5. Future Research

Because the diagnosis of bronchiolitis is primarily clinical, we could find little evidence in the literature to answer fully our Key Question 1. By contrast, the volume of literature available to answer Key Questions 2 and 3 was much greater. However, the strength of evidence was limited by trials that were underpowered and outcomes that were not comparable across studies (Table 12). Key Question 4 cannot be fully addressed without additional data on hospitalization rates and social costs, which are currently widely variable. Also, the evidence for Key Question 4 will need review upon release of new trial data on palivizumab. Given these significant gaps in the literature, we propose some priorities for further research. We also suggest some guidelines for the choice of outcomes and study design that will improve the reporting of research findings and allow meaningful comparisons of study results.

Priorities for Further Research

Diagnosis

Prospective trials of the utility of ancillary testing (chest x-rays, complete blood tests, RSV testing) are feasible and should be performed. Studies of diagnostic tools used in the management of bronchiolitis should measure clinical outcomes that are meaningful to both parents and clinicians. An important intermediate outcome for studies of diagnosis in the management of bronchiolitis is the change in physician practices (i.e., whether results of diagnostic steps alter the ways that physicians elect to manage their patients with this condition).

Treatment

Our review revealed that for several interventions for bronchiolitis, data are simply insufficient to exclude them as possible effective treatments. Until these interventions are shown to be efficacious, our conclusion is that their clinical use ought to be limited to study situations. The following interventions, in particular, should be studied with well-designed, rigorously conducted RCT, preferably with placebo control: (a) nebulized epinephrine; (b) nebulized salbutamol plus ipratropium bromide; (c) nebulized ipratropium bromide; (d) oral corticosteroids, preferably dexamethasone; (e) inhaled budesonide; (f) inhaled helium-oxygen for severely ill children; (g) Chinese herbal therapy with Shuang Huang Lian (if its use can be practically accomplished in U.S. settings); and (h) surfactant for ventilated children.

The treatment studies we reviewed were almost universally underpowered and as such do not give clinicians adequate guidance for management of bronchiolitis. There is substantial evidence that clinicians commonly use several interventions such as inhaled bronchodilators, inhaled corticosteroids, and inhaled epinephrine for which, currently, evidence is insufficient. These drugs are all available as generic products and, therefore, relatively inexpensive; clinicians also

consider them to be safe. We believe that clinicians will continue to use these types of treatments unless a large simple trial of these most common interventions is mounted. Such a trial would need to be large enough to examine each of the interventions not only in the overall population, but also in subpopulations of interest (e.g. infants with and without a history of atopy). This type of trial is unlikely to be funded by industry and would therefore require governmental support.

Prophylactic Therapy

Studies of the use of prophylaxis in at-risk groups that had been excluded from earlier studies will need to be released before this agent can be recommended more broadly for infants and children who are at increased risk of more severe bronchiolitis. Studies of prophylaxis should examine the effect on long-term outcomes such as the development of asthma.

Evidence is insufficient about the use of PFP-2 vaccine among high-risk infants with chronic lung disease or among children with cystic fibrosis. Our conclusion is that this vaccine ought not to be used except in the context of well-designed, properly powered RCTs to determine its effectiveness, safety, and cost-effectiveness.

Costs of Prophylaxis

Better estimates of the cost of palivizumab are needed to assess whether the drug is cost-effective. In particular, additional data are needed on the cost of administration. Key issues include typical dosage amount and number of doses, time required for parents and providers to administer it, and the actual cost of palivizumab to providers, which may be less than the average wholesale or catalog prices used in most previous analyses.

Estimates of baseline hospitalization rates for RSV bronchiolitis in the specific subgroups of interest (infants 32 through 35 weeks' EGA or with comorbidities) are needed to assess better whether prophylactic therapy is cost-effective for these populations. These analyses should also consider how hospitalization rates differ depending on socioeconomic characteristics of the population and region of residence.

To assess the cost-effectiveness of palivizumab from the societal perspective, data are needed on family costs. Family costs may be incurred for the receipt of prophylactic treatment (e.g., productivity losses and out-of-pocket expenditures) or for a child's infection with RSV bronchiolitis and subsequent treatment. Other data needed to estimate the societal costs of bronchiolitis are information on excess chronic morbidity for infants in the palivizumab treatment group (e.g., asthma) and premature death.

Data are needed to assess whether outpatient service utilization and costs and length of acute episodes differ between the prophylaxis and no-prophylaxis groups of infants for the populations of interest. Although the cost of outpatient services is largely dwarfed by hospitalization costs, if children who receive prophylactic therapy require much less ambulatory care and their families incur significantly less expenses and productivity loss, these differences may be significant.

Although many studies have attempted to measure the impact of EGA and the presence of comorbidities on RSV infection rates, the importance of other risk factors should also be considered. For example, the impact of day care attendance, multiple birth, exposure to

secondhand smoke, room-sharing with siblings, socioeconomic status, and general hygiene should also be considered when assessing the impact of palivizumab on RSV infection and subsequent illness.

General Guidelines for Further Research

Outcomes

In the future, investigators should choose clinically relevant outcomes. Most of the outcomes studied in this literature are short term; often they are only surrogate outcomes such as oxygen saturation or respiratory rate at 15-minute intervals after treatment. Investigators should concentrate on measuring outcomes that matter to parents, clinicians, and health systems. Examples include rates of hospitalization or rehospitalization, duration of hospitalization, need for more intensive services in hospital, costs of care, parental satisfaction with treatment, and development of chronic asthma.

Design

Studies should be powered to detect meaningful differences in clinically relevant outcomes. Power calculations must include sufficient numbers to account for multiple comparisons if multiple outcomes are to be measured.

Reporting of Adverse Events

Few studies reported adverse events associated with treatments. Determining whether the risks of particular treatments are sufficient to exclude their clinical use is difficult. Future investigations should carefully monitor and report adverse events associated with treatments.