Supplemental material

Supplement 1: Methods

Literature search

A search strategy (detailed search in **Supplement 2**) was developed in consultation with a federal reference librarian (LG) from the Health Library of Health Canada and the Public Health Agency of Canada to identify primary research studies of respiratory syncytial virus (RSV) burden. On September 6, 2018, electronic searches for literature were conducted in the following databases: Medline (via OVID), Embase, Cochrane Database of Clinical Trials, and ClinicalTrials.gov. Language (English or French) and date (January 1, 2014 to September 6, 2018) restrictions were applied. Grey literature from international public health authorities (e.g. World Health Organization, Pan American Health Organization, US Centers for Disease Control and Prevention, European Centre for Disease Prevention and Control, Australia, United Kingdom) were also searched.

Study selection and eligibility criteria

After exclusion of duplicates, level one screening (titles and abstracts) was performed independently by two of three reviewers (AS, DLM, SDB) for all retrieved citations against broad eligibility criteria using DistillerSR systematic review software (1). Discrepancies were resolved by discussion. The full texts of the studies selected for level two screening were each independently reviewed by two of three reviewers (AS, DLM, SDB) with discrepancies resolved via discussions. For unpublished conference abstracts, a search was made for subsequent publication and if found it was included. Abstracts alone were excluded due to insufficient data. Records from clinical trial registries were searched and none were found. Inclusion/exclusion criteria are detailed in **Supplement 3**.

Observational study designs were eligible for inclusion. Studies were conducted in high-income OECD countries. Children who did not receive prophylaxis and were diagnosed or hospitalized with RSV infection at up to 24 months of age were eligible. Studies that included children at greater chronological age during RSV infection/hospitalization were only included if data could be isolated for those at ≤24 months, with the exception of immunocompromised children (e.g. children with cancer, transplant recipients, sickle cell disease) for whom we did not impose age restrictions since these populations may have a higher burden of RSV disease regardless of age Studies that included <5% of the population with at least one dose of prophylaxis were eligible. When no information was provided on prophylaxis status, or children were not explicitly tested for RSV, we did not include these studies unless a reasonable assumption could be made upon consultation with the RSV clinical expert/lead that prophylaxis was unlikely (i.e. using additional/contextual information such as population cohort/date, local guidelines on palivizumab prophylaxis, and risk status). RSV infection must have been diagnosed or confirmed by laboratory testing, or a relevant international classification of disease (ICD)-code that required a positive laboratory test. Populations that included concurrent infections must report isolated data for RSV cases. Children without RSV infection were not eligible for outcomes of hospitalization (short-term outcomes); these were eligible as a comparator group for long-term outcomes.

Eligible studies included children (in one or more arms) with or without an identified risk condition: history of prematurity, chronic lung disease/bronchopulmonary dysplasia, congenital heart disease, cystic fibrosis, Down syndrome, identification as Inuit or other Indigenous group, remote geographical residence, cardiac/upper respiratory malformations/airway abnormalities/diaphragmatic hernia, chronic neuromuscular disease, immune-deficiencies/immunocompromised, or any other chronic medical condition.

Eligible studies must have reported on RSV-hospitalization, or at least one or more short-term or long-term outcomes. Short-term outcomes include hospital length of stay, intensive care unit (ICU) admission and length of stay, oxygen support and duration, mechanical ventilation therapy and duration, extracorporeal membrane oxygenation (ECMO) therapy and duration, and case fatality (death due to RSV). For short-term outcomes, at least 90% of the population must have a confirmed RSV infection. Short-term outcomes of any follow-up duration were eligible. Long-term outcomes included any wheeze, asthma, pulmonary function test results, cardiac function, or growth, as reported by study authors. All long-term outcomes must be reported for at least 50% of the population with RSV infection. Long-term outcomes of at least one-year follow-up were eligible.

The flow of screening and decisions were recorded in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Chart.

Methodological quality assessment

After piloting, one reviewer assessed the methodological quality or risk of bias of each included study, with verification by a second reviewer. Disagreements were resolved through discussion or third-reviewer consultation. Results for each study and across studies were reported by each domain. The risk of bias for each study were assessed on an outcome basis where needed, particularly when different outcomes are assumed to have different susceptibilities to bias; for example, subjective outcomes (e.g. hospital admission, parent-reported wheeze) are more prone to bias from non-blinding (to patient characteristics) than objective outcomes.

All cohort studies were appraised using a modified tool based on the Quality Assessment Tool for Observational Cohort and Cross-sectional Studies developed by the National Institutes of Health [NHLBI 2019], and the Quality In Prognosis Studies (QUIPS) tool (2). Comparison/control groups of interest are those related to population groups (i.e. with a risk condition), not interventions. Therefore, we considered a study to be a "controlled" study when it has one of our comparisons of interest. For studies investigating an intervention/treatment, we only included the non-treatment arm of the study; in such cases, the study design was considered an "uncontrolled" cohort. This tool assesses 19 items (research question, study population [3 items], recruitment and eligibility criteria [2 items], timeframe for outcome measurement, risk factor identification and measurement [5 items], outcomes measures and assessment [3 items], blinding of outcome assessors to exposure status, follow-up/missing data [2 items], and statistical analyses [e.g. adjustment for key confounders such as treatment]). Our assessment focused on the aspects relevant to our prognosis question rather than being (solely) led by the study design, particularly where the prognostic aspect may not have been the main or only focus of the study.

Case-control studies were planned to be appraised using a modified tool, based on the Newcastle-Ottawa Scale for case-control studies (3) and the QUIPS tool (2); however, we did not identify any case-control studies for inclusion.

See **Supplement 4** for quality assessment tools.

Data extraction

Additional studies that did not meet the inclusion criteria were excluded at data extraction (DLM, AW). One reviewer independently extracted data from each included study. Another reviewer verified (for accuracy and completeness) all results data as well as other important aspects of the studies (i.e. ascertainment of RSV and risk factors, classification of studies based on comparisons of interest). Disagreements were resolved through discussion or third-reviewer consultation.

Standardized extraction forms in Excel and Word (Microsoft 2016) were piloted and used for key data variables: population(s) including demographics and risk factor(s), exposure (RSV ascertainment), outcomes (definitions, follow-up duration and findings), setting, study design, and funding source. We extracted estimates of data points from graphs using Plot Digitizer software (4), when needed.

For dichotomous outcomes, we extracted the number of events and the number analysed in each eligible group, unless the authors only reported a relative measure (e.g. odds ratio) between two risk groups which we extracted in place of crude events. We extracted adjusted values whenever reported by study authors. For studies conducted in a hospital setting (100% RSV-hospitalized), all outcome data was extracted with respect to this population (e.g. number ICU admissions/number hospitalized for RSV). When the sample was community/population-based, the incidence of RSV-hospitalization was applicable (i.e. number hospitalized for RSV/number in population at risk being followed and other short-term outcomes were reported using the denominators of the total sample and the sample hospitalized for RSV. The risk ratio with its 95% confidence interval (95% CI) was used as the primary measure of association for all comparisons. For continuous outcomes, mean values for each time-point, and change scores, including standard deviations or measures of variability were extracted for each eligible study group. Mean difference (MD) was used for all comparisons between groups.

Single arms of case-control studies, which will not provide incidence or prevalence estimates, were not used.

When there were multiple publications associated with a study we considered the earliest report of the main (primary) outcome data to be the primary data source. We extracted data from the primary source first and then added outcome data reported in the secondary/associated publication(s) and data source(s). We referenced the primary source throughout the evidence report. We contacted authors of included studies via email, up to three contacts, for clarification of important missing outcome data.

Data transformation and analysis

Where required, standard deviations were computed from other statistics (e.g. standard errors, p-values), estimated from non-parametric summaries (e.g. inter-quartile ranges), or imputed when missing. Means were imputed from medians if needed. We planned to use time-to-event analyses (hazard ratios) to account for different lengths of follow-up, with potential for conversion to relative risk (RRs) for inclusion in meta-analysis when required and appropriate; however, there were insufficient studies reporting hazard ratios for pooling. We used individual patient data when available, and conducted our own analysis.

Where populations, outcomes, and analyses were considered sufficiently homogeneous, results across studies were pooled in a meta-analysis. For studies including premature infants, we

attempted to group populations into the following weeks of gestational age (wGA) categories: <29, 29–32, 33–35.

For analysis of risk-group comparisons, our primary interest was using data from studies that reported on two or more groups of children, either having different risk conditions or with versus without a risk condition (within-study/direct comparisons). For data on comparisons reported by more than one study, RRs were pooled using the DerSimonian Laird random effects model inverse variance method with Mantel-Haenszel weighting. Risk differences were used when rare or zero events appeared in at least one study group. We also made comparisons between risk groups reported by different studies (between-study/indirect comparisons). If combining data on single-group proportions from studies, we used the double-arc sine transformation to pool the proportions. Single-group means from studies were pooled using the exact weighted average. To estimate the difference between groups when using between-study comparisons, we calculated the ratio of proportions by dividing the overall proportion of one risk group by the overall proportion of the comparative risk group for binary outcomes to obtain the RR, while subtracting the mean of one group from the other to obtain the MD.

We planned to address heterogeneity by investigating sensitivity (for study design and risk of bias) and/or subgroup analyses (for pre-defined population characteristics; see Supplement 3) when possible and appropriate. We reported values for statistical heterogeneity (I^2) but did not rely on these for decisions about meta-analysis or subgroup analysis as prognostic studies typically present with large sample sizes and resulting precise estimates (making a large I^2 misleading); instead, we considered clinical and methodological differences between studies to identify potential sources of heterogeneity.

Outcomes from within-study comparisons were considered direct evidence and included as primary analyses. Outcomes from between-study comparisons (considered indirect evidence) utilized single arm proportions which were pooled when there were two or more studies with sufficiently similar populations and proportions.

Most, but not all, studies reported a denominator (e.g. birth cohort or community sample) to permit calculations of hospitalization incidence. No study reported on the number of infants who received ECMO. Two studies with different populations reported on different types of adverse events/ complications (e.g. secondary infection); therefore, we did not include this data for analysis.

On consultation with the National Advisory Committee on Immunization (NACI) clinical lead (DLM), we calculated effect estimates for all other outcomes with available data between each at-risk population versus healthy term population. We did not conduct effect estimates for between-study comparators for the outcome of oxygen therapy. As most children admitted to hospital for RSV receive supplemental oxygen, it is not an indicator of severe disease requiring intensive therapies. We did not conduct between-study comparisons for the outcome of case fatality (death due to RSV) since no relevant risk groups were identified among the included studies.

Analyses were performed using Excel (Microsoft 2016), Review Manager (Version 5.3), and STATA (Version 14.2) (5). For outcomes that demonstrated significant effects, we calculated absolute risk difference where values were calculated using absolute numbers from the evidence tables estimated using the control group event rate and RR with the 95% CI obtained from the meta-analysis (6).

Small-study effects

We planned to analyze small-study effects when there are at least eight studies in a meta-analysis (i.e. tendency for publication of small studies only when finding large event rates) quantitatively using Begg's test for observational studies (Begg 1994) and Egger's test (7) for comparative studies; however, there were insufficient number of studies to examine small-study effects.

Assessment of the overall certainty of the evidence using GRADE

Two reviewers independently assessed the overall certainty of the evidence (confidence in estimates of event rates) for each outcome from the within-study comparisons (direct evidence). Disagreements were resolved through discussion. The approach generally followed the principles from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (8) working group and considerations for a body of evidence that estimates the risk of future events (prognosis) rather than effectiveness (9); decision guidelines and considerations are outlined in **Supplement 5**. Quality of evidence for within-study comparisons across studies were assessed for each outcome and rated as high, moderate, low or very low. We did not conduct GRADE assessments for between-study comparisons.

References

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Supplement 2: Search strategy

Table S2-1: Database Ovid MEDLINE(R) ALL 1946 to September 05, 2018 search strategy
Table S2-2: Database Embase 1974 to 2018 September 5 search strategy
Table S2-3: Database(s) EBM reviews—Cochrane Central Register of Controlled Trials August 2018 search strategy

Table S2-1: Database Ovid MEDLINE(R) ALL 1946 to September 05, 2018 search strategy

#	Searches	Results
1	*RESPIRATORY SYNCYTIAL VIRUS, HUMAN/ or *RESPIRATORY SYNCYTIAL VIRUSES/	5,191
2	*RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/	5,175
3	RSV*.ti.	1,605
4	(RSV* or respiratory syncytial virus*).ab. /freq=2	10,542
5	or/1-4	13,415
6	exp infant/ or exp child/ or Gestational Age/	2,361,978
7	(infant* or infancy or newborn* or baby or babies or neonat* or preterm* or preemie* or prematur* or gestational age or gestation* or child*).ti.	1,077,698
8	(infant* or infancy or newborn* or baby or babies or neonat* or preterm* or preemie* or prematur* or gestational age or gestation* or child*).ab. /freq=2	949,076
9	or/6-8	2,747,110
10	Patient Admission/ or inpatient/ or HOSPITALIZATION/sn	65,291
11	Risk Factors/	737,380
12	GENETIC PREDISPOSITION TO DISEASE/	122,579
13	(predispos* or risk factor*).tw.	600,383
14	risk*.ti. or risk*.ab. /freq=2	978,325
15	inpatient*.tw.	91,804
16	((hospital* or patient) adj2 (admit* or admission*)).tw.	60,922
17	Palivizumab/ or (palivizumab or abbosynagis or synagys or synagis).mp.	986
18	prophylaxis/ or (health protection or immunoprophylax* or prevention or preventive measure* or preventive medication* or preventive therap* or preventive treatment* or prophylactic management or prophylactic medication or prophylactic therapy or prophylactic treatment or prophylax*).tw.	581,318
19	or/10-18	2,188,274
20	and/5,9,19	2,429
21	9 and (RSV* adj2 admission*).tw.	69
22	or/20-21	2,438
23	(comment or editorial or letter or news).pt.	1,831,761
24	22 and 23	141
25	22 not 24	2,297
26	limit 25 to (yr="2014 -Current" and (english or french))	631

Table S2-2: Database Embase 1974 to 2018 September 5 search strategy

#	Searches	Results
1	exp *human respiratory syncytial virus/	895
2	*respiratory syncytial virus infection/	2,227
3	RSV*.ti.	2,191
4	(RSV* or respiratory syncytial virus*).ab. /freq=2	13,160
5	or/1-4	14,108
6	exp infant/ or exp child/ or gestational age/	2,400,064
7	(infant* or infancy or newborn* or baby or babies or neonat* or preterm* or preemie* or prematur* or gestational age or gestation* or child*).ti.	1,165,559
8	(infant* or infancy or newborn* or baby or babies or neonat* or preterm* or preemie* or prematur* or gestational age or gestation* or child*).ab. /freq=2	1,249,098
9	or/6-8	2,823,969
10	hospital admission/ or hospital patient/	296,307
11	risk factor/	889,206
12	genetic predisposition/	53,408
13	(predispos* or risk factor*).tw.	858,630
14	risk*.ti. or risk.ab. /freq=2	1,330,125
15	inpatient*.tw.	147,070
16	((hospital* or patient) adj2 (admit* or admission*)).tw.	99,950
17	palivizumab/ or (palivizumab or abbosynagis or synagys or synagis).mp.	2,726
18	prophylaxis/ or (health protection or immunoprophylax* or prevention or preventive measure* or preventive medication* or preventive therap* or preventive treatment* or prophylactic management or prophylactic medication or prophylactic therapy or prophylactic treatment or prophylax*).tw.	781,490
19	or/10-18	2,937,805
20	and/5,9,19	2,930
21	9 and (RSV* adj2 admission*).tw.	99
22	or/20-21	2,947
23	(editorial or erratum or letter or note).pt.	2,490,067
24	22 and 23	80
25	22 not 24	2,867
26	limit 25 to (yr="2014 -Current" and (english or french))	918

Table S2-3: Database(s) EBM reviews—Cochrane Central Register of Controlled Trials August 2018 search strategy

#	Searches	Results
1	*RESPIRATORY SYNCYTIAL VIRUS, HUMAN/ or *RESPIRATORY SYNCYTIAL VIRUSES/	3
2	*RESPIRATORY SYNCYTIAL VIRUS INFECTIONS/	20
3	RSV*.ti.	202
4	(RSV* or respiratory syncytial virus*).ab. /freq=2	520
5	or/1-4	602
6	exp infant/ or exp child/ or Gestational Age/	67,538
7	(infant* or infancy or newborn* or baby or babies or neonat* or preterm* or preemie* or prematur* or gestational age or gestation* or child*).ti.	80,402
8	(infant* or infancy or newborn* or baby or babies or neonat* or preterm* or preemie* or prematur* or gestational age or gestation* or child*).ab. /freq=2	78,808
9	or/6-8	130,022
10	Patient Admission/ or inpatient/ or HOSPITALIZATION/sn	1,346
11	Risk Factors/	23,145
12	GENETIC PREDISPOSITION TO DISEASE/	1,065
13	(predispos* or risk factor*).tw.	34,342
14	risk*.ti. or risk*.ab. /freq=2	79,356
15	inpatient*.tw.	11,090
16	((hospital* or patient) adj2 (admit* or admission*)).tw.	7,999
17	Palivizumab/ or (palivizumab or abbosynagis or synagys or synagis).mp.	97
18	prophylaxis/ or (health protection or immunoprophylax* or prevention or preventive measure* or preventive medication* or preventive therap* or preventive treatment* or prophylactic management or prophylactic medication or prophylactic therapy or prophylactic treatment or prophylax*).tw.	70,901
19	or/10-18	171,156
20	and/5,9,19	161
21	9 and (RSV* adj2 admission*).tw.	1
22	or/20-21	161
23	(comment or editorial or letter or news).pt.	7,784
24	22 and 23	3
25	22 not 24	158
26	limit 25 to (yr="2014 -Current" and (english or french))	65

Supplement 3: Inclusion and exclusion criteria

Table S3-1: Detailed eligibility criteria for study selection

Criteria	Inclusion	Exclusion
Population	1. Infants and children (birth to 24 months of age) not having received palivizumab (or any other RSV prophylaxis), with or without risk condition(s), with RSV infection. 2. Studies including children >24 months of age will be included if data for ≤24 months can be isolated, or if the mean age (+1 SD) is ≤24 months. 3. Risk conditions: • Prematurity (gestational age) • Chronic lung disease/bronchopulmonary dysplasia • Congenital heart disease • Cystic fibrosis • Down syndrome/trisomy 21 • Children identified as Inuit or other Indigenous group • Children residing in remote geographical areas • Upper respiratory/pulmonary malformations abnormalities/diaphragmatic hernia • Chronic neuromuscular disease • Immune-deficiencies/immunocompromised (congenital, or acquired such as patients undergoing cancer therapy, transplant surgery or taking certain medications; may include children >24 months of age) • Other chronic medical conditions 4. RSV infection must be diagnosed/confirmed by laboratory testing, or a relevant ICD-9 code that includes a laboratory test. If a study presents data for laboratory diagnosed RSV and clinically diagnosed bronchiolitis separately, data for the laboratory portion should be used. If study includes some patients without confirmed RSV, ≥90% of the population must have RSV. <u>Population subgroups (applicable to all risk conditions unless indicated):</u> • Prematurity: GA subcategories: <29 wGA or <30 wGA, 29–30 to 32–33 wGA, 32–33 to 35 wGA • Not-at-high-risk for RSV versus high-risk patients • Age at RSV diagnosis: (e.g. 3, 6, 12 or 24 months) • RSV season: first/single, second (for children with congenital heart disease or chronic lung disease) • RSV management approaches (e.g. use of medications) Studies to set aside for potential inclusion/extraction: Less than 90% of the study population has confirmed RSV infection, and results are not reported separately for the RSV population.	• Children >24 months of age at time of RSV infection (unless immunocompromised) • Children who received any prophylaxis (any cut-off), including children with missed doses, inadequate prophylaxis or 'palivizumab failures'; studies (or a single arm of a study) where children without prophylaxis are combined with children who received inadequate prophylaxis will be included only if data is reported separately for the former population • Studies without information on RSV immunoprophylaxis or children untested for RSV • RSV infection not confirmed by a valid source (e.g. RSV diagnosed clinically only) • Populations with concurrent infection (RSV and another infection such as influenza, rhinovirus, bacterial pathogens)
Population comparator	• None • Population with a different risk condition (see above), with RSV • Population without risk conditions, with RSV • For long-term outcomes: population with same characteristics of the above population groups, but without RSV	• For short-term outcomes: children without RSV

Table S3-1: Detailed eligibility criteria for study selection (*continued*)

Criteria	Inclusion	Exclusion
Outcomes: Short-term	• Any RSV infection leading to hospitalization (requirement; duration) • ICU admission due to RSV (requirement; duration) • Mechanical ventilation therapy due to RSV (requirement; duration) • New requirement for oxygen therapy due to RSV (requirement; duration) • ECMO therapy due to RSV (requirement; duration) • Case-fatality (RSV) • Adverse events from RSV (e.g. secondary infection) Each short-term outcome must be reported for **at least 90%** of the population with RSV in order to be eligible. Studies to set aside for potential inclusion/extraction: Where outcome data is available for <90% of the population, this will be set aside for potential inclusion.	• Hospitalization for a respiratory illness unrelated to RSV • Bronchodilator therapy in-hospital (e.g. salbutamol) • RSV requiring outpatient medical treatment only (e.g. medically attended outpatient visit in emergency department, urgent care or pediatric clinic) • All-cause mortality (death not associated with RSV infection)
Outcomes: Long-term	• Any wheeze (as defined by the authors, e.g. ≥1 wheezing episode, recurrent wheezing, physician-diagnosed recurrent wheezing, days with wheeze per month) • Asthma (e.g. physician diagnosed; requiring long-term asthma controller medication including systemic corticosteroids, bronchodilator) • Pulmonary function impairment/deterioration; exacerbation of lung disease (e.g. cystic fibrosis) • Cardiac function impairment/deterioration • Impaired growth or development All long-term outcomes must be reported for **at least 50%** of the population with RSV in order to be eligible. Studies to set aside for potential inclusion/extraction: Where a long-term outcome data is available for <50% of the population, this will be set aside for potential inclusion.	• Study does not report ascertainment of RSV infection in infancy • Quality of life measurements (e.g. QALY) • IgE mediated allergy; allergic sensitization; allergic rhinitis; allergic conjunctivitis; skin allergies • Unscheduled healthcare visits (e.g. emergency department visits; general physician/primary care office visits)
Timing	• Follow-up duration: any duration for short-term outcomes; minimum of one-year follow-up for long-term outcomes • Study published January 1, 2014 to September 2018	N/A
Setting	• High-income (OECDa) countries	N/A
Study design	• Single-arm trials • Controlled clinical trials (of prophylaxis only) • Cohort (controlled or uncontrolled; prospective, retrospective, non-concurrent) • Case-control • Case series	• Qualitative studies • Case reports • Editorial, opinion, commentary, letter • News report
Language	• English; French	• Non-English/French

Abbreviations: ECMO, extracorporeal membrane oxygenation; GA, gestational age; ICD, International Classification of Diseases; ICU, intensive care admission; N/A, not applicable; OECD, Organisation for Economic Co-operation and Development; QALY, Quality Adjusted Life Year; RSV, respiratory syncytial virus; SD, standard deviation; wGA, weeks' gestational age

[a] OECD member countries (2019): Australia, Austria, Belgium, Chile, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea, Latvia, Lithuania, Luxembourg, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom, United States

Supplement 4: Methodological quality assessments

Table S4-1: Summary of methodological quality assessments
Table S4-2: Methodological quality assessment tool for cohort studies
Table S4-3: Methodological quality assessment tool for case-control studies

Table S4-1: Summary of methodological quality assessments

Study	Criteria								
	1) Research objective	2) Study population	3) Study participants	4) Exposure-to-outcome timeframe	5) Prognostic risk factors	6) Outcomes	7) Blinding of assessors to outcomes	8) Follow-up	9) Adjustment for confounders
Ambrose 2014[25] (PC)	Y	a) Y b) Y c) Y	a) Y b) Y	Y	a) Y b) Y c) Y d) Y e) Y	a) Y b) Y c) Y	NR (obj)	a) N b) Y	Y
Anderson 2017[26] (PC)	Y	a) Y b) Y c) Y	a) Y b) Y	Y	a) Y b) Y c) Y d) Y e) Y	a) Y b) Y c) Y	NR (obj)	a) Y b) N	Y
Backman 2018[27] (PC)	Y	a) NR b) NR c) Y	a) Y b) Y	Y	No risk factors	a) Y b) Y c) Y	NR (obj & subj)	a) Y b) N	Y
Backman 2014[28] (PC)	Y	a) Y b) NR c) Y	a) Y b) Y	Y	No risk factors	a) Y b) Y c) Y	NR (obj & subj)	a) Y b) N	Y
Banerji 2016[13] (PC)	Y	a) Y b) N c) Y	a) Y b) Y	Y	a) Y b) Y c) Y d) Y e) Y	a) Y b) Y c) Y	NR (obj)	a) Y b) N/A	Y
Bjornson 2018[29] (RC)	Y	a) Y b) N c) Y	a) Y b) Y	Y	No risk factors	a) Y b) Y c) Y	NR (obj)	a) Y b) N/A	N
Blanken 2016[30] (PC)	Y	a) Y b) Y c) Y	a) Y b) Y	Y	a) Y b) Y c) Y d) Y e) Y	a) Y b) Y c) Y	N (subj)	a) Y b) Y	Y
Bonnelykke 2015[31] (PC)	Y	a) Y b) N c) Y	a) Y b) Y	Y	No risk factors	a) Y b) Y c) Y	NR (obj)	a) Y b) N	Y
Carbonell-Estrany 2015[32] (PC)	Y	a) Y b) Y c) Y	a) Y b) Y	Y	a) Y b) Y c) Y d) Y e) Y	a) Y b) Y c) Y	N (subj)	a) Y b) Y	Y
Caserta 2017[33] (PC)	Y	a) NR b) Y c) Y	a) N b) Y	Y	No risk factors	a) Y b) Y c) Y	NR (obj)	a) Y b) N/A	Y
Chu 2017[34] (RC)	Y	a) Y b) Y c) Y	a) Y b) Y	Y	a) Y b) Y c) Y d) Y e) Y	a) Y b) Y c) Y	NR (obj)	a) Y b) N/A	Y

Table S4-1: Summary of methodological quality assessments (*continued*)

Study	Criteria								
	1) Research objective	2) Study population	3) Study participants	4) Exposure-to-outcome timeframe	5) Prognostic risk factors	6) Outcomes	7) Blinding of assessors to outcomes	8) Follow-up	9) Adjustment for confounders
Drummond 2016[35] (RC)	Y	a) Y b) Y c) Y	a) Y b) Y	Y	a) Y b) Y c) Y d) Y e) Y	a) Y b) Y c) Y	NR (obj)	a) Y b) N/A	N
Farber 2016[36] (RC)	Y	a) Y b) Y c) Y	a) Y b) Y	Y	a) Y b) Y c) Y d) Y e) Y	a) Y b) Y c) Y	NR (obj)	a) Y b) N/A	Y
Fauroux 2014[37] (RFU of PC)	Y	a) Y b) Y c) Y	a) Y b) Y	Y	a) Y b) Y c) Y d) Y e) Y	a) Y b) Y c) Y	N (subj)	a) Y b) Y	Y
Feldman 2014[38] (RC)	Y	a) Y b) Y c) Y	a) Y b) Y	Y	a) Y b) Y c) Y d) Y e) Y	a) Y b) Y c) Y	NR (obj)	a) Y b) N/A	Y
Franklin 2016[53] (PC)[a]	Y	a) Y b) Y c) Y	a) Y b) Y	Y	a) Y b) Y c) Y d) Y e) Y	a) Y b) Y c) Y	NR (obj)	a) N b) Y	Y
Groves 2016[39] (RC)	Y	a) Y b) Y c) Y	a) Y b) Y	Y	a) Y b) Y c) Y d) Y e) Y	a) Y b) Y c) Y	NR (obj)	a) Y b) Y	N
Hama 2015[40] (RC)	Y	a) Y b) Y c) Y	a) Y b) Y	Y	a) Y b) Y c) Y d) Y e) Y	a) Y b) Y c) Y	NR (obj)	a) Y b) Y	Y
Hatanaka 2015[41] (RC)	Y	a) Y b) Y c) Y	a) Y b) Y	Y	a) Y b) Y c) Y d) Y e) Y	a) N b) CD c) Y	N (obj)	a) Y b) N/A	N
Helfrich 2015[42] (RC)	Y	a) Y b) Y c) Y	a) Y b) Y	Y	a) Y b) Y c) Y d) Y e) Y	a) Y b) Y c) Y	NR (obj)	a) Y b) N/A	Y
Korsten 2016[43] (PC)	Y	a) Y b) N c) Y	a) Y b) Y	Y	a) Y b) Y c) Y d) Y e) Y	a) Y b) Y c) Y	NR (obj)	a) Y b) N/A	Y
Luchsinger 2018[44] (PC)	Y	a) Y b) Y c) Y	a) Y b) Y	Y	No risk factors	a) NR b) NR c) Y	N (obj)	a) Y b) N/A	N

Table S4-1: Summary of methodological quality assessments (*continued*)

Study	Criteria								
	1) Research objective	2) Study population	3) Study participants	4) Exposure-to-outcome timeframe	5) Prognostic risk factors	6) Outcomes	7) Blinding of assessors to outcomes	8) Follow-up	9) Adjustment for confounders
McLaurin 2016[45] (RC)	Y	a) Y b) N c) Y	a) Y b) Y	Y	a) Y b) Y c) Y d) Y e) Y	a) Y b) Y c) Y	NR (obj)	a) Y b) N/A	N
O'Brien 2015[46] (PC; placebo arm of RCT)	Y	a) Y b) Y c) Y	a) Y b) Y	CD	a) Y b) Y c) Y d) Y e) Y	a) Y b) Y c) Y	Y (obj)	a) Y b) CD	N
Rajah 2017[47] (RCNCC)	Y	a) Y b) Y c) Y	a) N b) Y	Y	a) Y b) Y c) Y d) Y e) Y	a) Y b) Y c) Y	NR (obj)	a) Y b) N/A	N
Ryan 2016[48] (RC)	Y	a) Y b) Y c) Y	a) Y b) Y	Y	a) Y b) Y c) Y d) Y e) Y	a) Y b) Y c) Y	NR (obj)	a) Y b) N/A	Y
Sadreameli 2014[49] (RC)	Y	a) Y b) Y c) Y	a) Y b) Y	Y	a) Y b) Y c) Y d) Y e) Y	a) Y b) Y c) Y	NR (obj)	a) Y b) N/A	Y
Simões 2016[54] (PC)[a]	Y	a) Y b) Y c) Y	a) Y b) Y	Y	a) Y b) Y c) Y d) Y e) Y	a) Y b) Y c) Y	NR (obj)	a) N b) Y	Y
Stagliano 2015[50] (RC)	Y	a) Y b) Y c) Y	a) Y b) Y	Y	a) Y b) Y c) Y d) Y e) Y	a) Y b) Y c) Y	NR (obj)	a) Y b) CD	Y
Straňák 2016[51] (PC)	Y	a) Y b) Y c) Y	a) Y b) Y	Y	a) Y b) Y c) Y d) Y e) Y	a) Y b) Y c) Y	NR (obj)	a) Y b) N/A	Y
Zomer-Kooijker 2014[52] (PC)	Y	a) CD b) Y c) Y	a) Y b) Y	Y	No risk factors	a) Y b) Y c) Y	N (obj & subj)	a) Y b) N/A	Y

Abbreviations: CD, cannot determine; N, no; N/A, not applicable; NR, not reported; obj, objective (outcome); PC, prospective cohort; RC, retrospective cohort; RCNCC, retrospective cohort with non-concurrent controls; RCT, randomized controlled trial; RFU, retrospective follow-up; subj, subjective (outcome); Y, yes

[a] Franklin 2016 and Simões 2016 are associated publications of Ambrose 2014 (primary publication), all reporting on the same study

Table S4-2: Quality assessment tool for cohort and observational studies[a]

Criteria	Yes	No	Other (CD, NR, N/A)	Comments
1. Was the research question or objective in this paper clearly described?				
2. Was the study population clearly specified and defined?				
a. Was there a representative sample of participants? Was there adequate participation in the study by eligible individuals (e.g. at least 50%)?				
b. Was the baseline study sample adequately described for key characteristics?				
c. Is the population free of the outcomes of interest at the time they were recruited?				
3. Were all the participants similar and identifiable?				
a. Were all the participants selected or recruited from the same or similar populations, including the same time period?				
b. Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants?				
4. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?				
5. Did the study report on risk factor(s)? **If so, complete 5a–5e. If not, please indicate "No" here, and proceed to criteria 6.**				
a. Was there a clear definition or description of risk factors (medical conditions, non-medical factors, duration of exposure, clear specification of method of measurement)??				
b. Was the method of risk factor measurement valid and reliable to limit misclassification bias (equal across all groups [non-differential misclassification bias] or differs between groups [differential misclassification bias]? (e.g. may include outside sources of information on measurement properties; also characteristics such as blind measurement and limited reliance on recall)				
c. Were the method and setting of the measurement of risk factor(s) the same for all study participants?				
d. Was there an adequate proportion of the study sample with complete data for risk factor(s)?				
e. For the analyses in this paper, were the risk factor(s) of interest measured prior to the outcome(s) being measured?				
6. Were the outcomes measure(s) clearly defined, valid, reliable, and implemented consistently across all study participants?				
a. Was there a clear definition or description of outcome measures (level/severity, duration of exposure, clear specification of method of measurement)?				
b. Was the method of outcome measurement valid and reliable to limit misclassification bias? (e.g. may include outside sources of information on measurement properties; also characteristics such as blind measurement and limited reliance on recall)				
c. Were the method and setting of outcome measurement the same for all study participants?				
7. **Were the outcome assessors blinded to the exposure status of participants?** This is mainly applicable to studies with a comparator group, where blinding to RSV status (and/or risk factors, depending on nature of comparator groups) may be important to reduce risk of performance bias (provision of treatment) or detection bias (outcome measurement).				
8. Was follow-up after baseline sufficient and complete?				
a. Was loss to follow-up after baseline: i. 10% or less for short-term outcomes? ii. 50% or less for long-term outcomes?				

Table S4-2: Quality assessment tool for cohort and observational studies[a] (*continued*)

Criteria	Yes	No	Other (CD, NR, N/A)	Comments
b. Were reason(s) for loss to follow-up provided, or participants lost to follow-up are described for key characteristics? Consider whether there are important differences between key characteristics and outcomes in participants who completed the study and those who did not.				

Abbreviations: CD, cannot determine; N/A, not applicable; NR, not reported; RSV, respiratory syncytial virus
[a] All cohort studies were appraised using a modified tool based on the Quality In Prognosis Studies (QUIPS) tool (1) and the Quality Assessment Tool for Observational Cohort and Cross-sectional Studies developed by the National Institutes of Health (NHLBI 2019)

Reference

1. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing Bias in Studies of Prognostic Factors. Ann Intern Med 2013;158(4):280-86. DOI PubMed

Table S4-3: Quality assessment tool for case-control studies[a]

Criteria	Yes	No	Other (CD, NR, N/A)	Comments
9. Were important confounders and treatments measured and adjusted statistically for their impact on the relationship between risk factor(s) and outcome(s)? For example, a study may adjust for confounders in their analysis, such as gestational age, chronic medical condition, male gender, birth month/season/year, severity of disease, or treatment(s). Or a study may report if, and the extent to which, treatment protocols differed between population groups or settings.				

Criteria	Yes	No	Other (CD, NR, N/A)	Comments
1. Is the case definition adequate?				
a. Was a case identified using independent validation (e.g. >1 person/record/time/process to extract information), with reference to a primary record source (e.g. lab, medical/hospital records)? Record linkage or self-report, without reference to a primary record, will not be considered adequate.				
2. Are cases representative of the population of interest?				
a. Was there a clear definition or description of all eligible cases, with outcome of interest (defined time period, all cases in defined catchment area, all cases in defined hospital(s) or clinic(s), or an appropriate sample (random) of those cases)?				
3. Are controls selected from the same population as cases?				

Table S4-3: Quality assessment tool for case-control studies[a] (*continued*)

Criteria	Yes	No	Other (CD, NR, N/A)	Comments
a. Controls should be as similar to the cases as possible, without the outcome of interest. Example 1: cases=hospitalized patients with RSV; ideally, controls=hospitalized patients (without RSV). Example 2: cases=preterm infants with RSV (from community) and outcome of wheeze at one year; ideally, controls=preterm infants without RSV (from community) and outcome of wheeze at one year.				
4. Are controls defined, in relation to cases?				
a. If cases are first occurrence of outcome, then controls must explicitly state that controls have no history of this outcome. If cases have new (not necessarily first) occurrence of outcome, then controls with previous occurrences of outcome are permitted.				
5. Are cases and controls comparable? Study must satisfy EITHER 5a OR 5b.				
a. Are cases and controls matched in the design? Statements of no differences between groups (or differences were not statistically significant) are not sufficient.				
b. Are confounders adjusted for in the analysis? If the estimates (e.g. odds ratio) for the exposure of interest is adjusted for each confounder listed, then the groups may be considered comparable on each variable used in the adjustment. Study should control for chronological age, in addition to other potential factors that may influence the outcome(s), such as: GA, sex, severity of RSV, having a medical condition/risk factor of interest.				
6. Did the study report on exposure/risk factors?				
a. Was there a clear definition of exposure or risk factors (medical conditions, non-medical factors, duration of exposure, clear specification of method of ascertainment)?				
b. Was the method of risk factor measurement valid and reliable to limit misclassification bias (equal across all groups [non-differential misclassification bias] or differs between groups [differential misclassification bias]? (e.g. may include outside sources of information on measurement properties; also characteristics such as blind measurement and limited reliance on recall). Lab/medical records or structured interview with blinding (vs. non-blinding) to case/control status are more reliable than self-report.				
c. Were the method and setting of the measurement of risk factor(s) the same for all study participants?				
d. Was the non-response rate reported, and similar for both groups?				

Abbreviations: CD, cannot determine; GA, gestational age; N/A, not applicable; NR, not reported; RSV, RSV, respiratory syncytial virus
[a] Case-control studies were appraised using a modified tool, based on the QUIPS tool (1) and the Newcastle-Ottawa Scale for case-control studies (2)

References

1. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing Bias in Studies of Prognostic Factors. Ann Intern Med 2013;158(4):280-86. DOI PubMed
2. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. "The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses," ed, 2000.

Supplement 5: Certainty of evidence assessment

Table S5-1: Overall certainty of evidence assessment following GRADE guidelines and considerations for prognosis studies

Table S5-2: Levels of evidence for risk of a broadly defined population

The approach generally followed the principles from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (Guyatt *et al.* (1)) working group and considerations for a body of evidence that estimates the risk of future events (prognosis) rather than effectiveness (Iorio *et al.* (2)). Quality of evidence for within-study comparisons across studies were assessed for each outcome and rated as high, moderate, low or very low. We did not conduct GRADE assessments for between-study comparisons; these were considered indirect and offered very low quality evidence.

In observational studies, patients tend to be enrolled using broad eligibility criteria and are considered representative of the typical patient population. Therefore, as a starting point, observational studies (including one-armed trials which can be conceptualized as single-arm observational studies) are assigned as high quality. Thereafter, we examined and potentially downgraded the quality based on five core domains: study limitations/risk of bias (ROB), inconsistency, indirectness, imprecision, and publication bias. For study limitations/ROB, we considered the definition and representativeness of the population, completeness of follow-up and objective and unbiased outcome measurements including selective reporting. For inconsistency, we assessed the extent of the variation in point estimates without relying on the I2 (heterogeneity) of pooled estimates, taking into consideration clinical and methodological heterogeneity. For indirectness, we assessed the degree to which the population under study matched the population of interest, and whether the measured outcomes (including their duration) capture what is considered as important. For imprecision, we rated down our confidence in the estimates of the event rate if the effect on the patient would differ depending on whether the upper or lower boundary of the confidence interval (CI) represents the truth. For publication bias, we planned to interpret the results of the Begg's test. For outcomes without major concerns from the five domains, we planned to consider the additional domains and strength of association (e.g. large estimates of event rate) to potentially upgrade the quality.

The decision guidelines outlined below were used to guide assessments for each domain. All studies (observational designs) were assessed at high quality as a starting point. The Imprecision domain was assessed as follows: when optimal information size (OIS) is met, and the 95% CI overlaps no effect, consideration of important benefit or harm will be assessed using a relative risk of 1.0 (0.75–1.25). When the GRADE certainty of evidence was assessed as very low for an outcome, the narrative for the overall conclusion was "Very Uncertain". For all other assessment (high, moderate, low), the narrative for the overall conclusion indicated the direction and/or magnitude of effect. See Table S2 below for levels of evidence and corresponding interpretations.

Table S5-1: Overall certainty of evidence assessment following GRADE guidelines and considerations for prognosis studies

GRADE domain	Main issues addressed	Concerns warranting downgrading[a]
Study limitations/ risk of bias (ROB)	**Main consideration:** Studies may be flawed in their design or conduct, potentially resulting in misleading findings. Key limitations of observational studies include use of inappropriate controls and failure to adequately adjust for prognostic imbalance. Methodological quality assessment, including: definition and representativeness of population; completeness of follow-up (at least 90% and 50% of the population for short-term and long-term outcomes, respectively); and, objective and unbiased outcomes measurements. Additional considerations: Selective reporting: The detection of possible selective reporting of outcomes, either wholly (missing) or reported in a manner that is selective or atypical. Consider across outcomes and comparators, which studies are missing outcomes that should have reasonably been reported. Consider whether potential selective reporting influences overall study conclusion.	**Short-term outcomes:** Hospitalization for RSV—knowledge of population risk factor, and therefore, lack of blinding, may influence healthcare provider care or triage behaviour. *Example [-1]: infants born premature may be more likely to be hospitalized when presenting to healthcare provider or hospital with symptoms during RSV season.* *Example [-0.5]: infants born late-premature may not necessarily be more likely to be hospitalized when compared to infants born term.* **Long-term outcomes:** Outcome assessor bias possible when outcomes are reported subjectively. *Example: parent-reported (questionnaire) wheeze episodes.* **Selective reporting:** One or more outcomes is/are not reported. *Example: hospital length of stay not reported by year, only for comparative arms across all years combined.*

Table S5-1: Overall certainty of evidence assessment following GRADE guidelines and considerations for prognosis studies (*continued*)

GRADE domain	Main issues addressed	Concerns warranting downgrading[a]
Inconsistency	**Main consideration:** Any variation in point estimates of pooled estimates, considering clinical and methodological heterogeneity. Additional considerations: If heterogeneity can be explained by subgroup analysis, each subgroup may be assessed separately and considered consistent. Consider whether estimate is consistent across outcomes and comparators (if sufficiently similar).	**All outcomes:** Single study contributing to pooled estimate—lack of demonstration of consistency with another study for comparison/outcome. No finding of inconsistency when two studies are similar in direction of effect.
Indirectness	**Main consideration:** The degree to which the population (including timing of RSV hospitalization) matches the population of interest. The degree to which the measured outcomes (including duration) capture what is considered as important. Additional considerations: Consider not downgrading for indirectness, and instead, applying assessment to applicable population. *Example: [LEVEL] certainty of evidence for [OUTCOME] for infants hospitalized for RSV at <6 months of age.*	**All outcomes:** Example [-0.5]: A small proportion (<5%) of the population at risk also have additional comorbidities.
Imprecision	**Main consideration:** The degree to which the effect on the patient would differ depending on whether the upper or lower bound of the CI represents the truth. Additional considerations: For rare events, consider sample size and absolute effects.	**All outcomes:** a. Optimal information size (OIS; at least 2,000 participants or 400 events) is not met; b. Small number of events led to wide CIs. *Example [-2]: One study with only 17 participants and 8 events; width of CI is very wide and consistent with both important benefit and harm.* *Example [-1]: Single study with fewer than 2,000 participants.*
Publication bias	**Main consideration:** The detection (suspected or undetected) of possible selective publication of small studies, often with positive findings; need at least eight studies to test quantitatively (Begg's test). Additional considerations: This domain is not applicable if there are insufficient number of studies to assess/detect publication bias. Consider funding source of study or of investigators (potential bias if funded by industry or key/for-profit interest group). Comprehensiveness of search strategies and methods to identify all available evidence.	**All outcomes:** There were insufficient number of studies to assess publication bias.

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; RSV, respiratory syncytial virus
[a] Concerns warranting downgrading: [-2] two decrements for very serious concerns, [-1] one decrement for serious concerns, [-0.5] half decrement for some concerns

Table S5-2: Levels of evidence for risk of a broadly defined population

Quality/certainty of evidence	Interpretation
High	We are very confident that the true association (probability of future evens) lies close to that of the estimate.
Moderate	We are moderately confident that the true association is likely to be close to the estimate, but there is a possibility that it is substantially different.
Low	Our confidence in the effect is limited: the true association may be substantially different from the estimate.
Very low	We have very little confidence/are very uncertain in the estimate: the true association is likely to be substantially different from the estimate.

References

1. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: A new series of articles in the Journal of Clinical Epidemiology. Journal of Clinical Epidemiology 2011;64(4):380-2. DOI PubMed

2. Iorio A, Spencer FA, Falavigna M, Alba C, Lang E, Burnand B, McGinn T, Hayden J, Williams K, Shea B, Wolff R, Kujpers T, Perel P, Vandvik PO, Glasziou P, Schunemann H, Guyatt G. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. BMJ 2015 Mar;350:h870. DOI PubMed

Supplement 6: Characteristics of included studies

Table S6-1: Characteristics and risk of bias of included studies

Study author & year; Study design; Study period; Setting; Country; Funding source	Enrolled cohort and study sample	RSV cases	Prophylaxis and other treatments/ therapies	Patient characteristics by risk factor(s)—included populations	Excluded populations	Outcomes	Risk of bias
Ambrose 2014[25]; associated publication Franklin 2016 & Simões 2016[a] Prospective cohort RSV seasons 2009–2010 & 2010–2011 (Nov–Mar) Clinics, ED & hospital US Industry	Premature infants (32^0–35^6 wGA) not receiving RSV prophylaxis, born May to February and <6 mo CA at enrollment; 1,642 infants: 32–34 wGA: 753 35 wGA: 889	**RSV-positive: 287** RSV-MAARI: 287	**Prophylaxis:** Premature infants who received or were considered for RSV IP were ineligible for study 63 (3.8%) of enrolled infants (n=1,646) who received RSV IP were lost to follow-up **Other treatments/ therapies:** Chest radiograph 61% Antibiotics 39%	Prematurity (32–35 wGA): 100%	CLD of prematurity HS-CHD Life expectancy <6 mo	**Short-term** Hospitalization Hospital LOS ICU admission Mechanical ventilation	**Moderate risk** Clinicians not blinded to risk factor (high risk for hospitalization) 84% follow-up

Table S6-1: Characteristics and risk of bias of included studies (*continued*)

Study author & year; Study design; Study period; Setting; Country; Funding source	Enrolled cohort and study sample	RSV cases	Prophylaxis and other treatments/ therapies	Patient characteristics by risk factor(s)—included populations	Excluded populations	Outcomes	Risk of bias
Anderson 2017[26] Prospective cohort Oct 2014–Apr 2015 Sites, outpatient or inpatient US Industry	Premature infants (29^0–35^6 wGA) hospitalized for RSV at <12 mo CA; 219 premature infants enrolled	**RSV-hospitalized, community-acquired & nosocomial-acquired: 219** Community-acquired: 212 29–32 wGA: 89 33–34 wGA: 81 35 wGA: 42 Nosocomial-acquired: 7 29–32 wGA: 3 33–34 wGA: 3 35 wGA: 1	**Prophylaxis:** Infants who received RSV IP ≤35 d before onset of respiratory symptoms associated with index RSV-H were ineligible for study **Other treatments/ therapies:** Of infants with procedures performed (n=200): Pulse oximetry: 86% Chest radiograph: 81% Complete blood count analysis: 56% Additional blood lab analyses: 62% Respiratory therapist care: 59% Of infants who received medications during index RSV-hospitalization (n=196): Bronchodilators: 58% Antibiotics: 52% Inhaled steroids: 13% Systemic steroids: 29%	Prematurity (29^0–35^6): 100% CLD (in community-acquired RSV cases): 3/219 (1.4%) CHD: 18/219 (8.2%) HS-CHD: 2/219 (0.9%) Non HS-CHD: 16/219 (7.3%) Down's syndrome: 3/212 (1.4%) Other chromosomal disorder: 4/212 (1.9%) American Indian/ Alaska Native 3/210 (1.4%)	NR	**Short-term** • Hospital LOS • ICU admission • ICU LOS • Mechanical ventilation (IMV includes ECMO) • Mechanical ventilation duration • Case fatality • Adverse events	**Moderate risk** • Clinicians not blinded to risk factor • Reasons for follow-up losses not reported (but follow-up adequate)
Backman 2018[27] Prospective cohort 1992–2010 Hospital & community Finland Non-industry	Follow-up (17–20 y) of infants hospitalized for RSV with wheezing in early childhood (<2 y; 1992–1993); 109 adults; 49 with hospitalization for RSV with wheezing; 60 population controls matched for age and sex	Hospitalized for RSV with wheeze, community-acquired: 14 RSV pathogen only: 8 RSV + co-infection (viruses): 6 Data (demographics & outcomes) combines RSV-without coinfection and RSV-with coinfection	**Prophylaxis**: NR **Other treatments/ therapies:** NR	NR	NR	**Long-term (at age 17–20 y)** • Asthma (patient-reported) • Lung function	**Moderate risk** • Study sample poorly described; potential for selection bias • Patient and clinician-based outcome assessment; unlikely blinded • Reasons for follow-up losses not reported (but follow-up adequate)

Table S6-1: Characteristics and risk of bias of included studies (*continued*)

Study author & year; Study design; Study period; Setting; Country; Funding source	Enrolled cohort and study sample	RSV cases	Prophylaxis and other treatments/ therapies	Patient characteristics by risk factor(s)—included populations	Excluded populations	Outcomes	Risk of bias
Backman 2014[28] Prospective cohort 1981–2010 Hospital & community Finland Funding NR	Follow-up (28–31 y) of infants, with or without RSV hospitalization in early childhood (<24 mo; 1981–1982); 129 adults; 43 with hospitalization for RSV infection 86 population controls	RSV-hospitalized, 43 Confirmed RSV: 24 Probable RSV: 19	**Prophylaxis**: NR **Other treatments/ therapies:** NR	NR	NR	**Long-term (at age 28–31 y)** • Asthma (physician & patient-reported) • Lung function	**Moderate risk** • Sample characteristics at enrollment not described • Patient and clinician-based outcome assessment; unlikely blinded • Reasons for follow-up losses not reported (but follow-up adequate)
Banerji 2016[13] Prospective cohort (retrospective cohort for Qikiqtaaluk region) Jan 1–Dec 31, 2009 Hospitals Arctic Canada (Northwest Territories, Nunavut & Nunavik) Industry	Infants born in 2009 and admitted to hospital with LRTI at <1 y CA; 1,838 infants; 293 infants admitted for LRTI (348 admissions)	Admissions for RSV among infants <1 y per 1,000 live births/ year: 66.9 Tested for RSV: 298 admissions RSV-positive: 124 admissions RSV pathogen only: 73 admissions RSV with co-infection: 51 admissions	**Prophylaxis:** One infant admitted with RSV infection had received prophylaxis with PVZ **Other treatments/ therapies:** NR	Remote geographic (Canadian Arctic): 100% Some infants had more than one underlying condition: • Any underlying condition: 70/1,838 (20.1%) admissions • Prematurity (<36 wGA): 65/1,838 (18.7%) admissions • Cardiac, respiratory: 14/1,838 (4.0%) admissions • Neurologic, congenital: 3/1,838 (0.9%) admissions	NR	**Short-term** • Hospitalization	**High risk** • Clinicians not blinded to risk factors (high-risk for hospitalization) • Baseline characteristics not reported • Primary outcome not reported for number of infants (number of admissions only)
Bjornson 2018[29] Retrospective cohort Cohort 1: Jan 1, 2000–Dec 31, 2009 Cohort 2: 2005–2017 Hospital Canada Industry	Infants diagnosed with CF, who did not receive prophylaxis, and were hospitalized for RSV at <2 y CA; 267 CF infants: 84 without PVZ	**RSV-hospitalized: 5** CF infants with respiratory illness hospitalization: 29 RSV testing rate among all hospitalized infants: 49/92 (53%)	**Prophylaxis:** No infants received PVZ (used non-PVZ group only) **Other treatments/ therapies:** NR; All CF patients in Canada are referred to accredited CF clinic for ongoing assessment and treatment	CF: 100%	NR	**Short-term** • Hospitalization • Hospital LOS • ICU admission • ICU LOS	**Moderate risk** • Clinicians not blinded to risk factor (high risk for hospitalization) • Baseline characteristics not reported • No adjustment for confounders

Table S6-1: Characteristics and risk of bias of included studies (*continued*)

Study author & year; Study design; Study period; Setting; Country; Funding source	Enrolled cohort and study sample	RSV cases	Prophylaxis and other treatments/ therapies	Patient characteristics by risk factor(s)—included populations	Excluded populations	Outcomes	Risk of bias
Blanken 2016[30] Prospective cohort Jun 2008–Feb 2014 Hospital Netherlands Industry and non-industry	Follow-up of premature infants (32^1–35^6 wGA) hospitalized with RSV at <1 y CA; 181 infants	**RSV-hospitalized: 181**	**Prophylaxis:** Premature infants who received PVZ were ineligible for study **Other treatments/ therapies:** NR	Prematurity (32^1–35^6 wGA): 100%	• Gross congenital abnormalities (e.g. Down's syndrome)	**Short-term** • Hospitalization	**Low risk** • Clinicians not blinded to risk factor (moderate risk for hospitalization)
Bonnelykke 2015[31] Prospective cohort 1998–2001 Clinic Denmark Industry and non-industry	Infants enrolled at 1 mo CA, followed up for first 3 y of life for LRTI and known asthma status at 7 y CA; 313 infants	**RSV-positive: 52 in first year of life (101 in first 3 y of life)**	**Prophylaxis:** NR **Other treatments/ therapies:** NR	Infants with specified risk factors were excluded	• Prematurity (<36 wGA) • Suspected chronic disease or lung symptoms • Need for mechanical ventilation after birth	**Long-term** • Asthma at age 7 y (physician-diagnosed)	**Low risk** • Baseline characteristics not reported • No data for risk factors reported; unclear if outcome assessment was blinded (unlikely to affect assessment) • Reasons for follow-up losses not reported (but follow-up adequate)
Carbonell-Estrany 2015[32] Prospective cohort Baseline: 2005–2006, 2006–2007 FU: 2008–2014 Hospital Spain Industry	Premature infants (32^1–35^0 wGA), with or without hospitalization for RSV at <12 mo CA; 125 infants with RSV-hospitalization; 362 population controls	**RSV-hospitalized: 125**	**Prophylaxis:** Four (3.2%) infants hospitalized for RSV received PVZ; 12 (3.3%) infants without hospitalization for RSV received PVZ **Other treatments/ therapies:** NR	Prematurity (32^1–35^0 wGA): 100%	• CLD of prematurity • Other chronic pulmonary diseases • HS-CHD • Congenital abnormalities of the airways • Neuromuscular disease • Immunodeficiency • Any illness/condition to preclude long-term survival • Participation in trial of RSV prophylaxis or therapeutic agent • Diagnosis of asthma at age 2 y	**Short-term** • Hospitalization Long-term • Wheeze at age 2–6 y (parent or physician) • Asthma med at 2–6 y (parent or physician) • Lung function at age 6 y (clinical assessment)	**Moderate risk** • Clinicians not blinded to risk factor (high risk for hospitalization) • Parent or physician-reported outcome assessment • Outcome assessment not blinded
Caserta 2017[33] Prospective cohort Oct 2012–Apr 2015 Clinic, community & hospital US Non-industry	Healthy full-term infants (≥36 wGA) born after May 1 of previous winter with RSV at <10 mo CA; 139 infants	RSV-positive: 139 RSV-positive, hospitalized: 84 RSV-positive, non-hospitalized: 55	Prophylaxis: Infants eligible for PVZ prophylaxis were ineligible for study **Other treatments/ therapies:** NR	Infants with specified risk factors were excluded	Any high-risk conditions: • Congenital cardiac disease • Neurologic conditions • Chronic aspiration • Immunosuppression • Malignancy • Qualified for PVZ prophylaxis • Inability to complete study	**Short-term** • Hospitalization • Hospital LOS • PICU admission • Oxygen duration • Mechanical ventilation	**Moderate risk** • Sampling strategy unclear; potential for selection bias • Participants selected from different populations • Blinding of outcome assessment not reported (objective outcomes)

Table S6-1: Characteristics and risk of bias of included studies (*continued*)

Study author & year; Study design; Study period; Setting; Country; Funding source	Enrolled cohort and study sample	RSV cases	Prophylaxis and other treatments/ therapies	Patient characteristics by risk factor(s)—included populations	Excluded populations	Outcomes	Risk of bias
Chu 2017[34] Retrospective cohort 1997–2012 tri-annually Hospital US Non-industry	Infants with or without CHD, hospitalized for RSV at <24 mo CA; 549,265 infants: HS-CHD: 2,518 Non HS-CHD: 546,747	**RSV, primary diagnosis** (hospitalization for RSV): 473313 RSV, primary with HS-CHD: 1531 RSV, primary without HS-CHD: 471782 RSV, any diagnosis (RSV bronchiolitis, RSV pneumonia, or RSV): 473313 RSV, with HS-CHD: 1531 RSV, without HS-CHD: 471782	**Prophylaxis:** NR; PVZ recommended in 2003 Pre-PVZ for CHD: 1997, 2000 Post-PVZ for CHD: 2006, 2009, 2012 **Other treatment/ therapies:** NR	HS-CHD: 2,518/549,265 (0.5%) Non HS-CHD: 546,747/549,265 (99.5%)	NR	**Short-term** • Hospitalization • Hospital LOS • Mechanical ventilation • ECMO • Case fatality	**Low risk** • Clinicians not blinded to risk factor (moderate risk for hospitalization) • Blinding of outcome assessment not reported (objective outcomes)
Drummond 2016[35] Retrospective cohort 2007–2013 Hospital France Non-industry	Infants with chILD treated with systemic corticosteroids during RSV season (Sep 1–Apr 1) from 2008–2015; 24 infants with chILD; Treated with CS in first vs. second season: 20 vs. 16 infants; No PVZ prophylaxis in first vs. second season: 9/20 vs. 9/16 infants	**RSV-hospitalized: 6** Admissions for bronchiolitis: 18 (two infants had RSV infection prior to receiving PVZ prophylaxis) Infants without PVZ: four infants hospitalized for RSV-bronchiolitis	**Prophylaxis:** 9/20 (45%) infants treated with corticosteroids in their first RSV season did not receive PVZ prophylaxis; 9/16 (56%) infants treated with corticosteroids in their second season did not receive PVZ prophylaxis **Other treatments/ therapies:** Most infants on supplemental oxygen at home prior to hospital admission; First vs. second season: Corticosteroid pulse: 89% vs. 100% Oral corticosteroids: 56% vs. 33% Hydroxycholoroquine: 11% vs. 11% Azathioprine: 11% vs. 44% Mycophenolate-mofetil 11% vs. 33%	Childhood interstitial lung disease 100%	• Prematurity (<32 wGA) • CLD of prematurity • Requirement of oxygen concentration >21% for at least 28 d after birth	**Short-term** • Hospitalization • Hospital LOS • ICU admission (zero cases) • Case fatality (zero cases)	**Moderate risk** • Clinicians not blinded to risk factor (high risk for hospitalization) • Blinding of outcome assessment not reported (objective outcomes) • No adjustment for confounders

Table S6-1: Characteristics and risk of bias of included studies (*continued*)

Study author & year; Study design; Study period; Setting; Country; Funding source	Enrolled cohort and study sample	RSV cases	Prophylaxis and other treatments/ therapies	Patient characteristics by risk factor(s)—included populations	Excluded populations	Outcomes	Risk of bias
Farber 2016[36] Retrospective cohort 2012–2014 Hospital US No funding	Premature infants (29–36 wGA) without PVZ, hospitalized for RSV at ≤6 mo CA at start of RSV season (on or after Apr 1); Premature infants without PVZ: 12,812 29–32 wGA: 1,188 33–36 wGA: 11,624	**RSV-hospitalized: 542** Prematurity: 29–32 wGA: 59 (10.9%) 33–36 wGA: 483 (89.1%)	**Prophylaxis:** Premature infants with PVZ prophylaxis (study comparator) were not used **Other treatments/ therapies:** NR	Prematurity (29–36 wGA): 100%	<29 wGA; >36 wGA CLD CHD Pulmonary hypertension Hematopoietic stem cell or other transplantation Severe genetic syndrome	**Short-term** Hospitalization Hospital LOS (<1 d & ≥1 d)	**Low risk** Clinicians not blinded to risk factor (moderate risk for hospitalization)
Fauroux 2014[37] Retrospective FU of prospective cohort Birth cohort: Mar 1–Oct 2, 2008 RSV FU: Sep 2008–Apr 2009 Respiratory FU: May 1, 2009–Apr 30, 2010 Community & hospital France Industry	Infants born Mar 31–Oct 2, 2008 and <6 mo CA at start of RSV season (Sep 2008–Apr 2009); Birth cohort: 443 infants: 17 infants with history of RSV hospitalization: 14 premature & 3 term 426 infants without history of RSV hospitalization: 228 premature & 198 term	**History of RSV hospitalization: 17** Premature (<33 wGA): 14 Term (39–41 wGA): 3 **No history of RSV hospitalization: 426 infants**	**Prophylaxis:** Infants with PVZ prophylaxis were ineligible for study **Other treatments/ therapies:** NR	Prematurity (<33 wGA): 14/17 (82.4%) with history of hospitalization for RSV bronchiolitis; 228/426 (53.5%) without history of hospitalization for RSV bronchiolitis	BPD (oxygen dependence at 28 d of life); No documented immune deficiency or other serious chronic illness at start of 2008–2009 RSV season	**Short-term** • Hospitalization **Long-term (at age 1–2 y)** • Wheeze (parent & physician-reported) • Respiratory morbidity, non-specified excluding bronchiolitis, wheezing, and asthma (parent- & physician-reported)	**Moderate risk** • Clinicians not blinded to risk factor (high risk for hospitalization) • Parent and physician-reported outcome assessment • Outcome assessment not blinded
Feldman 2016[38] Retrospective cohort Liver transplant recipients Jan 1, 2004–Dec 31, 2012 Community & hospital US Funding NR	Children <18 y with previous liver transplant followed up 2 y post-transplantation for RSV infection; 2,554 infants with liver transplant; 415 with RSV and vaccine-preventable infections (R/VPI) & 2,139 without R/VPI	**RSV-positive: 415** RSV hospitalization during transplant hospitalization (assumed nosocomial): 92 immunocompromised infants with R/VPI RSV hospitalization 2 y post-transplantation (assumed community-acquired): 135 liver transplant infants with R/VPI First hospitalization for RSV: 132 infants (timing NR—first and/ or second year post-transplant) Time from transplant to RSV infection, among all infants with R/VPI: mean 0.7 y; median 0.5 y	**Prophylaxis:** NR **Other treatments/ therapies:** NR	Immunocompromised (previous liver transplantation): 100% Prematurity (ND): 31/2554 (1.2%)	NR	**Short-term** • Hospitalization • Hospital LOS • ICU admission • Mechanical ventilation • Case fatality	**Low risk** • Clinicians not blinded to risk factor (moderate risk for hospitalization)

Table S6-1: Characteristics and risk of bias of included studies (*continued*)

Study author & year; Study design; Study period; Setting; Country; Funding source	Enrolled cohort and study sample	RSV cases	Prophylaxis and other treatments/ therapies	Patient characteristics by risk factor(s)—included populations	Excluded populations	Outcomes	Risk of bias
Franklin 2016[53]; associated publication Ambrose 2014 & Simões 2016[a] Prospective cohort RSV seasons 2009–2010 & 2010-2011 (Nov–Mar) Clinics, ED & hospital US Industry	Premature infants (32^0–35^6 wGA) not receiving RSV prophylaxis, born May to February and <6 mo CA at enrollment; 1,642 infants: 1,634 with insurance status (820 private vs. 814 public)	**RSV-positive, among infants with insurance status: 268**	**Prophylaxis:** Premature infants who received RSV IP were ineligible for study **Other treatments/ therapies:** NR	Prematurity (32–35 wGA) 100%	• CLD of prematurity • HS-CHD • Life expectancy <6 mo • Received RSV IP	Short-term • Hospitalization • ICU admission	Moderate risk • Clinicians not blinded to risk factor (high risk for hospitalization) • 84% follow-up
Groves 2016[39] Retrospective cohort Infants diagnosed with CF 1997–2002, with FU at 6 y CF clinic & hospital Northern Ireland Funding NR	Children born and diagnosed with cystic fibrosis (1997–2002) prior to PVZ prophylaxis and admitted to hospital with RSV-LRTI; 47 infants with CF; 10 (21.3%) hospitalized with RSV-LRTI	**RSV-hospitalized: 10**	**Prophylaxis:** Infants born 1997–2002 (study population) did not receive PVZ prophylaxis **Other treatments/ therapies:** All patients received flucloxacillin from birth	CF 100%	NR	**Short-term** • Hospitalization • Hospital LOS	Moderate risk • Clinicians not blinded to risk factor (high risk for hospitalization) • No adjustment for confounders

Table S6-1: Characteristics and risk of bias of included studies (*continued*)

Study author & year; Study design; Study period; Setting; Country; Funding source	Enrolled cohort and study sample	RSV cases	Prophylaxis and other treatments/ therapies	Patient characteristics by risk factor(s)—included populations	Excluded populations	Outcomes	Risk of bias
Hama 2015[40] Retrospective cohort Sep 2002–Oct 2011, <2 y chronologic age as of Mar 2012 Hospital Japan Funding NR	Infants with CCLD, hospitalized in NICU for RSV at <2 y CA; 48 infants with antenatal diagnosis of CCLD (14 with surgical treatment during neonatal period)	RSV-hospitalized: 4 0–12 mo CA: 3 12–23 mo CA: 1	**Prophylaxis:** Infants who received PVZ (e.g. premature <36 wGA or with CLD) were ineligible for study **Other treatments/ therapies:** Case 1: pleural effusion and thoracocentesis (before birth), surgical resection after RSV hospitalization Case 2: transplacental steroid (before birth), surgical resection after RSV hospitalization (BA diagnosed) Case 3: cystocentesis and cystoamniotic shunt (before birth), emergency surgical resection (after birth), intubation and mechanical ventilation (before RSV hospitalization) Case 4: cystocentesis and cystoamniotic shunt (before birth), emergency surgical resection (after birth), intubation and mechanical ventilation (before RSV hospitalization)	Infants with prematurity at birth or with CLD were excluded	Prematurity (<36 wGA) or with CLD	**Short-term** • Hospital (NICU) admission • Hospital (NICU) LOS • Supplemental oxygen • Mechanical ventilation (zero cases)	**Low risk** • Clinicians not blinded to risk factor (moderate risk for NICU admission)
Hatanaka 2015[41] Retrospective cohort RSV hospitalization Apr 2006–Mar 2009 Hospital Japan Non-industry	Infants with hematological malignancies with RSV infection ≤24 mo CA; 12 infants: Eight infants with AML & four infants with ALL	**RSV-hospitalized: 12** RSV infection onset: Sep–Nov: 8/12 (61.5%) Dec–Feb: 4/12 (33.3%)	**Prophylaxis:** No infant received PVZ prophylaxis; 4/12 (33.3%) received PVZ as treatment after developing severe respiratory failure **Other treatments/ therapies:** IV antibiotics: 11/12 (91.7%), median duration 21 d (11-66) Steroids: 7/12 (58.3%), all with progressive LRTI; PVZ: 4/12 (33.3%)	Down's syndrome, without heart disease or other complications: 2/12 (16.7%)	NR	**Short-term** • Oxygen support • Mechanical ventilation • Case fatality	**High risk** • Unclear how outcomes were ascertained • Outcome assessment not blinded (objective outcomes) • No adjustment for confounders

Table S6-1: Characteristics and risk of bias of included studies (*continued*)

Study author & year; Study design; Study period; Setting; Country; Funding source	Enrolled cohort and study sample	RSV cases	Prophylaxis and other treatments/ therapies	Patient characteristics by risk factor(s)—included populations	Excluded populations	Outcomes	Risk of bias
Helfrich 2015[42] Retrospective cohort Birth cohort: Oct 2005–Apr 2011 Community (military) US Funding NR	Late premature (33^0–36^6 wGA) and term (≥37 wGA) infants hospitalized for RSV at <24 mo chronologic age; 599,535 infants: 25,890 late premature & 573,645 term	RSV-hospitalized: 7597 643 late preterm & 6,954 term **33–34 wGA: 164** **35–36 wGA: 479**	**Prophylaxis:** Infants who received PVZ (in or out-patient) were ineligible for study **Other treatments/ therapies:** NR	Late premature (33^0–36^6 wGA): 643/7,597 (8.5%)	• Premature (≤32^6 wGA) • CLD • CHD • CF • Down syndrome • Congenital airway anomalies • Neuromuscular disease • Immunodeficiency	**Short-term** • Hospitalization • Hospital LOS • Mechanical ventilation	Low risk • Clinicians not blinded to risk factor (moderate risk for hospitalization)
Korsten 2016[43] Prospective cohorts Jun 2008-Feb 2011 (cohort 1) & Feb 2011–Feb 2015 (cohort 2) Hospital Netherlands Industry and non-industry	Late premature infants (32^1–35^6 wGA) hospitalized for RSV in the first year of life; Cohort 1 (risk tool derivation): Late premature infants: 2,524 Hospitalized for RTI: 185 Cohort 2 (risk tool validation): Late premature infants: 1,564 Hospitalized for RTI: 120	**RSV-positive, among hospitalized for RTI: 181** Cohort 1 (2008–2011): 127 Cohort 2 (2011–2015): 54	**Prophylaxis:** Infants who received PVZ for any reason were excluded from data analysis **Other treatments/ therapies:** NR	Late prematurity (32^1–35^6 wGA): 100%	Gross congenital abnormalities (e.g. trisomy associated disorders)	**Short-term** • Hospitalization • Hospital LOS • ICU admission	**Low risk** • Clinicians not blinded to risk factor (moderate risk for hospitalization) • Baseline data not reported for population of interest • Parent-reported outcomes with verification by hospital; likely not blinded
Luchsinger 2014[44] Prospective cohort Winter, 2010 & 2011 Clinic & hospital Chile Non-industry	Previously healthy and term infants with community-acquired ALRTI at <6 mo CA; 124 infants	**RSV-positive, community-acquired: 102** RSV only: 74 RSV+HRV (co-infection): 28 (27.5%) Hospitalized (inpatients): 57 (77%): Hospitalization among infants with: a) severe RSV: 33/33 b) moderate RSV: 17/19 c) mild RSV: 7/22 Non-hospitalized (outpatients): 17 (23%): moderate RSV: 2 a) mild RSV: 15	**Prophylaxis:** NR **Other treatments/ therapies:** NR	Infants with specified risk factors were excluded	Prematurity BPD CHD Primary or secondary immunodeficiency	Short-term Hospitalization Hospital LOS ICU admission (critical care unit, 100% of all severe RSV cases) Supplemental oxygen (100% of all moderate & severe RSV cases) Supplemental oxygen duration Mechanical ventilation (100% of all severe RSV cases) Case fatality (death, zero cases)	High risk Unclear how outcomes were ascertained Blinding of outcome assessment not reported No adjustment for confounders

Table S6-1: Characteristics and risk of bias of included studies (*continued*)

Study author & year; Study design; Study period; Setting; Country; Funding source	Enrolled cohort and study sample	RSV cases	Prophylaxis and other treatments/ therapies	Patient characteristics by risk factor(s)—included populations	Excluded populations	Outcomes	Risk of bias
McLaurin 2016[45] Retrospective cohort Birth cohort: Jul 1, 2003–Jun 30, 2013 Hospital US Industry	Medicaid and commercially insured infants born and followed to end of insurance enrollment, end of study period, or end of first year of life; Medicaid: 2,163,435 infants (1,501,590 full term) Commercial: 2,124,753 infants (1,516,598 full term)	**RSV-hospitalized, healthy & full term (≥37 wGA):** <90 days of age, total: 20,177 Medicaid: 12,699 Commercial: 7,478 <1 y of age, total: 38,372 Medicaid: 24,487 Commercial: 13,885	**Prophylaxis:** Included infants may have received PVZ during their first year of life, which would have influenced the outcomes observed for preterm infants, who are more likely to receive prophylaxis. **Other treatments/ therapies:** NR	Infants with risk factors other than prematurity were excluded * Only data for healthy full-term infants (≥37 wGA) were utilized for review (for whom prophylaxis is unlikely)	• BPD/CLD • HS-CHD • CF • Down syndrome • Immunodeficiencies • Organ transplants	**Short-term** • Hospitalization (<1 d & <90 d) • Hospital LOS • ICU admission	**Moderate risk** • No baseline demographics except wGA at birth • No adjustment for confounders
O'Brien 2015[46] Prospective cohort, placebo arm of RCT Nov 2004–Dec 2010 Community & hospital US Industry	Infants born at ≥36 wGA admitted to hospital for MALRI at <6 mo CA; ITT: 710 infants (nine infants received one dose of motavizumab) PP: 571 infants	**RSV-positive, hospitalized & non-hospitalized: 151**	**Prophylaxis:** Infants who received at least one dose of motavizumab (n=9; 1.3%) included in ITT analysis, but excluded from PP analysis **Other treatments/ therapies:** NR	• Indigenous: 100%, by tribe/ethnic origin: • Navajo: 81%; • White Mountain Apache: 14%; • San Carlos Apache: 2%; • Hopi: 1%; • Other: 1%	NR	**Short-term** • Hospitalization • Hospital LOS • ICU admission • ICU LOS • Supplemental oxygen • Supplemental oxygen duration • Mechanical ventilation • Mechanical ventilation duration • Case fatality • Adverse events	**Moderate risk** • Clinicians not blinded to risk factor (high risk for hospitalization) • Short (150-day) follow-up period for hospitalization outcome • No adjustment for confounders
Rajah 2017[47] Retrospective cohort with non-concurrent controls Oct 1, 2013–May 31, 2014 (Season 1, pre-2014 AAP guidance); Oct 1, 2014–May 31, 2015 (Season 2, post-2014 AAP guidance) Hospital US Non-industry	Premature infants (29^0–34^6 wGA), hospitalized with bronchiolitis, and RSV-positive at <12 mo CA; Hospitalized for bronchiolitis: 1471 Season 1: 671 Season 2: 800	**RSV-positive, among hospitalized: 91** Season 1: 34 <3 mo: 10 3–<6 mo: 7 6–<12 mo: 17 Season 2: 57 <3 mo: 19 3–<6 mo: 22 6–<12 mo:16	**Prophylaxis:** PVZ eligibility for infants decreased, 32.3% (11/34) to 1.8% (1/57), based on pre-2014 AAP vs. post-2014 guidance for the respective cohorts. Four (12%) infants in season 1 and one (2%) in season 2 received at least one dose of PVZ **Other treatments/ therapies:** NR	Six (6.6%) premature infants from both seasons combined had additional, mutually exclusive comorbidities: • CLD: 3.3% • CHD: 1.1% • Reactive airway disease: 1.1% • Central apnea receiving home oxygen therapy: 1.1%	NR	**Short-term** • Hospital LOS • PICU admission • PICU LOS • Supplemental oxygen • Supplemental oxygen duration • Mechanical ventilation • Mechanical ventilation duration	**Moderate risk** • Patients sampled from RSV seasons pre and post-AAP guidance (used data for post-AAP only) • No adjustment for confounders

Table S6-1: Characteristics and risk of bias of included studies (*continued*)

Study author & year; Study design; Study period; Setting; Country; Funding source	Enrolled cohort and study sample	RSV cases	Prophylaxis and other treatments/ therapies	Patient characteristics by risk factor(s)—included populations	Excluded populations	Outcomes	Risk of bias
Ryan 2016[48] Retrospective cohort Birth cohort: Jul 1, 1998–Jun 31, 2008 Hospital Canada No funding	Premature infants (32^0–35^6 wGA) hospitalized with RSV at <12 mo CA; Birth cohort: 2,811 infants	**RSV-hospitalized: 88**	**Prophylaxis:** • Infants who received PVZ were excluded from the study **Other treatments/ therapies:** NR	Prematurity (32^0–35^6 wGA) 100%	• Lung disease • Cardiac disease • Early or late neonatal death	**Short-term** • Hospitalization • Case fatality (zero cases attributable to RSV)	**Low risk** • Clinicians not blinded to risk factor (moderate risk for hospitalization)
Sadreameli 2014[49] Retrospective cohort Sep 1, 1993–Jun 30, 2011 Hospital US Non-industry	Children <18 y with sickle cell disease and RSV-positive at <2 y, <5 y and <18 y CA; 64 infants	**RSV-positive: 64**	**Prophylaxis:** NR **Other treatments/ therapies:** NR	Sickle cell disease 100%; Infants with dual infections (RSV and influenza A/B) or pandemic influenza (H1N1) were excluded	NR	**Short-term** • Hospitalization (<2 y) • Hospital LOS • ICU admission • Ventilator support	**Low risk** • Clinicians not blinded to risk factor (moderate risk for hospitalization)
Simões 2016[54]; associated publication Ambrose 2014 & Franklin 2016[a] Prospective cohort RSV seasons 2009–2010 or 2010–2011 (Nov–Mar) Clinics, ED & hospital US Industry	Premature infants (32^0–35^6 wGA) not receiving RSV prophylaxis, born May to February and <6 mo CA at enrollment; 1,642 infants	**RSV-positive: 287** RSV-positive, hospitalized: 57 By GA: 32 wGA: 3 33 wGA: 5 34 wGA: 13 35 wGA: 36	**Prophylaxis:** Infants who were considered or received immunoprophylaxis were excluded from the study **Other treatments/ therapies:** NR	Prematurity (32^0–35^6 wGA): 100%	• CLD of prematurity • HS-CHD • Life expectancy <6 mo	**Short-term** • Hospitalization • ICU admission	**Moderate risk** • Clinicians not blinded to risk factor (high risk for hospitalization) • 84% follow-up
Stagliano 2015[50] Retrospective cohort Birth cohort (Oct 1, 2005–Apr 30, 2011) Military treatment facilities US Funding NR	Children enrolled in military health database and hospitalized for RSV at <3 y CA; Birth cohort: 633,200 children With Down syndrome: 842 Without Down syndrome: 632,358	**RSV-hospitalized, without comorbidities: 7,206** With Down syndrome: 17 Without Down syndrome (≥37 wGA): 7,189	**Prophylaxis:** Children who received PVZ either as outpatients or inpatients were excluded from the study **Other treatments/ therapies:** NR	Down syndrome, without other risk factors: 17 children	Subgroup analysis (by study authors) for patients with vs. without Down syndrome, without other risk factors: • Prematurity • CLD • HS-CHD, other CHD • Neuromuscular disease • Immunodeficiency • CF • Congenital airway anomalies	**Short-term** • Hositalisation (<2 y) • Hospital LOS	Low risk • Clinicians not blinded to risk factor for infants with Down syndrome (moderate risk for hospitalization)

Table S6-1: Characteristics and risk of bias of included studies (*continued*)

Study author & year; Study design; Study period; Setting; Country; Funding source	Enrolled cohort and study sample	RSV cases	Prophylaxis and other treatments/ therapies	Patient characteristics by risk factor(s)—included populations	Excluded populations	Outcomes	Risk of bias
Straňák 2016[51] Prospective cohort Birth cohort (Apr 1, 2013–Feb 28, 2014); RSV season (Oct 1, 2013–Apr 30, 2014); Study period (Sep 2013–Jul 2014) Hospital Multi-national (Austria, Bahrain, Bosnia, Bulgaria, Czech Republic, Egypt, Estonia, France, Jordan, Latvia, Lebanon, Lithuania, Mexico, Norway, Oman, Portugal, Saudi Arabia, Slovakia, Slovenia, South Korea, Russia, Sweden, Switzerland) Industry	Premature infants (33^0–35^6 Wga) and ≤6 mo CA on Oct 1 with RSV-associated LRTI hospitalization; Birth cohort: 2,390 infants; 164 hospitalized for LRTI	**RSV-positive, among hospitalized for LRTI: 64** Hospitalized for LRTI: 164 Hospitalized for LRTI, RSV-positive: 64	**Prophylaxis:** Infants who were eligible for or received immunoprophylaxis were excluded from the study **Other treatments/ therapies**: NR	Prematurity (33^0–35^6 wGA): 100%; Infants with other underlying conditions (data NR), including CF or Down syndrome (zero cases), were included	Preterm infants with: • BPD/CLD • HS-CHD	**Short-term** • PICU/NICU admission • PICU/NICU LOS • Supplemental oxygen • Supplemental oxygen duration • Mechanical ventilation • Mechanical ventilation duration	Low risk • No major concerns
Zomer-Kooijker 2014[52] Prospective cohort Birth cohort: 2003–2005 and 2006–2007 Community & hospital Netherlands Industry and non-industry	Healthy term (≥36 wGA) infants <1 y CA; Cohort with successful lung function measurement at <2 mo CA: 2,133 infants	**RSV-positive, hospitalized & non-hospitalized: 102** RSV-positive, hospitalized: 18 RSV-positive, non-hospitalized: 84	**Prophylaxis:** NR **Other treatments/ therapies:** NR	Infants with specified risk factors were excluded	• Prematurity (<36 wGA) • Neonatal respiratory disease • Major congenital abnormalities	**Short-term** • Hospitalization • Long-term • Wheeze at age 1 y (parent-reported)	**Moderate risk** • Baseline characteristics not described for population of interest • Parent-reported outcome (wheeze; subjective)

Abbreviations: AAP, American Academy of Pediatrics; ALL, acute lymphoblastic leukemia; ALRI/LRI/LRTI/RTI, acute/lower respiratory tract infection; AML, acute myeloid leukemia; BPD, bronchopulmonary dysplasia; CA, chronologic age; CF, cystic fibrosis; CHD, congenital heart disease; chILD, childhood interstitial lung disease; CCLD, congenital cystic lung disease; CLD, chronic lung disease; CS, corticosteroids; d, day(s); ECMO, extracorporeal membrane oxygenation; ED, emergency department; FU, follow-up; GA, gestational age; HS, hemodynamically significant; HRV, rhinovirus; ICU, intensive care unit; IMV, intensive mechanical ventilation; IP, immunoprophylaxis; ITT, intention-to-treat; IV, intravenous; LOS, length of stay; MAARI, medically-attended illness; MALRI, medically attended acute lower respiratory tract infection; mo, month(s); ND, not defined; NICU, neonatal intensive care unit; NR, not reported; PICU, pediatric intensive care unit; PP, per-protocol; PVZ, palivizumab; RCT, randomized controlled trial; RSV, respiratory syncytial virus; RSV-H, respiratory syncytial virus hospitalization; R/VPI, RSV and vaccine-preventable infection; US, Unites States; vs., versus; wGA, weeks' gestational age; y, year(s)

[a] Associated publications: Ambrose 2014 (primary publication), Franklin 2016 (study cohort analyzed by insurance status for hospitalization and ICU admission), and Simões 2016 (hospitalization and ICU admission rates analyzed by chronologic age and birth month)

Supplement 7: Outcomes of included studies

Table S7-1: Short and long-term outcomes reported among included studies

Risk status and studies	Short-term outcomes									Long-term outcomes		
	Incidence of RSVH	Hospital LOS	ICU admission	ICU LOS	Oxygen therapy	Duration of oxygen therapy	MV therapy	Duration of MV	Case fatality	Wheeze	Asthma	Lung function
Prematurity												
Ambrose 2014 (PC)	■	■	■				■					
Anderson 2017 (PC)		■	■	■			■	■	■			
Blanken 2016 (PC)	■											
Carbonell-Estrany 2015 (PC)	■									■	■	■
Farber 2016 (PC)	■	■										
Fauroux 2014 (RFUPC)[a]	■									■		■
Helfrich 2015 (RC)[a]	■	■					■					
Korsten 2016 (PC)	■	■	■									
Rajah 2017 (RCNCC)		■	■	■	■	■	■	■				
Ryan 2016 (RC)	■								■			
Straňák 2016 (PC)	■		■	■	■	■	■	■				
CCLD												
Hama 2015 (RC)	■	■	■		■		■					
CF												
Bjornson 2018 (RC)	■	■	■	■								
Groves 2016 (RC)	■											
chILD												
Drummond 2016 (RC)	■	■	■						■			
Down syndrome												
Stagliano 2015 (RC)[a]	■	■										
HS-CHD												
Chu 2017 (RC)	■											
Remote geographic												
Banerji 2016 (PC)	■											
O'Brien 2015 (PC)	■	■	■	■	■	■	■	■	■			
Hatanaka 2015 (RC)					■		■		■			

Table S7-1: Short and long-term outcomes reported among included studies (*continued*)

Risk status and studies	Short-term outcomes									Long-term outcomes		
	Incidence of RSVH	Hospital LOS	ICU admission	ICU LOS	Oxygen therapy	Duration of oxygen therapy	MV therapy	Duration of MV	Case fatality	Wheeze	Asthma	Lung function
Liver transplant recipient												
Feldman 2016 (PC)	■	■	■				■		■			
Sickle cell disease												
Sadreameli 2014 (RC)	■	■	■				■					
Healthy term												
Backman 2018 (PC)											■	■
Backman 2014 (PC)											■	■
Bonnelykke 2015 (PC)											■	
Caserta 2017 (PC)	■	■	■			■	■					
Fauroux 2014 (RFUPC)[a]	■									■		■
Helfrich 2015 (RC)[a]	■	■					■					
Luchsinger 2014 (PC)	■	■	■		■	■	■		■			
McLaurin 2016 (PC)	■	■	■									
Stagliano 2015 (RC)[a,b]		■										
Zomer-Kooijker 2014 (PC)	■									■		

Abbreviations: CCLD, congenital cystic lung disease; CF, cystic fibrosis; chILD, childhood interstitial lung disease; HS-CHD, hemodynamically significant congenital heart disease; ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation; PC, prospective cohort; RC, retrospective cohort; RCNCC, retrospective cohort of non-concurrent controls; RFUPC, retrospective follow-up of prospective cohort; RSVH, respiratory syncytial virus hospitalization

[a] Study includes eligible at-risk and non-at-risk populations, and is therefore represented in more than one risk category

[b] Data was only included for within-study comparators; data from comparator group of children without Down syndrome (all <3 years) were not pooled with other studies having data for healthy term children (<2 years)

Supplement 8: Single group proportions for short-term outcomes

8a: Single group proportions for hospitalization
- Table S8-1: Single group proportions for hospitalization (dichotomous outcomes)
- Table S8-2: Single group proportions for hospital length of stay (continuous outcomes)

8b: Single group proportions for ICU outcomes
- Table S8-3: Single group proportions for ICU (dichotomous outcomes)
- Table S8-4: Single group proportions for ICU length of stay (continuous outcomes)

8c: Single group proportions for oxygen therapy
- Table S8-5: Single group proportions for oxygen therapy (dichotomous outcomes)
- Table S8-6: Single group proportions for duration of oxygen support (continuous outcomes)

8d: Single group proportions for mechanical ventilation therapy
- Table S8-7: Single group proportions for mechanical ventilation therapy (dichotomous outcomes)
- Table S8-8: Single group proportions for duration of mechanical ventilation (continuous outcomes)

8e: Single group proportions for ECMO therapy (no studies)
- Table S8-9: Single group proportions for ECMO therapy among a hospitalized population (no study)

8f: Single group proportions for case fatality
- Table S8-10: Single group proportions for case fatality (dichotomous outcomes)

8a: Single group proportions for hospitalization

Table S8-1: Single group proportions for hospitalization (dichotomous outcomes)

Outcome and risk status	Study (study design)	Risk of bias	Number of patients with events	Total number of patients	Proportion, % (95% CI)
Incidence of RSV-hospitalization among population *with risk*					
29 to <33 wGA	TOTAL (2 studies)		73	1,430	5.1 (4.0, 6.3)
29–32	Farber 2016 (PC)	Moderate	59	1,188	5.0 (3.7, 6.2)
<33	Fauroux 2014 (RFUPC)	Moderate	14	242	5.8 (2.8, 8.7)
32-34 wGA	TOTAL (1 study)		21	753	2.8 (1.6, 4.0)
	Ambrose 2014 (PC)	High	21	753	2.8 (1.6, 4.0)
35 wGA	TOTAL (1 study)		36	889	4.1 (2.8, 5.4)
	Ambrose 2014 (PC)	High	36	889	4.1 (2.8, 5.4)
32/33–35 wGA	TOTAL (8 studies)		1,906	57,838	3.3 (2.7, 4.1)
32^0–35^6	Ambrose 2014 (PC)	High	57	1,642	3.5 (2.6, 4.4)
32^1–35^6	Blanken 2016 (PC)	Moderate	181	3,952	4.6 (3.9, 5.2)
32^1–35^6	Carbonell-Estrany 2015 (PC)	High	125	5,441	2.3 (1.9, 2.7)
33–36	Farber 2016 (PC)	Moderate	483	11,624	4.2 (3.8, 4.5)
33–36	Helfrich 2015 (RC)	Moderate	643	25,890	2.5 (2.3, 2.7)
32^1–35^6	Korsten 2016 (PC)	Moderate	181	4,088	4.4 (3.8, 5.1)
32^0–35^6	Ryan 2016 (RC)	Moderate	88	2,811	3.1 (2.5, 3.8)
33^0–35^6	Stranak 2016 (PC)	Moderate	64	2,390	2.7 (2.0, 3.3)
29–36 wGA	TOTAL (1 study)		542	12,812	4.2 (3.9, 4.6)
	Farber 2016 (PC)	Moderate	542	12,812	4.2 (3.9, 4.6)
HS-CHD	TOTAL (1 study)				Not estimable

Table S8-1: Single group proportions for hospitalization (dichotomous outcomes) (*continued*)

Outcome and risk status	Study (study design)	Risk of bias	Number of patients with events	Total number of patients	Proportion, % (95% CI)
	Chu 2017 (RC), 1997 & 2000	Moderate	National estimate 734	NR	Incidence per 1,000 hospitalizations for HS-CHD: 23 (20, 26)
CCLD	TOTAL (1 study)		4	48	8.3 (0.5, 16.2)
	Hama 2015 (RC)	Moderate	4	48	8.3 (0.5, 16.2)
CF	TOTAL (2 studies)		15	131	12.3 (1.3, 30.8)[a]
	Bjornson 2018 (RC)	High	5	84	6.0 (0.9, 11.0)
	Groves 2016 (RC)	High	10	47	21.3 (9.6, 33.0)
chILD	TOTAL (1 study)		6	20	30.0 (9.9, 50.1)
	Drummond 2016 (RC)	High	6	20	30.0 (9.9, 50.1)
Down syndrome	TOTAL (1 study)				Not estimable
<3 y without comorbidities	Stagliano 2015 (RC)	Moderate	17	NR	2% absolute rate; Incidence density 12.7 per 1,000 person-years
Remote geographic	TOTAL (2 studies)				Not estimable
	Banerji 2016 (PC)	High	124 admissions positive for RSV	298 admissions tested for RSV	41.6 (36.0, 37.2) 66.9 admissions per 1,000 live births per year
	O'Brien 2015 (PC), PP	High	73	571	12.8 (10.1, 15.5)
Liver transplant recipient	TOTAL (1 study)		135	2,554	5.3 (4.4, 6.2)
<18 y	Feldman 2016 (RC), RSV-H 2 y post-transplant	Moderate	135	2,554	5.3 (4.4, 6.2)
SCD	TOTAL (1 study)				Not estimable
	Sadreameli 2014 (RC)	Moderate	NR	NR	63 per 1,000 person-years (44 to 87)
Incidence of RSV-hospitalization among population *without risk*					
Healthy term	TOTAL (4 studies)		45,347	3,594,167	1.2 (1.1, 1.2)
39–41 wGA	Fauroux 2014 (RFUPC)	Moderate	3	201	1.5 (-0.2, 3.2)
≥37 wGA	Helfrich 2015 (RC)	Moderate	6,954	573,645	1.2 (1.2, 1.2)
≥37 wGA	McLaurin 2016 (RC)	Moderate	38,372	3,018,188	1.3 (1.3, 1.3)
≥36 wGA	Zomer-Kooijker 2014 (PC)	Moderate	18	2,133	0.8 (0.5, 1.2)

Abbreviations: CCLD, congenital cystic lung disease; CF, cystic fibrosis; chILD, childhood interstitial lung disease; CI, confidence interval; HS-CHD, hemodynamically significant congenital heart disease; NR, not reported; PC, prospective cohort; PP, per protocol (patients who received prophylaxis were excluded in per protocol analysis); RC, retrospective cohort; RFUPC, retrospective follow-up of prospective cohort; RSV, respiratory syncytial virus; RSV-H, respiratory syncytial virus hospitalization; wGA, weeks' gestational age; y, year(s)

[a] Some uncertainty in pooled proportion of studies, with different individual study proportions

Table S8-2: Single group proportions for hospital length of stay (continuous outcomes)

Outcome and risk status	Study (study design)	Risk of bias	Number of patients	Mean (SD)	Mean (95% CI)
Hospital length of stay (days) among population *with risk*					
29–32 wGA	TOTAL (1 study)		89		10 (7.7, 12.3)
	Anderson 2017 (PC)	Moderate	89	10 (11)	10 (7.7, 12.3)
33–34 wGA	TOTAL (2 studies)		245		5.5 (0.6, 10.4)
	Anderson 2017 (PC)	Moderate	81	8 (6)	8 (6.7, 9.3)
	Helfrich 2015 (RC)	Low	164	3.00 (1.48)	3.00 (2.77, 3.22)
35 wGA	TOTAL (1 study)		42		7 (4.9, 9.1)
	Anderson 2017 (PC)	Moderate	42	7 (7)	7 (4.9, 9.1)
32/33–35 wGA	TOTAL (3 studies)		7,835		4.5 (2.3, 6.8)
32^0–35^6	Ambrose 2014 (PC)	Moderate	57	4.0 (3.5)	4.0 (3.1, 4.9)
32^1–35^6	Korsten 2016 (PC)	Low	181	6.7 (5.5)	6.7 (5.9, 7.5)
33–36	Helfrich 2015 (RC)	Low	7,597	3.00 (1.48)	3.00 (2.92, 3.08)
29–24/35 wGA	TOTAL (2 studies)		264		7.7 (6.1, 9.2)
29^0–34^6	Rajah 2017 (RCNCC)—post-AAP	Moderate	52	5.9 (13.2)	5.9 (2.3, 9.5)
29^0–35^6	Anderson 2017 (PC)	Moderate	212	8 (9)	8 (6.8, 9.2)
CCLD	TOTAL (1 study)		4		11.25 (9.29, 13.21)
	Hama 2015 (RC)	Low	4	11.25 (2.00)	11.25 (9.29, 13.21)
chILD	TOTAL (1 study)		4		6 (-0.6, 12.6)
	Drummond 2016 (RC)	Moderate	4	6 (7)	6 (-0.6, 12.6)
CF	TOTAL (2 studies)				Not estimable
	Bjornson 2018 (RC)	Moderate	5	47.00 (39.32)	47.00 (12.53, 81.47)
	Groves 2016 (RC)	Moderate	10	10 (NR)	Not estimable
Down syndrome	TOTAL (1 study)		17		5 (4.0, 6.0)
RSV <3 y, without comorbidities	Stagliano 2015 (RC)	Low	17	5 (2.2)	5 (4.0, 6.0)
Remote geographic	TOTAL (1 study)		80		4.7 (4.2, 5.2)
	O'Brien 2015 (PC), ITT	Moderate	80	4.7 (2.5)	4.7 (4.2, 5.2)
Liver transplant recipient	TOTAL (1 study)		135		Not estimable
<18 y	Feldman 2016 (RC)	Low	135	23 (NR)	Not estimable
Sickle cell disease	TOTAL (1 study)		64		2.0 (1.8, 2.2)
<18 y	Sadreameli 2014 (RC)	Low	64	2.0 (1.0)	2.0 (1.8, 2.2)
Hospital length of stay (days) among population *without risk*					
Healthy term	TOTAL (4 studies)		45,410		3.5 (2.3, 4.7)
≥36 wGA; RSV-H <10 mo	Caserta 2017 (PC)	Moderate	84	4.20 (2.6)	4.20 (-0.89, 9.30)
≥37 wGA; RSV-H <1 y	Helfrich 2015 (RC)	Low	6,954	2 (1.5)	2 (2.0, 2.0)
≥37 wGA; RSV-H <1 y	McLaurin 2016 (PC)	Moderate	38,372	4.2 (1.5)	4.2 (4.2, 4.2)
All RSV (severe+moderate+mild); Term	Luchsinger 2014 (PC)	High	57	Geometric means: severe RSV 11.09 (SE 0.93) Moderate RSV 4.32 (SE 0.34) Mild RSV 2.35 (SE 0.35)	Not estimable

Abbreviations: AAP, American Academy of Pediatrics; CCLD, congenital cystic lung disease; CF, cystic fibrosis; chILD, childhood interstitial lung disease; CI, confidence interval; ITT, intention to treat; mo, month(s); NR, not reported; PC, prospective cohort; RC, retrospective cohort; RCNCC, retrospective cohort with non-concurrent cohort; RSV, respiratory syncytial virus; RSV-H, respiratory syncytial virus hospitalization; SD, standard deviation; SE, standard error; wGA, weeks' gestational age; y, year(s)

8b: Single group proportions for ICU outcomes

Table S8-3: Single group proportions for ICU (dichotomous outcomes)

Outcome and risk status	Study (study design)	Risk of bias	Number of patients with events	Total number of patients	Proportion, % (95% CI)
ICU admission among population *with risk*					
32–34 wGA	TOTAL (1 study)		4	753	0.5 (0.01, 1.1)
	Ambrose 2014 (PC)	Moderate	4	753	0.5 (0.01, 1.1)
35 wGA	TOTAL (1 study)		5	889	0.6 (0.1, 1.1)
	Ambrose 2014 (PC)	Moderate	5	889	0.6 (0.1, 1.1)
32/33–35 wGA	TOTAL (3 studies)		44	6,120	0.7 (0.5, 0.9)
32^0–35^6	Ambrose 2014 (PC)	Moderate	9	1,642	0.6 (0.2, 0.9)
32^1–35^6	Korsten 2016 (PC)	Low	16	2,088	0.8 (0.4, 1.1)
33^0–35^6	Stranak 2016 (PC)	Low	19	2,390	0.8 (0.4, 1.2)
CF	TOTAL (1 study)		2	84	2.4 (-0.9, 5.6)
	Bjornson 2018 (RC)	Moderate	2	84	2.4 (-0.9, 5.6)
CCLD	TOTAL (1 study)		0	48	0.0 (0.0, 0.0)
	Hama 2015 (RC)	Low	0	48	0.0 (0.0, 0.0)
chILD	TOTAL (1 study)		0	20	0.0 (0.0, 0.0)
	Drummond 2016 (RC)	Moderate	0	20	0.0 (0.0, 0.0)
Remote geographic	TOTAL (1 study)		5	710	0.7 (0.1, 1.3)
	O'Brien 2015 (PC), ITT	Moderate	5	710	0.7 (0.1, 1.3)
Liver transplant recipient	TOTAL (1 study)		30	2,554	1.2 (0.8, 1.6)
<18 y	Feldman 2016 (RC)	Low	30	2,554	1.2 (0.8, 1.6)
ICU admission among hospitalized population *with risk*					
29–32 wGA	TOTAL (1 study)		46	89	51.7 (41.3, 62.1)
	Anderson 2017 (PC)	Moderate	46	89	51.7 (41.3, 62.1)
32–34 wGA	TOTAL (1 study)		4	21	19.1 (2.3, 35.8)
	Ambrose 2014 (PC)	Moderate	4	21	19.1 (2.3, 35.8)
35 wGA	TOTAL (1 study)		5	36	13.9 (2.6, 25.2)
	Ambrose 2014 (PC)	Moderate	5	36	13.9 (2.6, 25.2)
32-35 wGA	TOTAL (3 studies)		90	244	31.5 (13.1, 53.6)
32^0-35^6	Ambrose 2014 (PC)	Moderate	9	57	15.8 (6.3, 25.3)
33-35	Anderson 2017 (PC)	Moderate	62	123	50.4 (41.6, 59.2)
33^0-35^6	Stranak 2016 (PC)	Low	19	64	29.7 (18.5, 40.9)
29–34/35 wGA	TOTAL (2 studies)		138	264	52.0 (46.0, 58.0)
29^0–35^6	Anderson 2017 (PC)	Moderate	108	212	50.9 (44.2, 57.7)
29^0–34^6	Rajah 2017 (RCNCC)—post-AAP	Moderate	30	52	57.8 (44.3, 71.1)
CCLD	TOTAL (1 study)		0	4	0.0 (0.0, 0.0)
	Hama 2015 (RC)	Low	0	4	0.0 (0.0, 0.0)
chILD	TOTAL (1 study)		0	6	0.0 (0.0, 0.0)
	Drummond 2016 (RC)	Moderate	0	6	0.0 (0.0, 0.0)
Remote geographic	TOTAL (1 study)		5	80	6.3 (1.0, 11.6)
	O'Brien 2015 (PC), ITT	Moderate	5	80	6.3 (1.0, 11.6)
Liver transplant recipient	TOTAL (1 study)		30	135	22.2 (15.2, 29.2)
<18 y	Feldman 2016 (RC)	Low	30	135	22.2 (15.2, 29.2)

Table S8-3: Single group proportions for ICU (dichotomous outcomes) (*continued*)

Outcome and risk status	Study (study design)	Risk of bias	Number of patients with events	Total number of patients	Proportion, % (95% CI)
SCD	TOTAL (1 study)		3	64	4.7 (-0.5, 9.9)
<18 y	Sadreameli 2014 (RC)	Low	3	64	4.7 (-0.5, 9.9)
ICU admission among hospitalized population *without risk*					
Healthy term	TOTAL (3 studies)		3,168	38,513	15.8 (5.4, 30.0)[a]
PICU; ≥36 wGA	Caserta 2017 (PC)	Moderate	11	84	13.1 (5.9, 20.3)
Critical care unit; Term	Luchsinger 2014 (PC)	High	18	57	31.6 (19.5, 43.7)
ICU (Medicaid + Commercial insured); ≥37 wGA	McLaurin 2016 (RC)	Moderate	3,139	38,372	8.2 (7.8, 8.5)

Abbreviations: AAP, American Academy of Pediatrics; CCLD, congenital cystic lung disease; CF, cystic fibrosis; chILD, childhood interstitial lung disease; CI, confidence interval; ICU, intensive care unit; ITT, intention to treat; PC, prospective cohort; PICU, pediatric intensive care unit; RC, retrospective cohort; RCNCC, retrospective cohort with non-concurrent cohort; SCD, sickle cell disease; wGA, weeks' gestational age; y, year(s)
[a] Some uncertainty in pooled proportion among studies, with different individual study proportions

Table S8-4: Single group proportions for ICU length of stay (continuous outcomes)

Outcome and risk status	Study (study design)	Risk of bias	Number of patients	Mean (SD)	Mean (95% CI)
ICU length of stay (days) among hospitalized population *with risk*					
29–32 wGA	TOTAL (1 study)		46		9 (7.0, 11.0)
	Anderson 2017 (PC)	Moderate	46	9 (7)	9 (7.0, 11.0)
33–35 wGA	TOTAL (2 studies)		81		6.7 (5.5, 8.0)
	Anderson 2017 (PC)	Moderate	62	7 (6)	7 (5.5, 8.5)
NICU/PICU	Stranak 2016 (PC)	Low	19	6 (5)	6 (3.7, 8.3)
29–34/35 wGA	TOTAL (2 studies)		138		7.0 (4.7, 9.2)
29^0–35^6	Anderson 2017 (PC)	Moderate	108	8 (6)	8 (6.9, 9.1)
29^0–34^6	Rajah 2017 (RCNCC)—post-AAP	Moderate	30	5.7 (5.1)	5.7 (3.9, 7.5)
CF	TOTAL (1 study)		2		5.00 (-2.84, 12.84)
	Bjornson 2018 (RC)	Moderate	2	5.00 (5.66)	5.00 (-2.84, 12.84)
Remote geographic	TOTAL (1 study)		5		5.2 (2.1, 8.3)
	O'Brien 2015 (PC), ITT	Moderate	5	5.2 (3.5)	5.2 (2.1, 8.3)

Abbreviations: AAP, American Academy of Pediatrics; CF, cystic fibrosis; CI, confidence interval; ICU, intensive care unit; ITT, intention to treat; NICU, neonatal intensive care unit; PC, prospective cohort; PICU, pediatric intensive care unit; RC, retrospective cohort; RCNCC, retrospective cohort with non-concurrent cohort; SD, standard deviation; wGA, weeks' gestational age

8c: Single group proportions for oxygen therapy

Table S8-5: Single group proportions for oxygen therapy (dichotomous outcomes)

Outcome and risk status	Study (study design)	Risk of bias	Number of patients with events	Total number of patients	Proportion, % (95% CI)
Supplemental oxygen among population *with risk*					
29–34 wGA	TOTAL (1 study)		37	52	71.2 (58.9, 83.5)
29^0–34^6	Rajah 2017 (RCNCC)—post-AAP	Moderate	37	52	71.2 (58.9, 83.5)
33–35 wGA	TOTAL (1 study)		47	2,390	2.0 (1.4, 2.5)
33^0–35^6	Stranak 2016 (PC)	Low	47	2,390	2.0 (1.4, 2.5)
Remote geographic	TOTAL (1 study)		75	710	10.6 (8.3, 12.8)
	O'Brien 2015 (PC)	Moderate	75	710	10.6 (8.3, 12.8)
Supplemental oxygen among hospitalized population *with risk*					
33–35 wGA	TOTAL (1 study)		47	64	73.0 (62.6, 84.3)
33^0–35^6	Stranak 2016 (PC)	Low	47	204	23.0 (17.3, 28.8)
CCLD	TOTAL (1 study)		4	4	100.0 (100.0, 100.0)
	Hama 2015 (RC)	Low	4	4	100.0 (100.0, 100.0)
Remote geographic	TOTAL (1 study)		75	80	93.8 (88.5, 99.1)
	O'Brien 2015 (PC), ITT	Moderate	75	80	93.8 (88.5, 99.1)
Leukemia (AML & ALL)	TOTAL (1 study)		7	10	70.0 (41.6, 98.4)
	Hatanaka 2015 (RC)	High	7	10	70.0 (41.6, 98.4)

Abbreviations: AAP, American Academy of Pediatrics; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CCLD, congenital cystic lung disease; CI, confidence interval; ITT, intention to treat; PC, prospective cohort; RC, retrospective cohort; RCNCC, retrospective cohort with non-concurrent cohort; wGA, weeks' gestational age

Table S8-6: Single group proportions for duration of oxygen support (continuous outcomes)

Outcome and risk status	Study (study design)	Risk of bias	Number of patients	Mean (SD)	Mean (95% CI)
Duration of oxygen support (days) among population *with risk*					
29–34 wGA	TOTAL (1 study)		37		4.6 (0.5, 8.7)
29^0–34^6	Rajah 2017 (RCNCC)—post-AAP	Moderate	37	4.6 (12.7)	4.6 (0.5, 8.7)
32–35 wGA	TOTAL (1 study)		47		4 (3.2, 4.8)
	Stranak 2016 (PC)	Low	47	4 (3.0)	4 (3.2, 4.8)
Remote geographic	TOTAL (1 study)		75		4.3 (3.8, 4.8)
	O'Brien 2015 (PC), ITT	Moderate	75	4.3 (2.4)	4.3 (3.8, 4.8)
Duration of oxygen support (days) among population *without risk*					
Healthy term					
≥36 wGA	Caserta 2017 (PC)	Moderate	84	3.1 (4.6)	3.1 (2.1, 4.1)
Severe RSV; Term	Luchsinger 2014 (PC)	High	33	Geometric mean 8.94 (SE 0.86)	Not estimable
Moderate RSV; Term	Luchsinger 2014 (PC)	High	17	Geometric mean 2.47 (SE 0.23)	Not estimable
Mild RSV; Term	Luchsinger 2014 (PC)	High	7	Geometric mean 0.00 (SE 0.00)	Not estimable

Abbreviations: AAP, American Academy of Pediatrics; CI, confidence interval; ITT, intention to treat; PC, prospective cohort; RCNCC, retrospective cohort with non-concurrent cohort; RSV, respiratory syncytial virus; SD, standard deviation; SE, standard error; wGA, weeks' gestational age

8d: Single group proportions for mechanical ventilation therapy

Table S8-7: Single group proportions for mechanical ventilation therapy (dichotomous outcomes)

Outcome and risk status	Study (study design)	Risk of bias	Number of patient with events	Total number of patients	Proportion, % (95% CI)
Mechanical ventilation among hospitalized population *with risk*					
29–32 wGA	TOTAL (1 study)		24	89	27.0 (17.8, 36.2)
	Anderson 2017 (PC)	Moderate	24	89	27.0 (17.8, 36.2)
29–34/35 wGA	TOTAL (2 studies)		58	264	22.0 (18.0, 26.0)
29^0–35^6	Anderson 2017 (PC)	Moderate	45	212	21.2 (13.2, 36.8)
29^0–34^6	Rajah 2017 (RCNCC)—post-AAP	Moderate	13	52	25.0 (13.2, 36.8)
32–35 wGA	TOTAL (3 studies)		34	244	14.0 (10.0, 18.0)
32^0–35^6	Ambrose 2017 (PC)	Moderate	6	57	10.5 (2.6, 18.5)
33–35	Anderson 2017(PC)	Moderate	21	123	17.1 (10.4, 23.7)
33^0–35^6	Stranak 2016 (PC)	Low	7	64	10.9 (3.3, 18.6)
CCLD	TOTAL (1 study)		0	4	0.0 (0.0, 0.0)
	Hama 2015 (RC)	Low	0	4	0.0 (0.0, 0.0)
CF	TOTAL (1 study)		1	5	20.0 (-15.1, 55.1)
Inclusive of MV & oxygen during and post-discharge	Bjornson 2018 (RC)	Moderate	1	5	20.0 (-15.1, 55.1)
Leukemia (AML & ALL)	TOTAL (1 study)		3	10	30.0 (1.6, 58.4)
	Hatanaka 2015 (RC)	High	3	10	30.0 (1.6, 58.4)
Liver transplant recipient	TOTAL (1 study)		14	135	10.4 (5.2, 15.5)
<18 y	Feldman 2016 (RC)	Low	14	135	10.4 (5.2, 15.5)
Remote geographic	TOTAL (1 study)		2	80	2.5 (-0.9, 5.9)
	O'Brien 2015 (PC), ITT	Moderate	2	80	2.5 (-0.9, 5.9)
SCD	TOTAL (1 study)		3	64	4.7 (-0.5, 9.9)
<18 y	Sadreameli 2014 (RC)	Low	3	64	4.7 (-0.5, 9.9)
Mechanical ventilation among ICU population *with risk*					
29–32 wGA	TOTAL (1 study)		24	46	52.2 (37.7, 66.6)
	Anderson 2017 (PC)	Moderate	24	46	52.2 (37.7, 66.6)
32/33–35 wGA	TOTAL (3 studies)		34	90	40.0 (25.0, 56.0)
	Anderson 2017 (PC)	Moderate	21	62	33.9 (22.1, 45.7)
	Ambrose 2017 (PC)	Moderate	6	9	66.7 (35.9, 97.5)
	Stranak 2016 (PC)	Low	7	19	36.8 (15.2, 58.5)
29–34/35 wGA	TOTAL (2 studies)		58	138	42.0 (34.0, 50.0)
29^0–35^6	Anderson 2017 (PC)	Moderate	45	108	41.7 (32.4, 51.0)
29^0–34^6	Rajah 2017 (RCNCC)—post-AAP	Moderate	13	30	43.3 (25.6, 61.1)
CF	TOTAL (1 study)		1	2	50.0 (-19.3, 119.3)
Inclusive of MV & oxygen during and post-discharge	Bjornson 2018 (RC)	Moderate	1	2	50.0 (-19.3, 119.3)
Liver transplant recipient	TOTAL (1 study)		14	30	46.7 (28.8, 64.5)
<18 y	Feldman 2016 (RC)	Low	14	30	46.7 (28.8, 64.5)
Remote geographic	TOTAL (1 study)		2	5	40.0 (-2.9, 82.9)
	O'Brien 2015 (PC), ITT	Moderate	2	5	40.0 (-2.9, 82.9)

Table S8-7: Single group proportions for mechanical ventilation therapy (dichotomous outcomes) (*continued*)

Outcome and risk status	Study (study design)	Risk of bias	Number of patient with events	Total number of patients	Proportion, % (95% CI)
Mechanical ventilation among ICU population *with risk* (*continued*)					
SCD	TOTAL (1 study)		3	3	1.0 (1.0, 1.0)
<18 y	Sadreameli 2014 (RC)	Low	3	3	1.0 (1.0, 1.0)
Mechanical ventilation among hospitalized population *without risk*					
Healthy term	TOTAL (2 studies)		22	141	14.0 (9.0, 21.0)
≥36 wGA	Caserta 2017 (PC)	Moderate	6	84	7.1 (1.6, 12.7)
Term	Luchsinger 2014 (PC)	High	16	57	28.1 (16.4, 39.7)
Mechanical ventilation among ICU population *without risk*					
Healthy term	TOTAL (2 studies)		22	29	78.0 (60.0, 92.0)
≥36 wGA	Caserta 2017 (PC)	Moderate	6	11	54.6 (25.1, 84.0)
Term	Luchsinger 2014 (PC)	High	16	18	88.9 (74.4, 103.4)

Abbreviations: AAP, American Academy of Pediatrics; ALL, acute lymphoblastic leukemia; AML:, acute myeloid leukemia; CCLD, congenital cystic lung disease; CF, cystic fibrosis; CI, confidence interval; ICU, intensive care unit; ITT, intention to treat; MV, mechanical ventilation; PC, prospective cohort; RC, retrospective cohort; RCNCC, retrospective cohort with non-concurrent cohort; SCD, sickle cell disease; wGA, weeks' gestational age; y, year(s)

Table S8-8: Single group proportions for duration of mechanical ventilation (continuous outcomes)

Outcome and risk status	Study (study design)	Risk of bias	Number of patients	Mean (SD)	Mean (95% CI)
Duration of mechanical ventilation (days) among hospitalized population *with risk*					
29–32 wGA	TOTAL (1 study)		24		10 (7.6, 12.4)
	Anderson 2017 (PC)	Moderate	24	10 (6)	10 (7.6, 12.4)
33–35 wGA	TOTAL (2 studies)		28		6.5 (3.5, 9.4)
	Anderson 2017 (PC)	Moderate	21	8 (5)	8 (6.0, 10.0)
	Stranak 2016 (PC)	Low	7	4 (3)	4 (1.8, 6.2)
29–34/35 wGA	TOTAL (2 studies)		58		8.6 (7.3, 9.8)
29^0–35^6	Anderson 2017 (PC)	Moderate	45	9 (5)	9 (7.5, 10.5)
29^0–34^6	Rajah 2017 RCNCC—post-AAP	Moderate	13	7.0 (5)	7.0 (4.3, 9.7)
Remote geographic	TOTAL (1 study)		2	6.5 (2.1)	6.5 (3.6, 9.4)
	O'Brien 2015 (PC), ITT	Moderate	2	6.5 (2.1)	6.5 (3.6, 9.4)

Abbreviations: AAP, American Academy of Pediatrics; CI, confidence interval; ITT, intention to treat; PC, prospective cohort; RCNCC, retrospective cohort with non-concurrent cohort; SD, standard deviation; wGA, weeks' gestational age

8e: Single group proportions for ECMO therapy (no studies)

Table S8-9: Single group proportions for ECMO therapy among a hospitalized population (no study)

Outcome risk status	Study (study design)	Risk of bias	Number of patients with events	Total number of patients	Proportion, % (95% CI)
No study reported data for ECMO among a hospitalized population					

Abbreviations: CI, confidence interval; ECMO, extracorporeal membrane oxygenation

8f: Single group proportions for case fatality

Table S8-10: Single group proportions for case fatality (dichotomous outcomes)

Outcome and risk status	Study (study design)	Risk of bias	Number of patients with events	Total number of patients	Proportion, % (95% CI)
Case fatality among population *with risk*					
32–35 wGA	TOTAL (1 study)		0	2,811	0.0 (0.0, 0.0)
32^0–35^6	Ryan 2016 (RC)	Low	0	2,811	0.0 (0.0, 0.0)
chILD	TOTAL (1 study)		0	20	0.0 (0.0, 0.0)
	Drummond 2016 (RC)	Moderate	0	20	0.0 (0.0, 0.0)
Remote geographic	TOTAL (1 study)		2	710	0.3 (-0.1, 0.7)
	O'Brien 2015 (PC)	Moderate	2	710	0.3 (-0.1, 0.7)
Liver transplant recipient	TOTAL (1 study)		6	2,554	0.2 (0.1, 0.4)
<18 y	Feldman 2016 (RC)	Low	6	2,554	0.2 (0.1, 0.4)
Case fatality among hospitalized population *with risk*					
29–32 wGA	TOTAL (1 study)		1	89	1.1 (-1.1, 3.3)
	Anderson 2017 (PC)	Moderate	1	89	1.1 (-1.1, 3.3)
32–35 wGA	TOTAL (1 study)		0	88	0.0 (0.0, 0.0)
32^0–35^6	Ryan 2016 (RC)	Low	0	88	0.0 (0.0, 0.0)
29–35 wGA	TOTAL (1 study)		1	212	0.5 (-0.5, 1.4)
29^0–35^6	Anderson 2017 (PC)	Moderate	1	212	0.5 (-0.5, 1.4)
chILD	TOTAL (1 study)		0	6	0.0 (0.0, 0.0)
	Drummond 2016 (RC)	Moderate	0	6	0.0 (0.0, 0.0)
Remote geographic	TOTAL (1 study)		2	80	2.5 (-0.9, 5.9)
	O'Brien 2015 (PC)	Moderate	2	80	2.5 (-0.9, 5.9)
Leukemia (AML & ALL)	TOTAL (1 study)		4	10	40.0 (9.6, 70.4)
	Hatanaka 2015 (RC)	High	4	10	40.0 (9.6, 70.4)
Liver transplant recipient	TOTAL (1 study)		6	135	4.4 (1.0, 7.9)
<18 y	Feldman 2016 (RC)	Low	6	135	4.4 (1.0, 7.9)
Case fatality among ICU population *with risk*					
29–32 wGA	TOTAL (1 study)		1	45	2.2 (-2.1, 6.5)
	Anderson 2017 (PC)	Moderate	1	45	2.2 (-2.1, 6.5)
Remote geographic	TOTAL (1 study)		2	5	40.0 (-2.9, 82.9)
	O'Brien 2015 (PC)	Moderate	2	5	40.0 (-2.9, 82.9)
Liver transplant recipient	TOTAL (1 study)		6	30	20.0 (5.7, 34.3)
<18 y	Feldman 2016 (RC)	Low	6	30	20.0 (5.7, 34.3)
Case fatality among mechanically ventilated infants in ICU *with risk*					
29–32 wGA	TOTAL (1 study)		1	24	4.2 (-3.8, 12.2)
Single death in study (29 wGA male @ 2 mo of age)—do not double count for GA categories	Anderson 2017 (PC)	Moderate	1	24	4.2 (-3.8, 12.2)
29–35 wGA	TOTAL (1 study)		1	108	0.9 (-0.9, 2.7)
	Anderson 2017 (PC)	Moderate	1	108	0.9 (-0.9, 2.7)

Table S8-10: Single group proportions for case fatality (dichotomous outcomes) (*continued*)

Outcome and risk status	Study (study design)	Risk of bias	Number of patients with events	Total number of patients	Proportion, % (95% CI)
Case fatality among mechanically ventilated infants in ICU *with risk* (*continued*)					
Remote geographic	TOTAL (1 study)		2	2	100.0 (100.0, 100.0)
	O'Brien 2015 (PC)	Moderate	2	2	100.0 (100.0, 100.0)
Liver transplant recipient	TOTAL (1 study)		6	14	42.9 (16.9, 68.8)
<18 y	Feldman 2016 (RC)	Low	6	14	42.9 (16.9, 68.8)
Case fatality among hospitalized population *without risk*					
Healthy term	TOTAL (1 study)		0	57	0.0 (0.0, 0.0)
	Luchsinger 2014 (PC)	High	0	57	0.0 (0.0, 0.0)
Case fatality among ICU population *without risk*					
Healthy term	TOTAL (1 study)		0	18	0.0 (0.0, 0.0)
	Luchsinger 2014 (PC)	High	0	18	0.0 (0.0, 0.0)
Case fatality among mechanically ventilated infants in ICU *without risk*					
Healthy term	TOTAL (1 study)		0	16	0.0 (0.0, 0.0)
	Luchsinger 2014 (PC)	High	0	16	0.0 (0.0, 0.0)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; chILD, childhood interstitial lung disease; CI, confidence interval; GA, gestational age; ICU, intensive care unit; PC, prospective cohort; RC, retrospective cohort; wGA, weeks' gestational age; y, year(s)

Supplement 9: Summary of evidence for short-term outcomes—between-study

Table S9-1: Summary of evidence for hospitalization and length of stay among between-study population comparisons
Table S9-2: Summary of evidence for ICU admission associated with RSV infection among between-study population comparisons
Table S9-3: Summary of evidence for mechanical ventilation therapy among between-study population comparisons

Table S9-1: Summary of evidence for hospitalization and length of stay among between-study population comparisons

Outcome	Comparator 1 No. of studies (sample size)	Comparator 2 No. of studies (sample size)	Study design; No. of studies (sample size)	Relative risk or mean difference (95% CI), per 100; *p*-value[a]	Effect estimate (95% CI), per 100; *p*-value[a]
Incidence of RSV-hospitalization among population *with vs. without risk*					
At-risk vs. not-at-risk population	29–32 wGA/<33 wGA 2 (n=1,430)	Term (≥36 wGA) 4 (n=3,594,167)	PC, RC, RFUPC 6 (n=3,595,597)	RR 4.3 (3.7, 4.8) *p*<0.000	RD 3.9 (2.7, 5.1) *p*=0.000
	32–35 wGA 8 (n=57,838)	Term (≥36 wGA) 4 (n=3,594,167)	PC, RC, RFUPC 12 (n=3,652,005)	RR 2.8 (2.5, 3.1) *p*<0.000	RD 2.1 (1.4, 2.8) *p*=0.000
	CCLD (NICU hosp) 1 (n=48)	Term (≥36 wGA) 4 (n=3,594,167)	PC, RC, RFUPC 5 (n=3,594,215)	RR 6.9 (5.3, 8.9) *p*<0.000	RD 7.1 (1.5, 12.7) *p*=0.013
	CF 2 (n=131)	Term (≥36 wGA) 4 (n=3,594,167)	PC, RC, RFUPC 6 (n=3,594,298)	RR 10.3 (3.3, 31.6) *p*<0.000	RD 11.1 (-3.7, 25.9) *p*=0.140
	chILD 1 (n=20)	Term (≥36 wGA) 4 (n=3,594,167)	PC, RC, RFUPC 5 (n=3,594,187)	RR 25.0 (14.3, 43.6) *p*<0.000	RD 28.8 (8.7, 48.9) *p*=0.005
	Liver transplant recipient 1 (n=2,554)	Term (≥36 wGA) 4 (n=3,594,167)	PC, RC, RFUPC 5 (n=3,596,721)	RR 4.4 (4.0, 4.9) *p*<0.000	RD 4.1 (3.2, 5.0) *p*=0.000

Table S9-1: Summary of evidence for hospitalization and length of stay among between-study population comparisons (*continued*)

Outcome	Comparator 1 No. of studies (sample size)	Comparator 2 No. of studies (sample size)	Study design; No. of studies (sample size)	Relative risk or mean difference (95% CI), per 100; *p*-value[a]	Effect estimate (95% CI), per 100; *p*-value[a]
Hospital length of stay (days) among population *with vs. without risk*					
At-risk vs. not-at-risk population	29–32 wGA 1 (n=89)	Term (≥36 wGA) 3 (n=45,410)	PC, RC 4 (n=45,499)	MD 6.5 (3.9, 9.1) *p*<0.000	N/A
	32/33–35 wGA 3 (n=7,835)	Term (≥36 wGA) 3 (n=45,410)	PC, RC 6 (n=53,245)	MD 1.0 (-8.6, 10.6) *p*=0.839	N/A
	29–35 wGA 2 (n=264)	Term (≥36 wGA) 3 (n=45,410)	PC, RC, RCNCC 5 (n=45,674)	MD 4.2 (-5.3, 13.7) *p*=0.386	N/A
	CCLD (n=NICU LOS) 1 (n=4)	Term (≥36 wGA) 3 (n=45,410)	PC, RC 4 (n=45,414)	MD 7.8 (-1.8, 17.3) *p*=0.112	N/A
	CF 1 (n=5)	Term (≥36 wGA) 3 (n=45,410)	PC, RC 4 (n=45,415)	MD 43.5 (9.0, 78.0) *p*=0.013	N/A
	chILD 1 (n=4)	Term (≥36 wGA) 3 (n=45,410)	PC, RC 4 (n=45,414)	MD 2.5 (-4.2, 9.2) *p*=0.465	N/A
	Down syndrome 1 (n=17)	Term (≥36 wGA) 3 (n=45,410)	PC, RC 4 (n=45,427)	MD 1.5 (-0.1, 3.1) *p*=0.060	N/A
	Remote geographic 1 (n=80)	Term (≥36 wGA) 3 (n=45,410)	PC, RC 4 (n=45,490)	MD 1.2 (-0.10, 2.5) *p*=0.070	N/A
	Livertransplantrecipient 1 (n=135)	Term (≥36 wGA) 3 (n=45,410)	PC, RC 4 (n=45,545)	Not estimable[b]	N/A

Abbreviations: CCLD, congenital cystic lung disease; CF, cystic fibrosis; chILD, childhood interstitial lung disease; CI, confidence interval; LOS, length of stay; MD, mean difference; N/A, not applicable; NICU, neonatal intensive care unit; PC, prospective cohort; RC; retrospective cohort; RCNCC, retrospective cohort with non-concurrent controls; RD, risk difference; RFUPC, retrospective follow-up of prospective cohort; RR, risk ratio; RSV, respiratory syncytial virus; vs., versus; wGA, weeks' gestational age

[a] Boxes shaded in green indicate statistically significant ($p<0.05$) effect estimates

[b] Not estimable due to lack of SD reporting by study

Table S9-2: Summary of evidence for ICU admission associated with RSV infection among between-study population comparisons

Outcome	Comparator 1 No. of studies (sample size)	Comparator 2 No. of studies (sample size)	Study design; No. of studies (sample size)	Relative risk (95% CI), per 100; *p*-value[a]	Effect estimate (95% CI), per 100; *p*-value[a]
ICU admission among hospitalized population *with vs. without risk*					
At-risk vs. not-at-risk population	29–32 wGA 1 (n=89)	Term (≥36 wGA) 3 (n=38,513)	PC, RC 4 (n=38,602)	RR 3.3 (1.9, 5.7) *p*<0.000	RD 35.9 (19.8, 52.0) *p*=0.000
	32–35 wGA 3 (n=244)	Term (≥36 wGA) 3 (n=38,513)	PC, RC 5 (n=38,757)	RR 2.0 (1.0, 4.0) *p*<0.000	RD 15.7 (-8.0, 39.4) *p*=0.194
	29–35 wGA 2 (n=264)	Term (≥36 wGA) 3 (n=38,513)	PC, RC, RCNCC 5 (n=38,777)	RR 3.3 (1.9, 5.6) *p*<0.000	RD 36.2 (22.5, 49.9) *p*=0.000
	CCLD 1 (n=4)	Term (≥36 wGA) 3 (n=38,513)	PC, RC 4 (n=38,517)	Not estimableb	RD -15.8 (-28.1, -3.5) *p*=0.012
	chILD 1 (n=6)	Term (≥36 wGA) 3 (n=38,513)	PC, RC 4 (n=38,519)	Not estimable[b]	RD -15.8 (-28.1, -3.5) *p*=0.012
	Remote geographic 1 (n=80)	Term (≥36 wGA) 3 (n=38,513)	PC, RC 4 (n=38,593)	RR 0.4 (0.1, 1.2) *p*=0.091	RD -9.5 (-22.9, 3.9) *p*=0.164
	Liver transplant recipient 1 (n=135)	Term (≥36 wGA) 3 (n=38,513)	PC, RC 4 (n=38,648)	RR 1.4 (0.8, 2.5) *p*=0.242	RD 6.4 (-7.8, 20.6) *p*=0.375

Abbreviations: CCLD, congenital cystic lung disease; chILD, childhood interstitial lung disease; CI, confidence interval; ICU, intensive care unit; PC, prospective cohort; RC; retrospective cohort; RCNCC, retrospective cohort with non-concurrent controls; RD, risk difference; RR, risk ratio; RSV, respiratory syncytial virus; vs., versus; wGA, weeks' gestational age

[a] Boxes shaded in green indicate statistically significant ($p<0.05$) effect estimates

[b] Not estimable due to zero events in one arm

Table S9-3: Summary of evidence for mechanical ventilation therapy among between-study population comparison

Outcome	Comparator 1 No. of studies (sample size)	Comparator 2 No. of studies (sample size)	Study design; No. of studies (sample size)	Relative risk (95% CI), per 100; *p*-value[a]	Effect estimate (95% CI), per 100; *p*-value[a]
Mechanical ventilation among hospitalized population *with vs. without risk*					
At-risk vs. not-at-risk population	29–32 wGA 1 (n=89)	Term (≥36 wGA) 2 (n=141)	PC 3 (n=230)	RR 1.9 (1.4, 2.6) *p*<0.000	RD 13.0 (2.0, 24.0) *p*=0.020
	33–35 wGA 1 (n=244)	Term (≥36 wGA) 2 (n=141)	PC 3 (n=385)	RR 1.0 (0.76, 1.32) *p*<0.000	RD 0.00 (-7.2, 7.2) *p*=1.000
	29–35 wGA 2 (n=264)	Term (≥36 wGA) 2 (n=141)	PC, RCNCC 4 (n=405)	RR 2.3 (1.8, 2.9) *p*<0.000	RD 18.0 (9.9, 26.1) *p*=0.000
	CCLD 1 (n=4)	Term (≥36 wGA) 2 (n=141)	PC, RC 3 (n=145)	Not estimable[b]	RD -14.0 (-20.0, -8.0) *p*=0.000
	CF 1 (n=5)	Term (≥36 wGA) 2 (n=141)	PC, RC 3 (n=146)	Not estimable	RD 6.0 (-29.6, 41.6) *p*=0.741
	Leukemia 1 (n=10)	Term (≥36 wGA) 2 (n=141)	PC, RC 3 (n=151)	RR 2.14 (0.5, 9.43) *p*=0.314	RD 16.0 (-13.0, 45.0) *p*=0.280
	Liver transplant recipient 1 (n=135)	Term (≥36 wGA) 2 (n=141)	PC, RC 3 (n=276)	RR 0.7 (0.5, 1.1) *p*=0.156	RD -3.6 (-11.5, 4.3) *p*=0.372
	Remote geographic 1 (n=80)	Term (≥36 wGA) 2 (n=141)	PC, RC 3 (n=221)	Not estimable	RD -11.5 (-21.1, -1.9) *p*=0.018
Outcome	**Comparator 1 No. of studies (sample size)**	**Comparator 2 No. of studies (sample size)**	**Study design; No. of studies (sample size)**	**Relative risk (95% CI), per 100; *p*-value[a]**	**Effect estimate (95% CI), per 100; *p*-value[a]**
Mechanical ventilation among ICU population with vs. without risk					
At-risk vs. not-at-risk population	29–32 wGA 1 (n=46)	Term (≥36 wGA) 2 (n=29)	PC 3 (n=261)	RR 0.7 (0.5, 0.8) *p*<0.000	RD -25.8 (-47.4, -4.2) *p*=0.019
	32–35 wGA 3 (n=90)	Term (≥36 wGA) 2 (n=29)	PC 5 (n=119)	RR 0.5 (0.4, 0.7) *p*<0.000	RD -38.0 (-60.3, -15.7) *p*=0.001
	29–35 wGA 2 (n=138)	Term (≥36 wGA) 2 (n=29)	PC, RCNCC 4 (n=428)	RR 0.8 (0.7, 0.9) *p*=0.003	RD -16.0 (-34.1, 2.1) *p*=0.083
	CF 1 (n=2)	Term (≥36 wGA) 2 (n=29)	PC, RC 3 (n=31)	RR 0.6 (0.0, 453.9) *p*=0.894	RD -28.0 (-89.8, 33.8) *p*=0.374
	Liver transplant recipient 1 (n=30)	Term (≥36 wGA) 2 (n=29)	PC, RC 3 (n=59)	RR 0.6 (0.5, 0.8) *p*<0.000	RD -31.3 (-55.4, -7.3) *p*=0.010
	Remote geographic 1 (n=5)	Term (≥36 wGA) 2 (n=29)	PC 3 (n=34)	Not estimable	RD -38.0 (-83.8, 7.8) *p*=0.104

Abbreviations: CCLD, congenital cystic lung disease; CF, cystic fibrosis; CI, confidence interval; ICU, intensive care unit; PC, prospective cohort; RC; retrospective cohort; RCNCC, retrospective cohort with non-concurrent controls; RD, risk difference; RR, risk ratio; vs., versus; wGA, weeks' gestational age

[a] Boxes shaded in green indicate statistically significant ($p<0.05$) effect estimates

[b] Not estimable due to zero events in one arm

Supplement 10: Complications

One study of premature infants (29–35 weeks' gestational age [wGA]) reported 19 (9%) patients with serious clinical outcomes at time of discharge from their index respiratory syncytial virus (RSV)-hospitalization, including reactive airway disease or chronic lung disease (n=10), deep vein thrombosis (n=3), laryngomalacia (n=2), tracheal aspiration and difficulty feeding requiring physical therapy (n=1), difficulty feeding and muscle atrophy (n=1), difficulty gaining weight (n=1) and death (n=1) (1).

Reference

1. Anderson EJ, Krilov LR, DeVincenzo JP, Checchia PA, Halasa N, Simões EA, Domachowske JB, Forbes ML, Pannaraj PS, McBride SJ, McLaurin KK, Kumar VR, Ambrose CS. SENTINEL1: an observational study of respiratory syncytial virus hospitalizations among U.S. infants born at 29 to 35 weeks' gestational age not receiving immunoprophylaxis. Am J Perinatol. 2017;34(1):51-61. DOI

Supplement 11: Single group proportions for long-term outcomes

11a: Single group proportions for wheeze
- Table S11-1: Single group proportions for wheeze (dichotomous outcomes)
- Table S11-2: Single group proportions for wheeze (continuous outcomes)

11b: Single group proportions for asthma
- Table S11-3: Single group proportions for asthma (dichotomous outcomes)

11c: Single group proportions for lung function test results
- Table S11-4: Single group proportions for lung function test results (dichotomous outcomes)
- Table S11-5: Single group proportions for pulmonary function test results (continuous outcomes)

11a: Single group proportions for wheeze

Table S11-1: Single group proportions for wheeze (dichotomous outcomes)

Outcome; FU	Risk status	Study (study design)	Risk of bias	Number of patients with events	Total number of patients	Proportion, % (95% CI)
Simple wheeze (<3 episodes over 12 months) among population *with risk*; parent and/or physician-reported						
	<33 wGA	TOTAL (1 study)		5	14	35.7 (10.6, 60.8)
1 y	With history of RSV-hospitalization at <1 y	Fauroux 2014 (RFUPC)	Moderate	5	14	35.7 (10.6, 60.8)
	32–35 wGA					
During 6th y	Hospitalized for RSV-LRTI in first year of life	Carbonell-Estrany 2015 (PC)	Moderate	18	113	15.9 (9.2, 22.7)
Across 2–6 y	Hospitalized for RSV-LRTI in first year of life	Carbonell-Estrany 2015 (PC)	Moderate	80	120	66.7 (58.2, 75.1)
Recurrent wheeze (>=3 episodes over 12 months) among population *with risk*; parent and/or physician-reported						
	<33 wGA	TOTAL (1 study)		1	14	7.1 (-6.4, 20.6)
1 y	With history of RSV-hospitalization at <1 y	Fauroux 2014 (RFUPC)	Moderate	1	14	7.1 (-6.4, 20.6)
	32–35 wGA					
During 6th y	Hospitalized for RSV-LRTI in first year of life	Carbonell-Estrany 2015 (PC)	Moderate	14	113	12.4 (6.3, 18.5)
Across 2–6 y	Hospitalized for RSV-LRTI in first year of life	Carbonell-Estrany 2015 (PC)	Moderate	35	75	46.7 (35.4, 58.0)

Table S11-1: Single group proportions for wheeze (dichotomous outcomes) (*continued*)

Outcome; FU	Risk status	Study (study design)	Risk of bias	Number of patients with events	Total number of patients	Proportion, % (95% CI)
Wheeze (any/total) among population with risk; parent and/or physician-reported						
	<33 wGA	TOTAL (1 study)		6	14	42.9 (16.9, 68.8)
1 y	With history of RSV-hospitalization at <1 y	Fauroux 2014 (RFUPC)	Moderate	6	14	42.9 (16.9, 68.8)
	32–35 wGA					
During 6th y	Hospitalized for RSV-LRTI in first year of life	Carbonell-Estrany 2015 (PC)	Moderate	26	113	23.0 (15.3, 30.8)
Across 2–6 y	Hospitalized for RSV-LRTI in first year of life	Carbonell-Estrany 2015 (PC)	Moderate	50	70	71.4 (60.9, 82.0)
Severe wheeze (hospitalization) among population *with risk*; physician-reported/diagnosed						
	<33 wGA	TOTAL (1 study)		0	14	0.00 (0.0, 0.0)
Severe wheeze (hospitalization) among population *with risk*; physician-reported/diagnosed (*continued*)						
1 y	With history of RSV-hospitalization at <1 y	Fauroux 2014 (RFUPC)	Moderate	0	14	0.00 (0.0, 0.0)
	32–35 wGA					
During 6th y	Hospitalized for RSV-LRTI in first year of life	Carbonell-Estrany 2015 (PC)	Moderate	9	113	8.0 (3.0, 13.0)
Across 2–6 y	Hospitalized for RSV-LRTI in first year of life	Carbonell-Estrany 2015 (PC)	Moderate	29	77	37.7 (26.8, 48.5)
Wheeze among population *without risk*; parent-reported						
	Healthy term, hospitalized for RSV	TOTAL (2 studies)		12	15	82.0 (55.0, 99.0)
Any wheeze (1–3 episodes); 1 y	History of hospitalization for RSV at <1 y	Fauroux 2014 (RFUPC)	Moderate	2	3	66.7 (13.3, 120.1)
Post-RSV wheeze >=1 day; 1 y	Hospitalized RSV-positive in first year of life	Zomer-Kooijker 2014 (PC)	Moderate	10	12	83.3 (62.3, 104.4)

Abbreviations: CI, confidence interval; FU, follow-up; LRTI, lower respiratory tract infection; PC, prospective cohort; RFUPC, retrospective follow-up of prospective cohort; RSV, respiratory syncytial virus; wGA, weeks' gestational age; y, year(s)

Table S11-2: Single group proportions for wheeze (continuous outcomes)

Outcome; FU	Risk status	Study (study design)	Risk of bias	Number of patients	Mean (SD)	Mean (95% CI)
Wheeze (days per month) among population *without risk*; parent-reported						
	Healthy term hospitalized for RSV					
Change in days of wheeze per month, Pre-RSV vs. post-RSV	Hospitalized RSV-positive in first year of life	Zomer-Kooijker 2014 (PC)	Moderate	12	0.2 (1.9)	0.2 (-1.8, 2.2)
Post-RSV	Hospitalized RSV-positive in first year of life	Zomer-Kooijker 2014 (PC)	Moderate	12	0.7 (2.9)	0.7 (-0.9, 2.3)

Abbreviations: CI, confidence interval; FU, follow-up; PC, prospective cohort; RSV, respiratory syncytial virus; SD, standard deviation

11b: Single group proportions for asthma

Table S11-3: Single group proportions for asthma (dichotomous outcomes)

Outcome; FU	Risk status	Study (study design)	Risk of bias	Number of patients with events	Total number of patients	Proportion, % (95% CI)
Asthma medication among population *with risk;* parent or physician-reported						
	32–35 wGA					
Bronchodilator; 2–6 y	Hospitalized for RSV-LRTI in first year of life	Carbonell-Estrany 2015 (PC)	Moderate	78	125	62.4 (53.9, 70.9)
Inhaled CS; 2–6 y	Hospitalized for RSV-LRTI in first year of life	Carbonell-Estrany 2015 (PC)	Moderate	33	125	26.4 (18.7, 34.1)
Systemic CS; 2–6 y	Hospitalized for RSV-LRTI in first year of life	Carbonell-Estrany 2015 (PC)	Moderate	23	125	18.4 (11.6, 25.2)
Leukotriene antagonist; 2–6 y	Hospitalized for RSV-LRTI in first year of life	Carbonell-Estrany 2015 (PC)	Moderate	20	125	16.0 (9.6, 22.4)
Asthma among population *without risk*; physician-diagnosed						
	Healthy term, hospitalized for RSV					
7 y	RSV-positive in first year of life	Bonnelykke 2015 (PC)	Low	14	52	26.9 (14.9, 39.0)
7 y	RSV-positive in first 3 years of life	Bonnelykke 2015 (PC)	Low	24	101	23.8 (15.5, 32.1)
28–31 y	Hospitalized for RSV-LRTI at age <24 months	Backman 2014 (PC)	Moderate	10	43	23.3 (10.6, 35.9)
Asthma among population *without risk*; patient-reported						
	Healthy term, hospitalized for RSV	TOTAL (2 studies)		18	57	31.0 (19.0, 44.0)
17–20 y	Hospitalized for RSV with wheeze at age <24 months	Backman 2018 (PC)	Moderate	6	14	42.9 (16.9, 68.8)
28–31 y	Hospitalized for RSV-LRTI at <24 months	Backman 2014 (PC)	Moderate	12	43	27.9 (14.5, 41.3)
Asthma medication among population *without risk*; parent/patient (self)-reported						
	Healthy term, hospitalized for RSV					
Bronchodilator; 28–31 y	Hospitalized for RSV-LRTI at age <24 months	Backman 2014 (PC)	Moderate	13	43	30.2 (16.5, 44.0)
Inhaled CS; 28–31 y	Hospitalized for RSV-LRTI at age <24 months	Backman 2014 (PC)	Moderate	7	43	16.3 (5.2, 27.3)

Abbreviations: CI, confidence interval; CS, corticosteroid(s); FU, follow-up; LRTI, lower respiratory tract infection; PC, prospective cohort; RSV, respiratory syncytial virus; wGA; weeks' gestational age; y, year(s)

11c: Single group proportions for lung function test results

Table S11-4: Single group proportions for lung function test results (dichotomous outcomes)

Outcome; FU	Risk status	Study (study design)	Risk of bias	Number of patients with events	Total number of patients	Proportion, % (95% CI)
Lung function (FEV¹ Z-score ranking [-2, -1]) among population *with risk*						
	32–35 wGA					
During 6th y	Hospitalized for RSV-LRTI in first year of life, with history of simple wheeze	Carbonell-Estrany 2015 (PC)	Moderate	11	64	17.2 (7.9, 26.4)

Abbreviations: CI, confidence interval; FEV1, forced expiratory volume in one second; FU, follow-up; LRTI, lower respiratory tract infection; PC, prospective cohort; RSV, respiratory syncytial virus; wGA; weeks' gestational age; y, year(s)

Table S11-5: Single group proportions for pulmonary function test results (continuous outcomes)

Outcome; FU	Risk status	Study (study design)	Risk of bias	Number of patients	Mean (SD)	Mean (95% CI)
Pulmonary function (FEV¹) among population *without risk*						
	Healthy term, hospitalized for RSV	TOTAL (2 studies)		56		4.4 (3.2, 5.7)
BD response (% of predicted); 17–20 y	Hospitalized for RSV with wheeze at age <24 months	Backman 2018 (PC)	Moderate	14	3.8 (4.6)	3.8 (1.2, 6.5)
BD response (% of predicted); 28–31 y	Hospitalized for RSV-LRTI at age <24 months	Backman 2014 (PC)	Moderate	42	4.7 (5.0)	4.7 (3.1, 6.2)
	Healthy term, hospitalized for RSV	TOTAL (2 studies)		56		88.0 (84.9, 91.2)
Pre-BD (mean % of predicted); 17–20 y	Hospitalized for RSV with wheeze at age <24 months	Backman 2018 (PC)	Moderate	14	90 (10.0)	90 (84, 86)
Pre-BD (mean % of predicted); 28–31 y	Hospitalized for RSV-LRTI at age <24 months	Backman 2014 (PC)	Moderate	42	87 (13.0)	87 (83, 91)
Pulmonary function (FVC) among population *without risk*						
	Healthy term, hospitalized for RSV					
BD response (% of predicted); 17–20 y	Hospitalized for RSV with wheeze at age <24 months	Backman 2018 (PC)	Moderate	14	0.5 (2.4)	0.5 (-0.9, 1.9)
BD response (% of predicted); 28–31 y	Hospitalized for RSV-LRTI at age <24 months	Backman 2014 (PC)	Moderate	42	NR	NR
	Healthy term, hospitalized for RSV	TOTAL (2 studies)		56		98.0 (95.4, 100.6)
Pre-BD (mean % of predicted); 17–20 y	Hospitalized for RSV with wheeze at age <24 months	Backman 2018 (PC)	Moderate	14	98 (10.0)	98 (92, 104)

Table S11-5: Single group proportions for pulmonary function test results (continuous outcomes) (*continued*)

Outcome; FU	Risk status	Study (study design)	Risk of bias	Number of patients	Mean (SD)	Mean (95% CI)
Pulmonary function (FVC) among population *without risk* (*continued*)						
Pre-BD (mean % of predicted); 28–31 y	Hospitalized for RSV-LRTI at age <24 months	Backman 2014 (PC)	Moderate	42	98 (10.0)	98 (95, 101)
Pulmonary function (FEV^1/FVC) among population *without risk*						
	Healthy term, hospitalized for RSV					
BD response (% of predicted); 17–20 y	Hospitalized for RSV with wheeze at age <24 months	Backman 2018 (PC)	Moderate	14	3.5 (4.2)	3.5 (1.1, 6.0)
BD response (% of predicted); 28–31 y	Hospitalized for RSV-LRTI at age <24 months	Backman 2014 (PC)	Moderate	42	NR	NR
	Healthy term, hospitalized for RSV	TOTAL (2 studies)		56		89.6 (87.6, 91.6)
Pre-BD (mean % of predicted); 17–20 y	Hospitalized for RSV with wheeze at age <24 months	Backman 2018 (PC)	Moderate	14	91 (7.0)	91 (87, 95)
Pre-BD (mean % of predicted); 28–31 y	Hospitalized for RSV-LRTI at age <24 months	Backman 2014 (PC)	Moderate	42	89 (8.0)	89 (86, 91)
Pulmonary function (FENO) among population *without risk*						
	Healthy term, hospitalized for RSV	TOTAL (2 studies)		57		19.7 (13.9, 25.6)
Mean ppb; 17–20 y	Hospitalized for RSV with wheeze at age <24 months	Backman 2018 (PC)	Moderate	14	19 (21.6)	19 (range 6–32)
Mean ppb; 28–31 y	Hospitalized for RSV-LRTI at age <24 months	Backman 2014 (PC)	Moderate	43	20 (22.7)	20 (range 13–27)
Pulmonary function (MEF50) among population *without risk*						
	Healthy term, hospitalized for RSV	TOTAL (1 study)		14		15.9 (7.1, 24.7)
BD response (% of predicted); 17–20 y	Hospitalized for RSV with wheeze at age <24 months	Backman 2018 (PC)	Moderate	14	15.9 (15.2)	15.9 (7.1, 24.7)
	Healthy term, hospitalized for RSV	TOTAL (1 study)		14		75 (65, 86)
Pre-BD (mean % of predicted); 17–20 y	Hospitalized for RSV with wheeze at age < 24 months	Backman 2018 (PC)	Moderate	14	75 (18.0)	75 (65, 86)

Abbreviations: BD, bronchodilator; CI, confidence interval; FENO, fractional exhaled nitric oxide; FEV^1, forced expiratory volume in one second; FU, follow-up; FVC, forced vital capacity; LRTI, lower respiratory tract infection; MEF50, maximum expiratory flow after 50% of expired FVC; NR, not reported; PC, prospective cohort; ppb, parts per billion; RSV, respiratory syncytial virus; SD, standard deviation; y, year(s)