

Respiratory Syncytial Virus Hospitalizations in Healthy Preterm Infants

Systematic Review

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Background: Studies have explored the risk for and impact of respiratory syncytial virus (RSV) infection requiring hospitalization among healthy preterm infants born at 29–35 weeks of gestational age not given RSV immunoprophylaxis. We performed a systematic review and qualitative synthesis of these studies.

Methods: Two experienced reviewers used prespecified inclusion/exclusion criteria to screen titles/abstracts and full-text studies using MEDLINE, Embase, BIOSIS and Cochrane Library (January 1, 1985, to November 6, 2014). We abstracted data on risk factors for RSV hospitalization, incidence and short- and long-term outcomes of RSV hospitalization. Using standard procedures, we assessed study risk of bias and graded strength of evidence (SOE).

Results: We identified 4754 records and reviewed 27. Important risk factors for RSV hospitalization included young age during the RSV season, having school-age siblings and day-care attendance, with odds ratios >2.5 in at least one study (high SOE). Incidence rates for RSV hospitalizations ranged from 2.3% to 10% (low SOE). Length of hospital stays ranged from 3.8 to 6.1 days (low SOE). Recurrent wheezing rates ranged from 20.7% to 42.8% 1 to 2 years after RSV hospitalization (low SOE).

Conclusions: Young chronological age and some environmental risk factors are important clinical indicators of an increased risk of RSV hospitalization in healthy preterm infants 32 to 35 weeks of gestational age. SOE was low for estimates of incidence of RSV hospitalizations, in-hospital resource use and recurrent wheezing in this population. Studies were inconsistent in study characteristics, including weeks of gestational age, age during RSV season and control for confounding factors.

Key Words: preterm infants, risk factors, respiratory syncytial virus, hospitalization, infectious disease

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Respiratory syncytial virus (RSV) infection is an important cause of childhood morbidity from acute lower respiratory tract infections worldwide. An estimated 33.8 million new

episodes occur in children under 5 years of age, and 3.4 million RSV episodes require hospital admission.¹ Mortality from RSV is rare in developed countries.¹ Chronological age is the main risk factor for RSV hospitalization in term infants; most hospitalized episodes occur in infants under 1 year of age, with incidence rates of hospitalization decreasing during the first year of life.² Degrees of prematurity, chronic lung disease and some forms of congenital heart disease are generally considered additional risk factors; they may characterize subsets of children at heightened risk for RSV hospitalization.^{3,4}

Currently, no vaccine is available to prevent RSV infection in infants. In 1998, the US Food and Drug Administration approved immunoprophylaxis with the monoclonal antibody palivizumab to prevent RSV infection. The US Food and Drug Administration specified the indication “for the prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease.”⁵ Since the approval of palivizumab, the American Academy of Pediatrics (AAP) has produced several clinical practice guidelines for its use, focusing on subgroups of children who are at high risk of RSV infection.

In 2014, the AAP issued an updated guidance on palivizumab prophylaxis in high-risk infants and young children.^{3,4} In this guidance, the AAP Committee on Infectious Diseases and Bronchiolitis and the Guidelines Committee concluded, based on their literature review, that preterm infants born at 29 to 35 weeks of gestational age (WGA) without chronic lung disease, hemodynamically significant congenital heart disease or other coexisting conditions have only a small risk (<5%) of RSV hospitalization. The guideline recommended that this subpopulation of premature infants not be offered palivizumab prophylaxis.

Two additional reviews presented estimates of the risk of RSV hospitalization in healthy preterm infants.^{6,7} Neither these recent reviews nor the AAP guidance document presented their study selection criteria or assessed study characteristics or risk of bias. We have performed a systematic review and qualitative synthesis of the published evidence to elucidate further the risk of RSV hospitalization and its outcomes in healthy preterm infants born at 29 to 35 WGA.

METHODS

The target population for our review was preterm infants born at 29 to 35 WGA who did not receive RSV immunoprophylaxis and who did not have chronic lung disease or other major coexisting conditions (including hemodynamically significant congenital heart disease, anatomic pulmonary abnormalities, neuromuscular disorders, Down syndrome or cystic fibrosis).

We sought to answer the following 4 questions for the target population:

1. What are the risk factors for RSV hospitalization?
2. What is the incidence of RSV hospitalization?
3. What are the short-term outcomes during the RSV hospitalization?
4. What are the long-term outcomes after an RSV hospitalization?

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Short-term outcomes associated with RSV hospitalization include case fatality rate, length of hospital stay, intensive care unit (ICU) admission and length of stay and need for and duration of mechanical ventilation. Long-term outcomes after RSV hospitalization in infancy include childhood asthma and prolonged and recurrent wheezing up to 6 years of age.

Following a study protocol with prespecified search terms, an experienced research librarian conducted electronic searches to identify studies with publication dates from January 1, 1985, to the day of the search, November 6, 2014. We placed no limitations on publication language or geography. We searched the following electronic databases:

- MEDLINE and MEDLINE In-Process (using PubMed platform)
- Embase (using Elsevier Platform)
- BIOSIS (using Dialog platform)
- The Cochrane Library, including the following:

The Cochrane Central Register of Controlled Trials
The Cochrane Database of Systematic Reviews
Database of Abstracts of Reviews of Effectiveness.

We screened publications for inclusion based on prespecified inclusion/exclusion criteria, summarized in Table 1. Senior members of the research team responsible for the title/abstract (level 1) and full-text (level 2) screening included a pediatrician epidemiologist and a health economist. They also searched reference lists of selected studies in the level 2 screening, including all studies selected for data abstraction and recent systematic reviews and meta-analyses. Twenty-four articles were reviewed at level 2 in languages other than English. Disagreements were resolved by consensus or consultation with a third experienced researcher. We documented the inclusion and exclusion process using a spreadsheet, including completion of a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.⁸

One senior reviewer abstracted data from included studies into detailed evidence tables; a second researcher checked all abstractions against the original source. Data in evidence tables included information on study authors, year, country, funding source, infant population(s) studied, data source(s) used, study characteristics and key study endpoints presented. In addition to evidence tables, we prepared 4 summary tables presenting key information from the included studies for each research question and qualitatively synthesized study characteristics and results for each research question.

For each study, we assessed the risk of bias using an adapted version of the RTI Item Bank.⁹ We characterized the risk of bias of

each included study as low, medium or high based on the average score of the 11 items in the tool, defined as follows: 0 to <1.0 = high risk of bias; 1.0 to 1.5 = medium risk of bias; and 1.6 to 2.0 = low risk of bias.

We graded the strength of the body of evidence for each study question using the 5 domains recommended by the Agency for Healthcare Research and Quality Evidence-based Practice Center program¹⁰: study limitations, directness of evidence, consistency of evidence, precision of results and reporting bias. The 4 possible grades of evidence using the Agency for Healthcare Research and Quality approach are high, moderate, low and insufficient.

RESULTS

Of a total 4754 records, we included 454 studies for level 2 screening of full-text studies. After full-text review, we included 27 studies in our review (Fig. 1). Reasons for exclusion included data not presented for target population, RSV not laboratory confirmed or with diagnosis code, outcomes not relevant and study type.

Risk Factors for RSV Hospitalization

Six studies estimated risk factors for RSV hospitalization for the target population ($N = 557$ to 4761 infants; Table 2).^{11–16} Of these 6 studies, 5 were prospective cohort studies and 1 was a case-control study;¹¹ risk of bias was low in all 6 studies. All 6 studies estimated risk factors associated with RSV hospitalization in an infant's first RSV season and included only preterm infants born between 32 or 33 and 35 WGA; thus, they did not provide any information for infants born between 29 and 32 WGA.

Risk factors examined in the different studies were similar but not identical. All studies that included age showed that young chronological age at the start of or during the RSV season or birth month were statistically significant predictors of RSV hospitalization (odds ratios [OR] = 2.60–4.88). The presence of siblings of preschool or school age was also a significant predictor of RSV hospitalization (ORs = 1.91–2.85). Other family and environment factors that significantly increased the risk of RSV hospitalization in at least 1 study included infant day-care attendance, exposure to smoking, duration of breastfeeding, small for gestational age and family history of wheezing, atopy or eczema. The results were generally consistent even though the studies spanned 10 years, included data from 4 countries and used varying RSV testing strategies.

The strength of evidence (SOE) was high for those in the target population with WGA 32 to 35 for most of the risk factors in the analyses. Risk factors with the most impact on the risk of RSV hospitalization (OR > 2.0 in at least 1 study) were young chronological age during the RSV season, having school-age siblings, day-care attendance, breastfeeding less than 2 months and small for gestational age.

Incidence of RSV Hospitalization

Ten studies presented estimates of the incidence of RSV hospitalization in our target population ($N = 182$ to 5184); incidence ranged from 2.3% to 10.0% (Table 3).^{12,16–24} Two studies were randomized controlled trials, 2 were prospective cohort studies and 6 were retrospective cohort studies. Studies covered from 1 to 10 RSV seasons. Risk of bias was low in 6 studies and medium in 4 studies.

Study characteristics differed substantially among these 10 studies. Differences included range of WGA in infants who otherwise met our inclusion criteria, duration and timing of the observation period, age of the infant during the observed RSV season and ascertainment rates for RSV hospitalizations. We examined the extent to which these study characteristics affected the study results.

We found no consistent relationships in these studies between WGA range and estimated incidence of RSV hospitalizations.

TABLE 1. Summary of Study Inclusion Criteria

Study (observational or randomized trial) presents information on preterm infants who did not receive RSV immunoprophylaxis and who did not have chronic lung disease or other major coexisting conditions. These infants can be the focus of the study or a subset of the study population.
Studies in infants born at 33 to 36 WGA can be included when they do not mention chronic lung disease, major coexisting conditions or RSV immunoprophylaxis because the likelihood of these is low.
Studies that report the prevalence of chronic lung disease, other major coexisting conditions or RSV immunoprophylaxis in infants born at 29 to 36 WGA can be included if prevalence $\leq 2\%$ for each factor.
Study presents information on outcomes to respond one or more of our study questions in a full-length research article.
Study defines RSV hospitalization through RSV-specific codes in the data source (eg, hospital discharge records) or through laboratory-based confirmation.

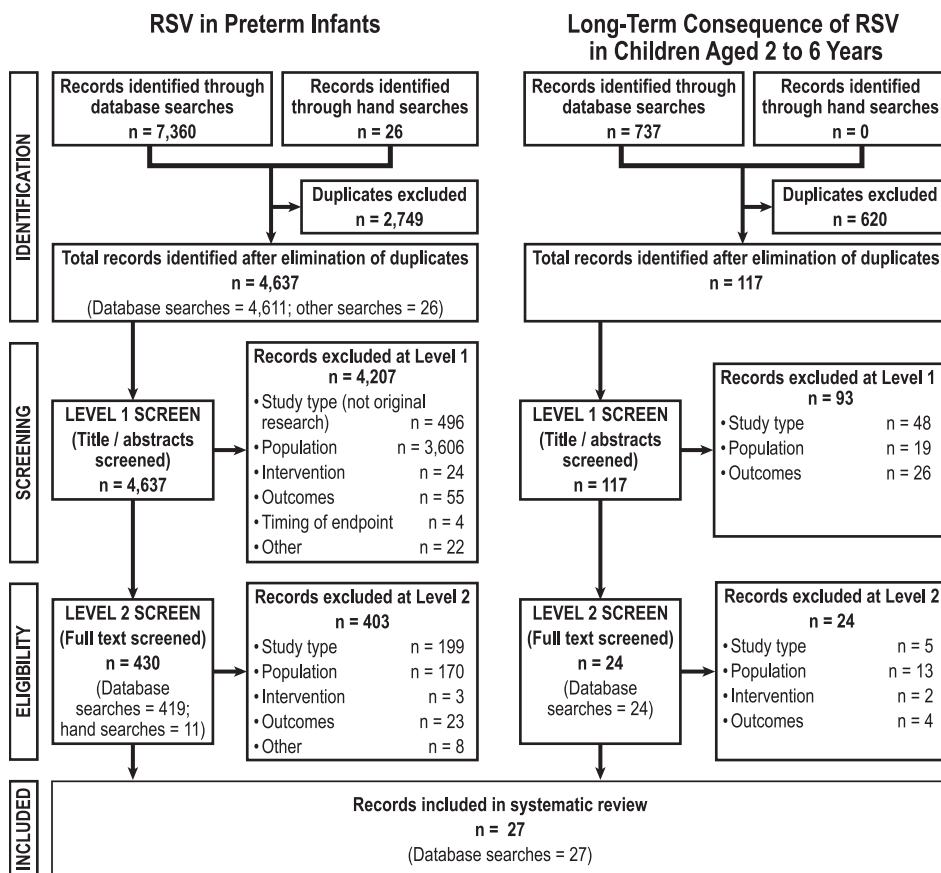


FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram

Thus, the 6 studies presenting incidence rates for infants born between 32/33 and 35/36 WGA^{12,16,18,20,22,24} estimated incidence of RSV hospitalizations ranging from 3.2% to 6.6%; incidence rates in the 2 studies that presented estimates for all preterm infants with ≤ 35 or < 36 WGA^{17,18} ranged from 2.3% to 8.1%; and incidence rates in the 5 studies that presented estimates for those with < 33 WGA^{18,19,21,23,24} ranged from 4.2% to 10.0%.

We saw no consistent relationship between estimated incidence of RSV hospitalizations and duration and timing of the observation period for RSV for each infant. Some studies estimated the incidence of RSV hospitalizations for the first year of life (5.1%–10.0%)^{19,22} or the first 2 years of life (4.8%–9.7%).²⁴ Others estimated incidence of RSV hospitalizations in the first complete RSV season after birth (2.3%–8.1%)^{17,18,23} or in infants born either before or during a single RSV season (2.3%–6.6%)^{16,18,20,21} or only in those born during an RSV season (3.6%).¹²

Chronological age of preterm infants has been associated with risk of RSV hospitalization.^{11–16} Ages of infants during the observation period in these 10 studies ranged from born during the observation period to up to 2 years. Only 1 study presented estimates for infants with different chronological ages during the observed RSV season. Joffe et al¹⁸ estimated the lowest overall incidence of RSV hospitalization (2.3%); they included estimates for all infants born up to 1 year before the RSV season, during which the infants were observed. However, only 28.1% of these infants were less than 3 months of age at the beginning of the observed RSV season; for these infants, estimated RSV hospitalization rates were 3.2% (33–36 WGA) and 8.0% (23–32 WGA).

More complete ascertainment of RSV infections was not consistently related to higher incidence of hospitalization. One study

conducted RSV testing for all infants hospitalized with a respiratory tract infection¹⁹; 3 studies conducted RSV testing in $> 90\%$ of potentially eligible hospitalizations.^{16–18} Nevertheless, in these 4 studies, incidence rates ranged from 2.3% to 10.0%. Two studies tested for RSV at the physician's discretion in 60%–80% of potentially eligible hospitalizations,^{12,23} and another study had parents take and send samples to the laboratory, resulting in testing of only 27% of inpatient and outpatient respiratory episodes.²² In these 3 studies, the incidence rates for hospitalization ranged from 3.6% to 6.4%.

Most studies reported rates in which the numerator included only the tested RSV-positive or RSV-coded hospitalizations, and the denominator included all infants in the study. RSV hospitalization rates may be underestimated in such studies if not all infants hospitalized with respiratory tract infections were tested. One study conducted sensitivity analyses to explore the impact of having tested only 80% of potentially eligible hospitalizations.²³ For infants born at 28–32 WGA, hospitalization rates varied from 6.4% (numerator included only RSV-positive cases among those tested) to 9.6% (assuming all non-RSV-tested cases were RSV-positive).

Because hospitalization rates might vary according to the risk of bias as well as in studies across countries because of different treatment patterns, and over time, we looked at the rates in subgroups of our identified studies. Among the 7 studies with a low risk of bias,^{12,16–18,20,22,24} the hospitalization rates ranged between 2.3% and 9.7%. In the 6 US studies,^{16–21} the hospitalization rates ranged between 2.3% and 10.0%. Similarly, looking only at studies published since 2010, the rates ranged between 3.5% and 9.7%. For all the different subgroups, however, the included studies had different characteristics; moreover, for the studies with low risk of bias and for the US studies, publication dates ranged from 1998 to 2014.

TABLE 2. Significant Risk Factors for RSV Hospitalization in Target Population

Reference, Country, Funding Source	Study Design, RSV Seasons, ROB Score,* Number of Preterm Infants in Target Population	Significant Risk Factors	Odds Ratio or Case vs. Control or Hazard Ratio	95% Confidence Interval or P Value
Figueras-Aloy et al., ¹¹ Spain, Abbott	Case control, 2002–2003, ROB score 1.9, N = 557 (33–35 WGA): 186 hospital cases; 371 nonhospital controls	Age at start of RSV season <10 weeks	OR: 3.95	95% CI: 2.65, 5.90
		Breastfeeding ≤2 months	OR: 3.26	95% CI: 1.96, 5.42
		School-age siblings	OR: 2.85	95% CI: 1.88, 4.33
		Other residents ≥4	OR: 1.91	95% CI: 1.19, 3.07
		Family history of wheezing	OR: 1.90	95% CI: 1.19, 3.01
Law et al., ¹² Canada, Abbott	Prospective cohort, 2000–2002, ROB score 2.0, N = 1758 (33–35 WGA): 66 hospital cases; 1692 nonhospital controls	Born November, December, January	OR: 4.88	95% CI: 2.57, 9.29
		Male sex	OR: 1.91	95% CI: 1.10, 3.31
		Small for gestational age	OR: 2.19	95% CI: 1.14, 4.22
		Subject attending day care	OR: 12.32	95% CI: 2.56, 59.34
		Any preschool-age siblings	OR: 2.76	95% CI: 1.51, 5.03
		Eczema in first-degree relative	OR: 0.42	95% CI: 0.18, 0.996
		Age <0 weeks at start of RSV season or born during first 10 weeks of RSV season	OR: 2.95	95% CI: 2.19, 3.97
		Sibling in school or day care	OR: 2.07	95% CI: 1.54, 2.79
Carbonell et al., ¹⁴ Spain, No statement on funding source	Prospective cohort, 2005–2007, ROB score 1.6, N = 4756 (32–35 WGA): 190 hospital cases; 4566 nonhospital controls	Mother smoking during pregnancy	OR: 1.50	95% CI: 1.06, 2.11
		Male sex	OR: 1.36	95% CI: 1.01, 1.84
		Male sex	CvC: 60.5% vs. 53.2%	P = 0.049
		Birth month (mode)	CvC: Nov vs. Apr	P < 0.001
		Smoking while pregnant	CvC: 24.7% vs. 16.9%	P = 0.005
		Number of siblings at school (median)	CvC: 1 vs. 0	P < 0.001
		Number of smokers in household (median)	CvC: 0 vs. 0	P = 0.015
Blanken et al., ¹⁵ The Netherlands, Abbott	Prospective cohort, 2008–2011, ROB score 1.6, N = 2421 (32 to <36 WGA): 129 hospital cases; 2292 nonhospital controls	Breastfeeding duration (mean)	CvC: 1.5 vs. 1.8 months	P = 0.043
		Born August 14 to December 1	OR: 2.6	95% CI: 1.6, 4.2
		Siblings or planned day care	OR: 4.7	95% CI: 1.7, 13.1
		Planned breastfeeding ≤2 months	OR: 1.7	95% CI: 1.0, 2.7
		Atopy in first-degree family member	OR: 1.9	95% CI: 1.1, 3.2
Ambrose et al., ¹⁶ United States, Medimmune	Prospective cohort, 2009–2011, ROB score 1.9, N = 1642 (< 36 WGA): 57 hospital cases; 1585 nonhospital controls	Preschool-age non–multiple-birth siblings	HR: 1.91	P = 0.016
		Age at RSV infection (<3 vs. ≥6 months)	HR: 2.82	P = 0.004
		Exposed to smoking	HR: 1.98	P = 0.022
		Multiple birth	HR: 0.48	P = 0.043

*Average score over 11 questions, where 0 indicates maximum risk of bias and 2 indicates no risk of bias for each question; risk of bias characterized as low (1.6–2.0), medium (1.0–1.5) and high (0–0.9).

CI indicates confidence interval; CvC, case vs. control; HR, hazard ratio; OR, odds ratio; ROB, risk of bias.

Based on our review, the SOE for incidence of RSV hospitalization in the target population is low. Estimates are inconsistent and not clearly related to variability in study characteristics, including the WGA group ranges included, duration of observation, age during the observation period, RSV ascertainment method and study country and publication date.

Short-Term Outcomes During RSV Hospitalization

Eleven studies presented estimates of the short-term outcomes during an RSV hospital stay in the target population (N = 28 to 378 infants; Table 4).^{19,20,23,25–32} Of these, 1 was a prospective survey, 1 was a prospective cohort study and 9 were retrospective cohort studies. The number of RSV seasons studied ranged from 1 to 4. The studies included different ranges of WGA in infants who otherwise met our inclusion criteria. Risk of bias was low in 6 studies and medium in 5 studies.

Outcomes included case fatality rate in the hospital and hospital service use; the latter covered total length of stay, percentage with care in the ICU, mean length of stay in the ICU, percentage on mechanical ventilation and mean duration on mechanical ventilation. The need for ICU care and mechanical ventilation are particularly important outcomes because they are indicators of more severe disease.

The estimated in-hospital mortality rate for all healthy infants <36 WGA ranged from 0% to 2.9% in 3 studies (published between 1992 and 2000), with a range of 0.95% to 2.9% in the

2 studies with a low risk of bias.^{27,29,30} Moler et al.,²⁸ in a study with low risk of bias, included only infants requiring mechanical ventilation enrolled in a clinical trial of ribavirin; they reported a mortality rate of 1.7% for healthy preterm infants whether or not they were treated with ribavirin.

Of these 11 studies, 10 estimated length of stay in the hospital for the target population. In the 6 studies with a low risk of bias,^{20,26,28–31} the mean length of stay for all infants ranged from 3.75 to 6.1 days; for those requiring mechanical ventilation, the mean length of stay was 12.7 days.²⁸ Six studies included US patients. Five of these studies estimated a mean length of stay for all infants ranging between 3.75 and 6.1 days^{19,20,25,26,30}; the sixth study estimated a mean length of stay of 12.7 days for those requiring mechanical ventilation.²⁸ Two Canadian studies estimated a median length of stay of 7.0 and 5.0 days for all infants.^{27,29} Studies in France²³ and Tunisia³² estimated a mean length of stay of 7.2 and 9.1 days, respectively. In a subgroup analysis, Stevens et al.¹⁹ showed a longer length of stay for those between 30 and 32 WGA than for those between 28 and 30 WGA.

The percentage of healthy preterm infants admitted to the ICU ranged from 13.3% to 60.7% in the 7 studies reporting this outcome.^{19,23,25–27,30,32} In the 2 studies with a low risk of bias,^{26,30} the percentage admitted to the ICU ranged from 12.6% to 38%; both studies were more than 10 years old but included infants with similar WGA. Four studies included US patients. Of these studies, 3

TABLE 3. Incidence of RSV Hospitalization in Target Population

Reference, Country, Funding Source	Study Design, RSV Seasons, ROB Score,* Number of Preterm Infants in Target Population	RSV Ascertainment	Age at Start of RSV Season; Duration of Follow-up	Incidence of RSV Hospitalization
Impact Study Group, ¹⁷ US, UK, Canada, MedImmune	Randomized clinical trial, 1996–1997, ROB score: 2.0, N = 234 (≤35 WGA)	>99% laboratory tested	<6 months at start of RSV season; 150 days follow-up in first season	≤35 WGA 8.1%
Joffe et al., ¹⁸ US, Kaiser Foundation	Retrospective cohort, 1992–1996, Predicted values for age at start of RSV season, ROB score: 1.8, N = 1597 (23–36 WGA)	91% laboratory tested at physician discretion	28.1% <3 months at start of RSV season; 71.9% 3 months to 1 year at start of RSV season; Data for first complete season	23–36 WGA 2.3% <3 months at start of RSV season: 23–32 WGA 8.0%; 33–36 WGA 3.2% >3 months at start of RSV season: 23–32 WGA 3.1%; 33–36 WGA 1.2%
Stevens et al., ¹⁹ US, No statement on funding source	Retrospective cohort, 1992–1996, ROB score: 1.5, N = 898 (≤32 WGA)	100% laboratory tested	Age at start of RSV season not stated; Data up to 1 year after 40 weeks' conceptual age	>28–30 WGA 10% >30–32 WGA 6.4%
Law et al., ¹² Canada, Abbott	Prospective cohort, 2000–2002, ROB score: 2.0, N = 1,832 (33–35 WGA)	69% laboratory tested at physician discretion	Born during RSV season; 48.7% born early in season (November, December, January); Data for first RSV season	33–35 WGA 3.6%
Wegner et al., ²⁰ US, Access Care	Retrospective cohort, 2002–2003, ROB score: 1.9, N = 182 (32–35 WGA)	% tested not stated; Included either laboratory tested or RSV diagnosis code	<6 months at start of RSV season or born during RSV season; Data for first RSV season	32–35 WGA 6.6%
Hampp et al., ²¹ US, Florida Agency for Health Care Administration	Retrospective cohort, 2004–2005, ROB score 1.5, N = not stated (≤32 WGA)	Included if RSV diagnosis codes	<6 months each month during RSV season	≤32 WGA 4.2%
Blanken et al., ²² The Netherlands, Abbott + NOW-AGIKO	Randomized clinical trial, 2008–2010, ROB score: 2.0, N = 215 (33–35 WGA)	27% laboratory tested using sample taken by parents	<6 months at start of RSV season; Data for first year of life	33–35 WGA 5.1%
Gouyon et al., ²³ France, Abbott	Retrospective cohort, 2008–2009, ROB score: 1.3, N = 249 (< 33 WGA)	80% laboratory tested at physician discretion	<6 months at start of RSV season or born during RSV season; Mean age 2.8 months at start of RSV season; Data for first complete RSV season	28–32 WGA 6.4%
Ambrose et al., ¹⁶ US, MedImmune	Prospective cohort, 2009–2011, ROB score: 1.9, N = 1,646 (32–35 WGA)	95% laboratory tested	42% <3 months at start of RSV season; 58% 3 months to 6 months at start of RSV season; Data from first season	32–35 WGA 3.5%
Hsu et al., ²⁴ Taiwan, No support received	Retrospective cohort, 2000–2010, ROB score: 2.0, N = 5,184 (≤ 36 WGA)	100% laboratory tested	Age during RSV season ≤24 months	29–32 WGA 9.7% 33–36 WGA 4.8%

*Average score over 11 questions, where 0 indicates maximum risk of bias and 2 indicates no risk of bias for each question; risk of bias characterized as low (1.6–2.0), medium (1.0–1.5) and high (0–0.9).

ROB indicates risk of bias; UK, United Kingdom; US, United States; and WGA, weeks of gestational age.

included all preterm infants,^{25,26,30} and the estimated percentages admitted to the ICU ranged from 12.6% to 38%. Stevens et al¹⁹ included only infants with ≤32 WGA; they estimated ICU admissions to be 13.3% for those with 28–30 WGA and 26.3% for those with 30–32 WGA. One Canadian study (medium risk of bias) estimated that 33.6% of preterm infants with ≤36 WGA were admitted to the ICU.²⁷ A US study by Wegner et al²⁰ (low risk of bias) estimated mean ICU stay of 1.08 days for all hospitalized infants with 32–35 WGA. This length of stay in the ICU is similar to the estimate by Meert et al²⁵ (medium risk of bias) of 0.9 days for infants with ≤37 WGA.

Dougherty and Meissner³⁰ (low risk of bias) estimated a mean ICU length of stay of 7 days for infants with ICU admissions; Moler et al²⁸ (low risk of bias) estimated a mean length of stay of 8.2 days for those admitted to the ICU and requiring mechanical ventilation.

The percentage of all healthy preterm infants hospitalized who required mechanical ventilation ranged from 11.8% to 24.0% in the 2 studies with low risk of bias^{26,30} and in the 3 US studies^{25,26,30} and the 1 Canadian study²⁷ that presented these estimates. One other

study with low risk of bias estimated a 33% mechanical ventilation rate in preterm infants with 29–32 WGA admitted to the pediatric ICU in Israel.³¹ Meert et al²⁵ (medium risk of bias) estimated a mean duration of 0.7 days of mechanical ventilation for all hospitalized infants; Dougherty and Meissner³⁰ and Moler et al²⁸ estimated means of 10 and 6.3 days, respectively, for those requiring mechanical ventilation.

The SOE for short-term outcomes of RSV hospitalization in the target population is low. Five of the studies had a medium risk of bias. Moreover, estimates across the studies were inconsistent overall and for the risk of bias or country-specific subgroups analyzed. In addition, 9 of the studies were published before 2005 and so do not capture any recent changes in treatment patterns.

Long-Term Outcomes After RSV Hospitalization

Five studies^{33–37} presented estimates of the long-term outcomes after an RSV hospitalization in our target population (N = 14 to 408 hospitalized for RSV; N = 154 to 20,250 infants not hospitalized for RSV; Table 5). Two studies were prospective cohort studies;

TABLE 4. Short-Term Outcomes During RSV Hospitalization in the Target Population

Reference, Country, Funding Source	Study Design, RSV Seasons, ROB Score,* Number of Preterm Infants in Target Population	RSV Hospital Resource Type	Use of Resource in Target Population
Meert et al., ²⁵ US, No statement on funding source	Retrospective cohort, 1985–1988, ROB score: 1.4, N = 56 (≤ 37 WGA)	Mean hospital LOS	5.7 days
		% in intensive care	21.8%
		Mean ICU days [†]	0.9 days
		% on MV	20%
		Mean MV days [†]	0.7 days
		% O ₂ supplementation	43.6%
		Mean O ₂ days [†]	2.3 days
		% on NPO	21.8%
		Mean NPO days [†]	0.7 days
		Mean PSI	6.5
Mean TISS	8.2		
Meert et al., ²⁶ US, No statement on funding source	Retrospective cohort, 1985–1989, ROB score: 2.0, N = 132 (mean 33.6 WGA)	Mean hospital LOS	5.4 days
		% in intensive care	12.6%
		% on MV	11.8%
		% O ₂ supplementation	39.4%
		% on NPO	17.3%
		Mean PSI	6.4
		Mean TISS	7.4
		% Mortality	0%
		Median hospital LOS	7.0 days
		% in intensive care	33.6%
% on MV	15.6%		
Median MV days [‡]	4.0 days		
% O ₂ supplementation	78.8%		
Median O ₂ days [‡]	5.0 days		
% Mortality	1.7%		
Moler et al., ²⁸ US and Canada, Society of Critical Care Medicine	Prospective cohort, Not reported, ROB score: 1.8, N = 116 (≤ 36 WGA requiring MV–no ribavirin)	Mean hospital LOS	12.7 days
		Mean ICU days [§]	8.2 days
		Mean MV days [§]	6.3 days
		% Mortality [¶]	0.95%
Law et al., ²⁹ Canada, American Cyanamid/Lederle Praxis Biologics Inc	Retrospective cohort, 1993–1994, ROB score: 1.7, N = 161 not ventilated and no ribavirin (18 ventilated and no ribavirin) (< 36 WGA)	Median hospital LOS ^{¶¶}	5 days (11.5 days)
		Median ICU days ^{¶¶}	0 days (7.0 days)
		Median MV days ^{¶¶}	0 days (6.0 days)
		Median hypoxia days ^{¶¶}	1 day (7.5 days)
		% Mortality	2.9%
Dougherty and Meissner, ³⁰ US, No statement on funding source	Retrospective cohort, 1994–1997, ROB score: 1.7, N = 34 (≤ 35 WGA)	Mean hospital LOS	6.1 days
		% in intensive care	38%
		Mean ICU days [‡]	7.0 days
		% on MV	24%
		Mean MV days [‡]	10.0 days
		Mean hospital LOS	>28–30 WGA 4.0 days; >30–32 WGA 5.1 days
		% in intensive care	>28–30 WGA 13.3%; >30–32 WGA 26.3%
Stevens et al., ¹⁹ US, No statement on funding source	Retrospective cohort, 1992–1996, ROB score: 1.5, N = 78 (≤ 32 WGA)	Infants in PICU needing MV (%)	33.3%
Prais et al., ³¹ Israel, No statement on funding source	Prospective survey, 2000–2001, ROB score: 1.6, N = 32 (≤ 32 WGA)		
Wegner et al., ²⁰ US, Access Care	Retrospective cohort, 2002–2003, ROB score: 1.9, N = 182 (32–35 WGA)	Mean hospital LOS	3.75 days
		Mean ICU days [†]	1.08 days
Fodha et al., ³² Tunisia, No statement on funding source	Retrospective cohort, Not stated, ROB score: 1.3, N = 28 (< 37 WGA)	Mean hospital LOS	9.1 days
		% Hospital LOS >7 days	67.9%
		% ICU or MV	60.7%
Gouyon et al., ²³ France, Abbott	Retrospective cohort, 2008–2009, ROB score: 1.3, N = 249 (< 33 WGA)	Mean hospital LOS	7.2 days
		% in intensive care	5.9%

*Average score over 11 questions, where 0 indicates maximum risk of bias and 2 indicates no risk of bias for each question; risk of bias characterized as low (1.6–2.0), medium (1.0–1.5) and high (0–0.9).

[†]Calculated using all hospitalized as denominator.

[‡]Calculated using those using the service as denominator.

[§]Calculated using those on mechanical ventilation as denominator.

[¶]Presented separately for those not using mechanical ventilation and those using mechanical ventilation.

LOS indicates length of stay; MV, mechanical ventilation; NPO, nothing by mouth; PICU, pediatric intensive care unit; PSI, Physiologic Stability Index; ROB, risk of bias; TISS, Therapeutic Intervention Score; and US, United States.

TABLE 5. Long-Term Outcomes After RSV Hospitalization in Target Population

Reference, Country, Funding Source	Study Design, ROB Score,* Number of Preterm Infants in Target Population	Duration of Follow-up	Long-Term Outcome Measures	Long-Term Outcomes With or Without RSV Hospitalization
Sampalis, ³³ Canada, JSS Medical Research Inc	Retrospective cohort, 1997–2001, ROB score: 1.2, N = 152 (<36 WGA) with RSV hospitalization; 20,254 without	2.1 years follow-up after RSV hospitalization	Mean hospital stays Mean special care visits Mean respiratory therapy visits Mean physician consults Mean procedures Mean hospital days Mean outpatient department visits	With: 2.89; Without: 1.28 With: 1.41; Without: 0.40 With: 0.38; Without: 0.13 With: 4.77; Without: 0.89 With: 2.06; Without: 0.81 With: 22.0; Without: 5.04 With: 16.4; Without: 7.54
Simoes et al., ³⁴ Spain, Germany, the Netherlands, Canada, Poland, and Sweden; Abbott	Prospective cohort, 2001–2004, ROB score: 1.3, N = 76 (24–35 WGA) with RSV hospitalization in first 12 months of life; 154 without	2 years follow-up after enrollment (mean age at enrollment 18–20 months)	% with recurrent wheezing % with physician-diagnosed recurrent wheezing	With: 31.6%; Without: 23.0% With: 17.1%; Without: 16.0%
Palmer et al., ³⁵ US, MedImmune	Retrospective cohort, 2003–2006, ROB score: 1.4, N = 408 (33–36 WGA) with RSV hospitalization; 1804 without	1 year follow-up after index RSV hospitalization	% with wheezing % with asthma % with any respiratory procedure	With: 24.6%; Without: 6.5% With: 36.7%; Without: 7.5% With: 87.6%; Without: 35.5%
Palmer et al., ³⁶ US, MedImmune	Retrospective cohort, 2003–2007, ROB score: 1.6, N = 88 (33–36 WGA) with RSV hospitalization; 1870 without	1 year follow-up after index RSV hospitalization	% with wheezing % with asthma % with any respiratory procedure No. of inpatient admissions No. of ED visits No. of office visits	With: 20.7%; Without: 4.1% With: 27.5%; Without: 3.8% With: 71.7%; Without: 28.5% With: 1.3; Without: 0.1 With: 1.7; Without: 0.5 With: 12.0; Without: 6.9
Fauroux et al., ³⁷ France, AbbVie	Prospective cohort, 2009–2010, ROB score: 1.3, N = 14 (<33 WGA) with RSV hospitalization; 242 without	1 year follow-up after first RSV season	≥1 wheezing episode ≥1 episode of nonspecific morbidity	With: 42.8%; Without: 10.6% With: 78.6%; Without: 23.7%

*Average score over 11 questions, where 0 indicates maximum risk of bias and 2 indicates no risk of bias for each question; risk of bias characterized as low (1.6–2.0), medium (1.0–1.5) and high (0–0.9).

ED indicates emergency department; ROB, risk of bias; UK, United Kingdom; and US, United States.

3 were retrospective cohort studies. Follow-up after the index RSV hospitalization ranged from 1 year to a mean of 2.1 years. Risk of bias was low in 1 study³⁶ and medium in 4 studies.^{33,35,37} Outcomes estimated in these studies included recurrent wheezing, asthma, respiratory procedures and health care service use.

Four studies with 1 to 2 years' follow-up^{33–35,37} estimated higher rates of clinical outcomes for the healthy preterm infants with an RSV hospitalization than for those without such a hospitalization. Wheezing rates ranged from 20.7% to 42.8% for the target population with an RSV hospitalization and from 4.1% to 23.0% for those without an RSV hospitalization. In the study with a low risk of bias, the wheezing rate was 20.7% for those with an RSV hospitalization and 4.1% for those without a hospitalization. In addition, Sampalis³³ (medium risk of bias) followed preterm infants with 32 to <36 WGA for a mean time of 2.1 years after RSV hospitalization; rates of use of respiratory-related health care services were higher for this group than for a matched population of healthy preterm infants without a proven or probable RSV hospitalization.

The SOE for long-term outcomes of RSV hospitalization in the target population is low. Four of the 5 studies had a medium risk of bias. Moreover, no study controlled for confounding factors that might be correlated with both risk of RSV hospitalization and recurrent wheezing and childhood asthma.

DISCUSSION

The results of our systematic review clarify the strength of the published evidence for the risk of RSV hospitalization and its

consequences in preterm infants born between 29 and 35 WGA who do not have chronic lung disease or other major coexisting conditions and who did not receive RSV immunoprophylaxis (the target population). We found that strong evidence exists for the risk factors associated with hospitalization for RSV. However, estimates of the magnitude of the incidence rates of hospitalization and the short- and long-term outcomes from hospitalization are inconsistent or inadequately controlled.

With respect to the risk of RSV hospitalization in our target population, 6 studies were relatively homogeneous in the gestational ages and risk factors investigated. More important for clinicians and parents, they suggested that factors with the most impact (OR >2.0 in at least 1 study) are young chronological age during the RSV season, having school-age siblings, day-care attendance, breastfeeding less than 2 months and small for gestational age (all high SOE). These are the most definitive findings from our study; they should provide practitioners and others with important indicators of risk of RSV hospitalization in healthy preterm infants.

We identified 10 studies that estimated the incidence of RSV hospitalization and 11 that estimated short-term outcomes of these hospitalizations. Estimates in these studies were inconsistent even when only considering studies with a low risk of bias (low SOE). Inconsistency in the results might be explained partially by differences in study characteristics. For example, studies estimating the incidence of RSV in the target population included infants with different WGA ranges, different ages and lengths of follow-up during the observed RSV season, and different rates of ascertainment of

RSV infection. In addition, the date of the study might influence hospitalization rates or short-term outcomes because of changes in practice patterns. For example, changes in the recommendations for the use of continuous pulse oximetry in hospitalized infants in the AAP bronchiolitis guidelines might influence length of stay in the hospital for RSV hospitalizations for all infants in the United States.³⁸

We identified 5 studies that reported long-term impacts of RSV hospitalizations. None of these studies controlled for potential confounders such as family history, underlying pulmonary physiology and environmental factors. Other studies have shown that these factors all increase the risk of both an RSV hospitalization and recurrent wheezing.^{39,40}

Three recent reviews summarize RSV hospitalization rates for our target population.^{4,6,7} Although we identified all the studies in these reviews and reviewed the full-text articles, we ultimately excluded many because they did not meet our eligibility criteria. For instance, they did not require laboratory confirmation of RSV, included infants with chronic lung disease or other major coexisting conditions (or did not explicitly exclude them), and included infants who were given immunoprophylaxis.^{2,41–57} In addition, several articles in our review^{14,16–18,20–24} were not included in at least one of the published reviews. Despite these differences, the ranges of estimated incidence rates for RSV hospitalization in the target population in the 3 reviews were similar to those that we reported.

Our study was not designed to compare outcomes between our target population and other infant subgroups. However, many studies in our review presented data for other infant subgroups. These studies generally showed that the incidence of RSV hospitalization in the target population was higher than for those receiving immunoprophylaxis or for term infants but lower than for preterm infants with chronic lung disease or congenital heart disease. A recent large US study published after the date of our searches⁵⁸ has also shown higher hospitalization rates for healthy preterm infants 33–36 WGA than for healthy term infants.

In studies looking at short-term outcomes, the target population tended to use more hospital resources than healthy term infants. The Helfrich et al⁵⁸ study also showed longer hospital length of stay and greater need for respiratory support for healthy preterm infants 33–36 WGA than for healthy term infants. Our included studies showed fewer hospital resources for those in our target population hospitalized with RSV than for those with chronic lung disease or congenital heart disease in most cases; however, these results were not seen in all studies. In particular, 2 studies estimated higher ICU use for the target population than for either infants with chronic lung disease¹⁹ or those with bronchopulmonary dysplasia.³⁰ Finally, for infants with RSV hospitalizations, rates of long-term wheezing for those in the target population were similar to rates for term infants in one study.³⁵

Our included studies varied widely in their characteristics, particularly in the WGA range for the infants included in the study and the calendar age of the infants during their first RSV season. Risk-factor studies clearly demonstrated that calendar age during the first RSV season and other risk factors were significant predictors of hospitalization for RSV infection. Given this finding, we suggest that future studies to determine the incidence of hospitalizations in our target population focus on infants born less than 3 months before the RSV season or during the season, both with and without other risk factors. This will allow investigators to assess whether the incidence of hospitalization in these infants is high enough to consider prophylaxis. In addition, studies comparing wheezing rates for those with and without an RSV hospitalization should always control for other factors associated with long-term wheezing to ensure that differences in the 2 populations are accounted for in the analysis. Finally, we

would like to emphasize the importance of thorough reporting of all characteristics of the included population and analyses that allow the impact of different population characteristics to be determined for understanding the impact of RSV on our target population.

Strengths and Limitations of Our Review

We implemented a formal systematic review that followed rigorous and prespecified processes for library searches; screening of titles, abstracts and full-text articles; assessment of risk of bias; and grading of evidence. Our eligibility criteria were designed to include only studies with laboratory-confirmed RSV or an RSV diagnosis code (to avoid overestimating the incidence of RSV hospitalization), but we did include studies reflecting broad geographic locations. Our qualitative synthesis of results discussed key study characteristics and their relationship to study results.

The evidence base ultimately had several important drawbacks. All but 2 studies were observational studies and thus subject to issues of bias and confounding that affect observational research. Observational studies do reflect routine care in the general population more closely than randomized studies and so may be quite relevant for our research questions. In the studies presenting estimates of the incidence of RSV hospitalizations, ages of the preterm infants during the RSV season studied varied; ages ranged from “born during the RSV season” to 2 years. Some studies included only a subset of our target population (eg, infants born at 32–35 WGA), and some studies included all preterm infants who otherwise met our criteria (eg, <36 WGA). Studies used different definitions of chronic lung disease, coexisting conditions, risk factors and both short- and long-term outcomes; they also did not present information on disease severity, which can affect hospital length of stay and outcomes. Yet other limitations were the broad span of time covered (15 years), during which clinical practices might have changed, and small sample sizes (eg, fewer than 50 infants in the target population). All these differences made qualitative synthesis challenging.

Of the 27 studies we included, 44% reported receiving funding from industry, 7% from the government and 15% from other nonindustry sources or no funding; 33% did not specify funding source in the publication. In this particular field of inquiry, relatively few teams are conducting research; of these, many are funded by the manufacturer of palivizumab.

Conclusions

Evidence from our systematic literature review was limited for the target population: preterm infants born 29–35 WGA and without chronic lung disease, congenital heart disease or other significant comorbidity and not receiving immunoprophylaxis. Estimates of incidence of RSV hospitalization, in-hospital resource use and recurrent wheezing varied widely, possibly because of inconsistencies in study characteristics, especially the characteristics of the study population. This heterogeneity in the study populations and in the results severely limited our ability to draw clinical or policy conclusions for the target population for these outcomes. By contrast, studies that estimated risk factors for RSV hospitalizations included similar populations, and their results consistently indicated that young chronological age during the RSV season, having school-age siblings, day-care attendance, breastfeeding less than 2 months and small for gestational age are significant risk factors for RSV hospitalization. We regard these as important clinical indicators for practitioners caring for preterm infants.

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APPENDIX

Copies of the review protocol, reasons for study exclusion, details of quality and bias assessments and detailed extraction tables are available at www.rtihs.org/RSVsupplement.

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