Mean duration of ventilation was 4.4 days in the surfactant group versus 8.9 days in the control group ($P < 0.05$). Similarly, mean ICU stay duration was 10.1 days in the surfactant group versus 15.7 days in the control group ($P < 0.05$). The authors do not address the question of whether differential use of sedation and paralytic agents in the surfactant group might have influenced any of the outcome variables considered, but the effects of these types of medications are generally transient.

Van Bever et al. studied the effect of inhaled aerosolized furosemide versus saline placebo on 28 infants having a first episode of acute bronchiolitis with wheezing.[85] The primary outcome was the mean clinical score at baseline, and 15 and 30 minutes after treatment. Although clinical

scores improved for both groups, they did not differ significantly between groups. The study reported power of 79 percent to detect a clinical score difference at 30 minutes post treatment.

Nasr et al. conducted a randomized placebo-controlled study of nebulized recombinant human deoxyribonuclease (rhDNase) in 86 previously healthy hospitalized children under 2 years of age with proven RSV infection.[40] The treatment group received 2.5 mg of nebulized rhDNase in an excipient vehicle daily for up to 5 days and the placebo group received the excipient alone. The primary outcome was mean duration of hospitalization, which was nearly identical between the two groups (3.34 days in the placebo group vs. 3.33 days in the rhDNase group, $P = 0.97$). The treatment and control groups did not differ significantly in terms of secondary outcomes of mean change in respiratory, wheezing, and retraction scores; they did differ significantly in the chest x-ray change score, but the clinical meaningfulness of this measure is dubious in view of the other outcomes. There was a trend toward more severe disease in the rhDNase group compared with the placebo group, but these differences did not reach statistical significance. No adverse events were reported.

Conclusions

The one trial of alpha-2-interferon was small and underpowered to detect meaningful clinical outcomes.[47] It was stopped early because of concerns about cardiotoxicity, although the researchers reported no such adverse events. On this basis alpha-2-interferon does not appear to offer promise as a treatment for bronchiolitis.

The Hollman et al. study of inhaled helium-oxygen for severely ill children with RSV bronchiolitis was very small; it is statistically significant difference in asthma scores may be due to chance or to the specific choice of outcome.[84] However, helium-oxygen may be worth studying in a well-designed and adequately powered RCT to determine whether positive outcomes can be replicated. This intervention is clearly not applicable to the majority of infants and children with bronchiolitis, who rarely have severe disease.

Although the results of the Kong et al. study are intriguing, we do not believe this intervention to be practical in the United States because of the paucity of clinical locations able to administer this type of traditional Chinese herbal therapy and because the sheer length of hospitalization required does not match current U.S. practice patterns.[51] Length of hospital stay differed significantly, but the range among study groups was 7 to nearly 10 days.

The Luchetti et al. study was also small, but its positive results in both primary outcomes (both of which would be of clinical relevance to both clinicians and parents) argue for a well-designed and adequately powered RCT to determine whether the use of surfactant as an adjuctive treatment for severely ill, ventilated infants with bronchiolitis is efficacious.[39]

The Van Bever et al. study was small; the longest time frame for outcome measurement was 30 minutes.[85] If an adequately powered study is mounted, then it will need to measure patient-oriented outcomes at appropriate time intervals.

The study from the Nasr team did not demonstrate that nebulized rhDNase provides a clinical benefit in the treatment of bronchiolitis.[40] Any use of this agent should be restricted to properly designed trials.

Key Question 3: The Role of Prophylaxis in Prevention of Bronchiolitis

RSVIG IV versus Placebo or Standard Care to Prevent RSV Bronchiolitis

We located four studies of intravenous RSVIG to prevent bronchiolitis among both high-risk and standard-risk infants (Evidence Table 13).[86-89] This medication is administered monthly during the RSV season and may be administered in the hospital or a clinic. In some locations, the infusion may also be administered by a home intravenous therapy team. In clinical practice its use has largely been superceded by palivizumab, which will be addressed in the next section.

Groothuis and colleagues studied 249 children less than 48 months of age with BPD due to prematurity, congenital heart disease or cardiomyopathy, or a history of prematurity along with a chronological age of less than 6 months.[87] These children, who were all at high risk for RSV infections, were randomized to either high-dose (750 mg/kg IV every month) or low-dose (150 mg/kg IV every month) RSVIG or a standard care and control group. Primary outcomes included total and moderate-to-severe episodes of RSV and non-RSV respiratory illness. They found both significantly fewer total cases RSV-related lower respiratory infections and fewer severe cases in the higher-dose RSVIG IV group compared to the standard-care group. The low-dose group and the control group did not differ significantly on primary outcomes. Differences between the high- and low-dose groups were not reported. In secondary outcomes they also reported significantly fewer hospitalizations, hospital days, and ICU days for the high-dose group compared to the standard-care group. Eight-five percent of the 249 enrollees were followed into the subsequent RSV season and there was no suggestion of enhanced disease in either the high or low dose groups who were hospitalized for RSV infections. Enhanced disease had been a concern in early RSV vaccine trials such that these investigators were asked to specifically look for this adverse effect.

Groothuis et al. also published a subgroup analysis of the 162 premature infant from this study, excluding the children with congenital heart disease.[86] There were 102 preterm children with BPD and the remaining 60 had no evidence of lung disease. The analysis was further restricted to a comparison of the high-dose (n = 58) and control groups (n = 58) as the original analysis had not demonstrated efficacy of the low-dose therapy. Subjects were followed monthly during the 5 months of the intervention and then into the subsequent RSV season. Primary outcomes for this analysis included total incidence of RSV illnesses, incidence of severe RSV illness, hospitalizations for RSV infections, mean duration of ICU admission, and mean worst respiratory score. There were statistically significant differences favoring the high-dose group over the control group with the exception of the mean difference in duration of hospitalization which achieved borderline significance ($P = 0.06$). This study had potential problems with the masking of study personnel because an unblinded team was responsible for enrollment, examinations at the time of infusion, and well-infant examinations. A masked team was responsible for weekly followup and evaluation of all respiratory illnesses. Follow up of all of the preterm children into their second RSV season did not demonstrate any enhanced RSV illness upon infection with RSV.

Simoes et al. studied a group of 425 children under 48 months of age with congenital heart disease or cardiomyopathy; they randomized subjects to 750 mg/kg IV RSVIG every month during RSV season or to a control group that received no intervention.[88] As with the Groothuis et al. studies, the Simoes et al. team responsible for enrollment, treatment, and clinical assessment was not masked, whereas the team responsible for weekly surveillance and clinical evaluation of respiratory illnesses was masked. The primary outcomes were total acute respiratory illnesses, total upper and lower RSV-associated respiratory illnesses, and both RSV-associated and nonassociated lower respiratory tract illness hospitalizations.

The investigators reported significantly fewer acute respiratory illnesses (73 percent vs. 82 percent, $P = 0.02$) and total hospitalizations for lower respiratory tract illnesses (17 percent vs. 27 percent, $P = 0.02$) in the RSVIG group compared to the no-treatment group. In subgroup analysis they found fewer RSV hospitalizations in the treatment group under 6 months of age. They found no significant overall differences for RSV hospitalization by cardiac subgroup, but when they removed the group of children with biventricular heart disease with right-to-left shunt from the analysis, they detected a trend toward a decrease among infants with all other types of heart disease (biventricular without shunts, biventricular with left-to-right shunt, and single ventricle or hypoplastic left heart) included in the study (11 percent vs. 27 percent, $P = 0.06$.) A randomization imbalance resulted in more children with left-to-right cardiac shunt in the control group and more with right-to-left shunt in the treatment group. A significantly increased rate of serious adverse events related to cardiac surgery and increased rate of cyanotic spells was observed in children with cyanotic congenital heart disease receiving RSVIG IV and were thought due to receipt of the RSVIG IV treatment

The PREVENT Study Group conducted a multicenter trial involving 510 high-risk infants less than 2 years of age with BPD or who were premature (= 35 weeks) and under 6 months of age at the time of enrollment.[89] The intervention group received 750 mg/kg IV RSVIG monthly during RSV season; the control group received albumin placebo. Several significant positive differences between groups occurred, including fewer RSV-related hospitalizations (8 percent vs. 13.5 percent, $P = 0.047$), fewer total number of RSV-related hospital days (60 vs. 129, $P = 0.045$) and days in hospital requiring oxygen therapy per 100 children (34 vs. 85, $P = 0.007$). The RSVIG IV treatment group also experienced fewer hospital days with severe clinical scores per 100 children (49 vs. 106, $P = 0.049$), incidence of total respiratory hospitalizations (16 percent vs. 27 percent, $P = 0.005$) and total number of respiratory hospital days per 100 children (170 vs. 317, $P = 0.005$). In a set of subgroup analyses for prematurity, presence of BPD, age less than 6 months at trial entry, and weight under 4.3 kg, trends emerged toward fewer hospitalizations in all subgroups receiving RSVIG IV, but statistical testing was not performed for these exploratory secondary analyses. The paper does not mention statistical correction for multiple comparisons. When infusions were incomplete or prolonged because of an adverse event judged potentially related to the study drug, the problem occurred more often in the group receiving RSVIG IV (3.2 percent vs. 1 percent).

Conclusions

RSVIG IV administered at a dose of 750 mg/kg IV on a monthly basis during RSV season appears to be an effective prophylactic treatment for children at high risk of RSV disease and its complications. The adverse effects of this therapy included fluid overload and respiratory distress, but all deaths in studies were judged to have been caused by underlying disease rather than receipt of the drug.

Monoclonal Antibody for Prophylaxis of RSV Bronchiolitis

We located one large randomized placebo-controlled study of palivizumab as a prophylactic intervention (Evidence Table 14).[90] This agent is a humanized monoclonal IgG antibody that binds to the RSV fusion protein providing passive immunity against RSV. Like RSVIG IV it must be administered monthly during RSV season. Palivizumab was approved by the U.S. Food and Drug Administration in June 1998. Further trials of this intervention are in process and data are expected to be released later in 2002, including results of a study among children with congenital heart disease. We also located one preliminary trial of another monoclonal antibody, (SB 209763), which has not been subject to further study and is not available for use.

The IMpact-RSV Study Group studied 1,502 high-risk infants who were premature (= 35 weeks) and under 6 months of age or were 24 months of age and younger with symptomatic BPD.[91] Children were randomized in a two-to-one ratio to either palivizumab 15 mg/kg IM or placebo every 30 days for up to 5 month. The primary outcome was incidence of RSV hospitalizations. In the placebo group, 53 of 500 children (10.6 percent) were hospitalized for RSV infection, compared to 48 of 1,002 children (4.8 percent) in the palivizumab group ($P <$ 0.001.) The majority of secondary outcomes showed statistically significant benefits of the treatment as well. Among these secondary outcomes were total numbers of hospitalizations and hospital days per 100 children (62.6 vs. 36.4 days, $P < 0.001$), total days of RSV hospitalizations requiring oxygen therapy per 100 children (50.6 vs. 30.3 days, $P < 0.001$), hospital days with a severe clinical score per 100 children (47.4 vs. 29.6 days, $P < 0.001$), and incidence of ICU care (3 percent vs. 1.3 percent, $P = 0.026$). The differences observed in secondary outcomes are attributable to decreased RSV incidence and severity in the palivizumab group as the incidence of respiratory hospitalization unrelated to RSV was similar between the groups (14 percent vs. 13 percent, $P = 0.505$). Subgroup analyses examined the incidence of RSV hospitalization by weight, prematurity without BPD and BPD alone. All of these subgroup analyses showed a significant benefit of palivizumab. Adverse events, including development of fever, nervousness/irritability, injection site reaction, and diarrhea were not significantly different between the treatment and control groups. The overall rate of reported adverse events judged to be related to the study drug was 10 percent in the placebo group and 11 percent in the palivizumab group.

Meissner and colleagues conducted a trial to evaluate the safety, pharmokinetics and immungenicity of SB 209763, a humanized monoclonal antibody against RSV fusion protein.[92] The study population consisted of 43 infants with BPD or without BPD who had been born prematurely at less than or equal to 35 weeks of gestation. Infants were randomized to receive two doses of the antibody 8 weeks apart, at one of four dosage levels ranging from 0.25 to 10.0 mg/kg per dose at each administration. The so-called "placebo" group was actually a group of infants who received placebo at the first administration and then were crossed over to receive a dose of SB 209763 at the dosage level that had been assigned in their randomization scheme 8 weeks later. The 5.0 and 10.0 mg/kg doses of both SB 209763 and placebo were split into two syringes and administered one into each thigh. However, there was no attempt made to completely blind the administration of lower dose levels by giving two injections as well. There was a trend toward fewer episodes of proven RSV infection in the group that received the 10.0 mg/kg dose of SB 209763 vaccine compared to placebo (1 of 22 vs. 2 of 10, $P = 0.20$) this difference did not reach statistical significance. There was a lower rate of proven RSV infection at the three other dose levels as well, but the P-values ranged from 0.72 at the 0.25 mg/kg dose to

0.49 at the 5.0 mg/kg dose level. Four adverse events judged related to the study drug were identified and included three episodes of mild/moderate purpura and one episode of thrombocytosis. The authors suggested that the doses used might have been too low to confer adequate clinical immunity and that future trials test higher doses of monoclonal antibody.

Conclusions

Palivizumab administered monthly during RSV season is an effective and safe intervention to prevent severe disease and decrease hospitalizations among infants and children at high risk for developing severe RSV infections. This prophylactic agent is more convenient for children and parents than RSVIG IV as it does not require intravenous access or other associated care. There is insufficient evidence on SB 209763 to recommend its further study, particularly when another monoclonal antibody, palivizumab, is available as the standard of care.

Additional information on palivizumab comes from a single-arm, unblinded cohort study by Groothuis and colleagues. They studied 565 high-risk infants with BPD or who were less than 6 months of age at the time of enrollment and born prematurely at less than or equal to 35 weeks gestation.[90] The purpose of the study was to gather additional safety data from areas in the Northern Hemisphere where palivizumab was not yet licensed. The treatment consisted of 15mg/kg of RSVIG administered intramuscularly once every 30 days during RSV season for a maximum of five doses. There were 78 hospital admissions during the 150 days after enrollment; 65 percent of these admissions (51 cases) were attributed to respiratory causes. Of these 51 children, 29 were tested for RSV; seven tested positive, for an RSV positivity rate of 24 percent. Forty-five percent of subjects experienced some sort of adverse event, with 2 percent of subjects (11 of 564) discontinuing treatment because of the adverse event. However, the investigators believed that only three of these 11 adverse events were directly attributable to the treatment. Adverse events reported in this single-arm study were equal to or fewer than those reported in the more restricted IMpact trial described above. There were two deaths, neither thought related to the drug.

Vaccines to Prevent RSV Bronchiolitis

Our literature search revealed three studies of purified fusion protein (PFP) vaccination to prevent RSV disease (Evidence Table 15).[92-95] These are all small studies with enrollment ranging from 21 to 43. The first two studies were in high risk young children with a history of BPD and/or prematurity while the Piedra studies were conducted in older children with cystic fibrosis.

Groothuis and colleagues randomized 21 infants under 12 months of age with BPD. All infants had a proven RSV infection in the previous RSV season. These infants had previously had influenza vaccination in the previous year and were then randomized to vaccination with PFP-2 vaccine or trivalent influenza vaccine in the subsequent year.[93] Their primary outcome was RSV infection in the subsequent season. One of 10 in the treatment group and six of 11 in the control group had subsequent season RSV infections. This result was borderline statistical significance with a *P* value of 0.06. Some of the immunological secondary outcomes, including such items as mean neutralizing antibody 1 and 6 months after vaccination, were found to be statistically higher in the group that received PFP-2 compared to the placebo group. This is obviously a small study lacking sufficient power to detect even large differences between groups.

Piedra and colleagues reported the results of two studies using PFP-2 vaccine in children at high risk from RSV infection because of underlying cystic fibrosis. The first study of 34 children randomized groups to PFP-2 or saline placebo.[94] There were baseline group imbalances with the PFP group being taller, older and with lower body fat composition. There were no differences demonstrated in the development of RSV or total days of RSV illness between groups. However, there were significantly more children with one or more than one acute lower respiratory tract infection (15 of 17 vs. 9 of 17, $P = 0.024$) and with more ill days per subject (67 vs.30.5, $P < 0.001$) in the control group compared with the vaccine group. The vaccine group had fewer antibiotic courses (4.5 vs.2.2, $P < 0.001$) and fewer acute lower respiratory tract infections per subject (2.1 vs.0.8, $P = 0.005$) than did the control group. There were no significant differences in adverse events between the groups, although the vaccine group did report more cases of tenderness at the vaccine site ($P = 0.09$).

A second study by Piedra was conducted to evaluate the effectiveness of sequential yearly administration of PFP-2 versus a single administration in children with underlying cystic fibrosis.[95] A group of 29 or the 34 children who had participated in the previous study of PFP-2 vaccine discussed above were recruited into this study of sequential annual administration of vaccine. They were enrolled in this open label study to PFP-2 vaccine and all enrollees received a 50 microgram dose of the vaccine in the second season. Thus there were two groups, one which received vaccine each autumn for two seasons or saline placebo in the first year followed by PFP-2 vaccine in the second season. The sequential vaccine group which received active vaccine in both seasons had fewer children with more than one acute lower respiratory tract infection during the second season (9 of 13 vs.15 of 15, $P = 0.035$.) The sequential vaccine group was also found to have fewer acute lower respiratory tract infections per subject (1.2 vs. 2.1, $P = 0.004$) and ill days per subject (36 vs. 64.8, $P = 0.001$) compared with the group that only received the active vaccine in the second season. There were no significant differences in total number of illnesses per subject or mean number of courses of antibiotics per subject. Although only a total of 11 children had confirmed RSV infections in the second season, the sequential vaccine group of RSV infected children did have significantly fewer episodes of acute lower respiratory tract infections, days of illness and courses of antibiotics per subject. There were baseline differences between the two groups with the control group being taller, older and more likely to attend day care. Given the nature of cystic fibrosis disease and day care exposures, these baseline differences could have accounted for the outcome differences seen between the two groups. Adverse events and their distribution was comparable to those which were seen in the first Piedra study.

Conclusions

PFP-2 vaccines appear to be a promising prophylactic intervention for high risk children with BPD and/or prematurity. The available studies are small such that well-designed and properly powered studies are needed to make a definitive conclusion regarding this intervention. Administration of PFP-2 vaccine to children with cystic fibrosis may be effective at preventing acute lower respiratory tract infections and lessening the need for antibiotic use in these subjects as well. If future studies are done they may want to explore initiating the vaccine at earlier ages and further examining the effectiveness of single versus multiple vaccinations to confer immunity.

Key Question 4: Cost-effectiveness of Prophylaxis for Management of Bronchiolitis

Although palivizumab has demonstrated that it reduces RSV hospitalization in infants 32-35 weeks estimated gestational age (EGA), indication of its use in this population is reserved for infants with additional risk factors due to questions over its cost-effectiveness in the wider population. To gather and synthesize findings on the cost-effectiveness of prophylactic therapy in two particularly vulnerable subgroups of infants, we conducted a review of the published literature on the cost-effectiveness of prophylactic therapy. We sought to address the following specific questions:

- What is the evidence concerning the cost-effectiveness of prophylactic therapy for prevention of bronchiolitis among infants born from 32 through 35 weeks EGA?
- What is the evidence concerning the cost-effectiveness of prophylactic therapy for prevention of bronchiolitis among infants born from 32 through 40 weeks EGA with comorbid conditions?
- Can the cost-effectiveness of prophylactic therapy for children in the target populations be assessed from a societal perspective using information from secondary sources or the literature?

Cost-effectiveness denotes an economic evaluation producing either an incremental cost or a ratio intended to provide guidance to policy-makers tasked with health-care resource allocation. Cost-effectiveness ratios indicate the cost incurred per measure of disease avoided, such as cost per life-year saved or cost per hospitalization. Palivizumab prophylaxis has been demonstrated to reduce hospitalizations, so we adopt a standard measure of effectiveness of cost per hospitalization avoided when comparing results. Thus, policy-makers must consider quality of life and ethical issues when interpreting the value society should place on avoiding RSV hospitalization.

We identified a total of 10 studies in the literature that considered the economic consequences of prophylactic therapy for the prevention of RSV bronchiolitis. Evidence from these studies is mixed with regards to the cost-effectiveness of prophylaxis for infants born from 32 through 35 weeks EGA and infants with comorbidities, such as BPD. Some of the analyses were for RSVG-IV, an intravenous form of prophylaxis that has largely been replaced by palivizumab. Because palivizumab is less invasive and less costly than RSVIG IV, and because the TEAG members indicated that the question of cost-effectiveness should focus on the use of palivizumab versus no intervention, the economic findings described in this section are taken only from analyses of palivizumab. Four studies concentrated exclusively on palivizumab, one addressed palivizumab and RSVIG IV separately, and one analyzed a population in which approximately 75 percent of infants were given palivizumab and the other 25 percent were given RSVIG IV.

The IMpact RSV trial is the only study to date that has assessed the effectiveness of palivizumab for preventing healthcare utilization related to RSV infection among preterm infants.[91] IMpact RSV was a randomized, placebo controlled trial conducted during the 1996-1997 RSV season. The trial included 1502 children (500 in the placebo group and 1002 in the palivizumab group) born 35 weeks EGA or less, including children diagnosed with BPD. The trial did not include infants with other comorbidities, such as congenital heart disease or immune

deficiencies. Study infants were administered five monthly doses of palivizumab during the course of the RSV season, and 92 percent received all five doses.

The trial tracked hospitalization outcomes among study infants, and upon hospitalization, infants were given an RSV antigen test and a Lower Respiratory Tract Illness/Infection (LRI) score. Other outcomes measured included days of hospitalization for RSV, days with increased oxygen, total days with a moderate or severe respiratory illness (based on LRI), days of stay in ICU, and the use of mechanical ventilation. All subjects were included in the safety and efficacy analyses, but no statistically significant differences in adverse event rates were reported between treatment and control groups. Among the adverse events where the palivizumab group reported statistically insignificant, although higher, rates (such as rash at injection site) none were serious and no measurable costs were associated with these events. Key findings from the IMpact RSV trial are shown in Table 8.

The IMpact RSV trial demonstrated the effectiveness of palivizumab in preventing episodes of hospitalization and other healthcare resource utilization associated with RSV bronchiolitis. However, questions over the cost-effectiveness of palivizumab among infants 32-35 weeks EGA did not lead to un-reserved indication of palivizumab prophylaxis for this population. Consequently, evidence on the cost-effectiveness of palivizumab could prove valuable for deciding whether to administer palivizumab to the large group of infants born from 32 through 35 weeks EGA and infants with comorbid conditions. In the next subsection, we summarize findings from economic analyses of palivizumab.

Summary of Findings from the Literature on the Cost-effectiveness of Palivizumab Prophylaxis

As mentioned previously, six studies have assessed the cost or cost-effectiveness of palivizumab in preventing RSV bronchiolitis. For each of these studies, we provide a brief description, present key findings, and discuss limitations.

Summary of Findings from Marchetti et al.

Marchetti et al. assessed the cost-effectiveness of palivizumab using providers' charges.[96] Their analysis used baseline hospitalization rates from the Impact RSV trial, two trials of RSVIG IV (PREVENT and the National Institute of Allergy and Infectious Diseases [NIAID]-Respiratory Syncytial Virus Immune Globulin), and the literature (rates ranging from 10.6 to 42.6 percent). Costs were estimated as hospital charges drawn from the literature, and ranged from $10,000 to $166,000 per RSV episode requiring hospitalization. Charges do not reflect costs to society, and are usually converted to costs using a cost/charge ratio. The impact of palivizumab on hospitalization rates and severity of infection (based on LRI scores) was taken from the IMpact RSV trial.

Assuming a 55 percent reduction in hospitalization rates for children who received prophylactic therapy, the authors estimated incremental charges (charges above the costs for infants who did not receive prophylaxis) ranging from saving of $36,040 to costs of $3,424 per infant. They found that prophylaxis was most cost-effective in infants born at 32 through 35 weeks EGA with no diagnosis of CLD and least cost-effective in infants with CLD.

The authors did not provide the sources of information for the cost of prophylaxis or for their baseline hospital charges, and the cost of prophylactic therapy was not provided. The year in which costs were valued was not provided and authors did not explain how LRI scores were used in the calculation of expected costs. Additionally, the authors used charges, which overstate costs, and this biases results to appear more cost-effective.

Summary of Findings from Joffe et al.

Joffe et al. analyzed the cost-effectiveness of both palivizumab and RSVIG IV in the prevention of bronchiolitis.[13] Theirs is the only study reviewed in this report which adopted a societal perspective. In addition to medical costs, the authors attempted to value parents' lost time from work, travel costs, and future productivity losses associated with premature mortality. Hospitalization rates and costs were obtained from a cohort of 1721 premature infants discharged from six Kaiser Permanente NICUs in Northern California (KPMCP-NC). The infants in this cohort were divided into eight subgroups based on gestational age at birth, length of oxygen therapy, and month of NICU discharge. For each subgroup, Joffe et al., calculated the baseline, or no intervention, hospitalization rate for subsequent RSV-related inpatient stays. These rates ranged from 1.2 to 24.6 percent. The impact of prophylaxis on hospitalization rates was taken from the IMpact RSV trial for palivizumab (55 percent reduction in hospitalization). The authors pooled data from the IMpact RSV trial and two previous studies on RSVIG IV, PREVENT and NIAD, to estimate the mortality rate for RSV bronchiolitis among hospitalized infants (1.2 percent of all hospitalizations). Cost data were compiled from internal KPMCP-NC records as well as from published sources. Prophylaxis costs were estimated for four doses per infant, and were $2,800 for palivizumab (drug and administration costs).

Parents' lost time from work was estimated to be $44 for treatment with palivizumab and $358 for an average hospitalization (regardless of whether prophylactic therapy was given). The estimated medical cost of outpatient services for RSV bronchiolitis was $198; the estimated cost for hospitalization was $8,502. The authors found that results varied greatly by subgroup. For the highest risk subgroup (23-32 weeks EGA, = 28 days on oxygen, and discharged from September through November), estimated costs were $12,000 per hospitalization avoided (not including productivity losses resulting from premature mortality). For infants born from 33 through 36 weeks EGA, the most cost-effective group was those requiring = 28 days of oxygen and released from the neonatal intensive care unit (NICU) from September through November. The estimated cost-effectiveness ratio for this subgroup was $38,000 per hospitalization avoided.

Although Joffe et al. attempted to include important nonmedical costs, such as parents' lost time from work and travel expenses to obtain treatments, these cost estimates were based on assumptions about parents' behavior rather than actual data.[13] The authors also use data on hospitalization rates for each of eight subgroups of vulnerable children, but these rates vary widely, possibly in part because of the small number of observations in some subgroups. In analyses of the productivity losses resulting from premature mortality, Joffe et al. used a mortality rate of 1.2 percent among hospitalized infants, but there is no evidence that palivizumab prevents death.

Summary of Findings from Numa

Numa performed an economic analysis of palivizumab from the Australian providers' perspective.[97] The analysis was based on record review from the Sydney Children's Hospital

(SCH) to identify children younger than 2 years of age with an admission for RSV infection. For this cohort, Numa calculated average hospitalization costs for both the general ward and the ICU. The impact of prophylaxis was based on results from the IMpact RSV trial for palivizumab and from the PREVENT trial for RSVIG IV.

Numa compared the estimated cost of administering prophylactic therapy to the estimated cost savings of prophylaxis (through reduced hospitalization and ICU lengths of stay) for the SCH cohort and concluded that the cost of administering either palivizumab or RSVIG IV outweighed the potential cost savings.

Cost differences for children who received prophylactic therapy versus those who did not were assumed to be entirely due to differences in lengths of stay in the hospital and ICU. Because of data limitations in the SCH records, Numa's analysis did not account for differences in the incidence of hospitalization that may be associated with prophylactic therapy receipt.

Summary of Findings from Lofland et al.

Lofland et al. assessed the cost-effectiveness of palivizumab from the providers' perspective.[14] The authors used healthcare resource utilization and effectiveness data from the literature and from the IMpact RSV trial. Data on hospitalization costs were obtained from a university-affiliated hospital cost-accounting system. A range of values was used for baseline hospitalization rates (10 to 38 percent) and for palivizumab costs ($2,500 to $4,500 per child per season). The authors estimated a mean cost of $10,486 per RSV hospitalization, but this value was also varied.

Results indicated that the cost per episode of RSV infection avoided—where an episode included outpatient care, home healthcare, and hospitalization—ranged from cost saving (i.e., the cost of palivizumab therapy was more than offset by the cost savings associated with reduced healthcare resource use for the intervention group) to $79,706. Results were sensitive to changes in hospitalization cost, cost of palivizumab therapy, and the baseline incidence of hospitalization.

Because results were not provided separately for the 32 through 35 week EGA subgroup of infants or those with comorbidities, the Lofland et al. results may not be applicable to these subgroups. Lofland's analysis assumed a 5 percent hospitalization rate for infants who received palivizumab, which is significantly higher than the 1.9 percent hospitalization rate from the IMpact RSV trial for infants born 32 through 35 weeks EGA.

Summary of Findings from Schrand et al.

Schrand et al. conducted an economic analysis from the providers' perspective.[98] They used data on costs and effectiveness from the University of Iowa Hospitals and Clinics (UIHC). The UIHC introduced RSVIG IV to the formulary in 1996, and by the 1998-99 RSV season, all infants meeting the healthcare organization's criteria for receiving prophylaxis were being given palivizumab, and in some cases, RSVIG IV. Baseline hospitalization rates were generated by searching UIHC hospital records for relevant diagnosis codes for infants meeting the criteria for prophylaxis during the 1994-95 RSV season (the period prior to the implementation of the prophylaxis policy). Hospitalization rates for infants receiving prophylactic therapy were generated using the same approach for the 1998-99 RSV season (the post-implementation period). Estimated rates were based on 10 hospitalizations among 40 infants (25 percent) in the baseline group and one hospitalization among 61 infants (1.6 percent) in the prophylaxis group.

Hospitalization costs were estimated for infants in the 1994-95 RSV cohort and adjusted to 1999 dollars.

Estimated cost for hospitalization with RSV infection was $17,031 (in 1999 dollars) and for prophylactic therapy (drug and administration costs) was $3,461. Because the authors' estimates of hospitalization incidence suggested a much larger impact of prophylaxis than was found in the IMpact RSV trial (i.e., a relative rate of hospitalization of approximately 0.06), rates from the IMpact RSV trial and from a study that focused on chronic lung disease[99] were used in sensitivity analyses. When using data on hospitalization rates from the IMpact RSV trial, findings suggested that the cost savings of prophylactic therapy (i.e., reduced hospitalization costs) approximately offset the costs of administration. Prophylaxis was cost saving when assessed using data from the UIHC system and Groothuis et al.

Schrand's analysis did not focus on the subgroups of interest for our review (infants born 32-35 weeks EGA or with comorbidities), which may limit the applicability of these results. Additionally, hospitalization rate estimates were based on extremely small sample sizes, and estimates for the baseline group were for a period 4 years prior to the time period for which rates were estimated for the prophylaxis group, which may affect the comparability of findings.

Summary of Findings from Fariña et al.

Fariña et al. conducted a regional analysis of the cost-effectiveness of palivizumab therapy among high-risk infants in Argentina.[100] They identified patients enrolled in a publicly supported hospital, which serves a population of primarily low income households within 62 miles of the facility. Forty-two child patients were tracked for two years, and over the two-year period, the rate of hospitalization for RSV infection was 23.8 percent. Average cost was $18,477 for hospitalization and $1,100 per patient per dose for palivizumab therapy.

By applying the 55 percent relative reduction in hospitalization rates from the IMpact RSV trial, the authors estimated a cost to prevent one hospitalization of $15,358. These findings are very sensitive to the baseline hospitalization rate used in the analysis, and the high rate among this study population was largely due to poor living conditions, such as overcrowding, poverty, and a lack of education among family members.

The number of observations used to estimate the hospitalization rate among this population is very small. Moreover, because the socioeconomic characteristics of the study population are so different from the population studied in the IMpact RSV trial, it is not clear whether the IMpact RSV results are applicable.

General Findings Across Economic Analyses

The CEAs summarized in the previous subsection varied greatly in the approaches used, estimates of key parameters, and findings. Although the Panel on Cost-Effectiveness in Health and Medicine has recommended that a societal perspective be used for economic evaluations of clinical interventions, only Joffe et al. attempted to incorporate a societal perspective; the other studies adopted a payers' or providers' perspective.[13] Three factors had a large impact on cost-effectiveness results from all of the studies: hospitalization incidence, healthcare costs, and the costs of palvizumab therapy. In this subsection, we discuss differences identified in these factors across studies and how these differences are likely to affect the cost-effectiveness of palivizumab.

Incidence of Hospitalization

Estimates of the incidence of hospitalization for RSV bronchiolitis vary widely, and these differences can have a considerable impact on the estimated cost and cost-effectiveness of prophylactic therapy. Table 9 shows some of the RSV hospitalization rates found in the literature. Note that baseline hospitalization rates for infants from about 32 through 35 weeks EGA vary from 1.2 to 25 percent.

One possible reason for the limited evidence on hospitalization rates is because of the difficulty of obtaining consistent diagnoses of RSV bronchiolitis across hospital settings. Bronchiolitis is generally a clinical diagnosis, and therefore hospitalization incidence rates based on a diagnosis of bronchiolitis may under- or over-attribute RSV as the infectious agent. For studies that used universal antigen testing to determine the presence of RSV, variations in the epidemiology and prevalence of RSV by geographic or socioeconomic group as well as variations in virulence and subspecies, can greatly affect findings.

Cost of Health Care Resource Utilization

Hospital and other medical resource costs can vary by severity of illness, geographical area, and institution. The source of cost information can also change the value of the estimate. Charges overstate costs to society, as most payers pay significantly less. Cost to charge ratios to convert charges can be calculated from Medicare data and indicate that costs are typically less than 60 percent as high as charges, but use of cost to charge ratios for non-Medicare hospitalizations introduces even more uncertainty into the actual costs. The values obtained from hospital cost accounting systems are likely to be the most accurate measures of cost available, although they best reflect medical costs for a particular geographical region and may not reflect any profit. In the economic analyses of palivizumab described in the previous subsection, hospitalization and other medical care cost estimates varied widely. These estimates, adjusted to 2001 dollars using the MCPI, are shown in Table 10. Diagnosis codes designating RSV hospitalization are now available, and may facilitate estimation of more accurate cost values.

Cost of Palivizumab Therapy

The single largest barrier to wide-scale use of palivizumab is its cost. Palivizumab cost estimates from the literature are shown in Table 11. Most of the analyses used the average wholesale price (AWP), or a catalog price, as an estimate of the cost of palivizumab. However, AWPs are not calculated from actual sales; they are essentially suggested wholesale prices and may not accurately reflect actual costs. Wholesalers sometimes use the AWP as a list price in catalogs and then negotiate discounts with customers. Physician practices and insurance companies, especially those that use group purchasing organizations and pharmacy benefits managers, may be able to obtain palivizumab at a much lower unit cost than the published AWP. Indeed, certain Federal agencies (Department of Defense [DoD], Veterans Affairs [VA], and Health and Human Services [HHS], and the Coast Guard) are able to purchase palivizumab for 48 percent less than the published AWP.

Another component of the cost of palivizumab that varies across economic analyses is the number of doses required for a successful prophylaxis program. Palivizumab is recommended to be taken monthly during the 5 months of RSV season, but infants born during RSV season may

take less than the full five doses. Schrand et al. reported that all infants in their treatment group received all required doses, but that the average number of doses per infant was 3.28.[98] Analyses that used an estimate of five, or nearly five, doses may overstate the costs for full administration.

Cost to Avoid Hospitalization

Table 11 lists results from the four palivizumab cost-effectiveness analyses conducted in the U.S and indicates cost-effectiveness ratios when average parameter values from Tables 9 and 10 (Marchetti's hospital charges were converted to costs with a cost to charge ratio of 0.6) were used in the analysis. The costs are expressed in terms of cost per hospitalization avoided. The costs listed for Marchetti were derived by using the incremental cost per infant for the general population, and then multiplying this by the number needed to treat to avoid a hospitalization based on incidence rates from the IMpact-RSV trial.[96] Marchetti did not indicate incremental costs for the subpopulations, but provided a break-even analysis which indicated that infants born 32-35 weeks EGA were the most cost-effective, and those with a diagnosis of CLD were the least cost-effective. Had incremental costs for the appropriate subpopulations been used instead of the cost for the general population, one could expect that the cost to prevent a hospitalization for the 32-35 week EGA group would be lower, and the corresponding cost for infants with CLD would be higher.

Schrand et al. reported results as incremental costs, based on the hospitalization rates seen in their institution, as well as based on rates from the IMpact-RSV trial as part of the sensitivity analysis.[98] It was not possible to derive the incremental costs or hospitalization rates specific for the sub-populations of interest, but since this CEA reported all of their parameter values, we were able to derive an incremental cost for each subpopulation for the IMpact-RSV rate results. Lofland et al. and Joffe et al. reported cost per hospitalization avoided for certain subpopulations. Joffe reported based on sub-populations grouped by EGA, as well as oxygen usage and month of discharge from NICU, which were found to have significant correlation with hospitalization rates.[13] Lofland reported results for the $4,500 prophylaxis cost provided by MedImmune, Inc.[14] Given that this estimate is higher than the others, Lofland also provided results based on a $2,500 prophylaxis cost, which is lower than other estimates. The final row in Table 11 presents the cost to prevent a hospitalization if the average parameter values from Tables 9 and 10 were used. The costs represent the average hospitalization cost reported for the four U.S.-based CEAs, as well as the societal costs used by Joffe. The prophylaxis cost is also based on the average cost (using the $2,500 estimate from Lofland et al.), and includes the relevant social costs of palivizumab prophylaxis from Joffe et al. Hospitalization rates for those taking and not taking palivizumab, as compiled from the literature, are used to predict the effect of palivizumab prophylaxis. These rates should be treated with caution, since they are compiled from rates from disparate sources and the baseline characteristics, study design, and horizon will differ between the prophylaxis and no prophylaxis groups. These costs per hospitalization avoided should not be used for interpreting the cost-effectiveness of prophylaxis; they are intended only to facilitate comparison of the published literature.

Cost to Avoid a Hospitalization by Administering Palivizumab to Infants Born 32-35 Weeks EGA

The cost to avoid a hospitalization for infants born from 32 through 35 weeks EGA range from savings to costs of $328,000 for infants discharged from the NICU during low-risk months

and with less than 28 days of supplemental oxygen use in Joffe et al. The results based on averages for parameter values in the literature suggest a $54,500 cost to avoid a hospitalization. The average cost to avoid one RSV hospitalization among the four U.S.-based CEAs was $54,214, but this dropped to $33,595 when the two lowest risk cohorts from Joffe et al. were excluded. The average cost of RSV hospitalization was $14,485, in addition to intrinsic morbidity costs associated with hospitalization.

Cost to Avoid a Hospitalization by Administering Palivizumab to Infants with CLD

The evidence on the cost-effectiveness of palivizumab prophylaxis on infants based on a diagnosis of CLD is less conclusive. The IMpact-RSV trial indicated that palivizumab was least effective on this group but Table 9 indicates that this population may have higher RSV-hospitalization incidence rates.[91] Based on this effectiveness data, the four analyses indicated that infants with CLD would require higher expenditures to avoid a hospitalization. If the use of supplemental oxygen for 28 days or more is used as an approximation for a diagnosis of CLD to allow the inclusion of data from Joffe et al., then the average cost to prevent a hospitalization reported by the CEAs would be $40,168. This contrasts greatly with the cost obtained when using the average parameters from Tables 9 and 10, which was $19,540 to prevent a hospitalization. This result is so low because the incidence data for this group in Table 9 would yield a lower number of infants need to treat to avoid a hospitalization. If Groothuis et al. 1988 was eliminated from consideration, the cost to prevent a hospitalization would be $24,176. If Sorrentino and Powers was eliminated, the cost to prevent a hospitalization would be $38,015. If both were eliminated, the result would be $49,935, which is similar to the average of the results for infants born 32-35 weeks EGA. If the result of $19,540 were included in the average of the results of the CEAs, the cost to prevent a hospitalization by administering palivizumab to infants with CLD would be $36,713, with one RSV hospitalization costing $14,485 in addition to morbidity costs.