Burden of illness in infants and young children hospitalized for respiratory syncytial virus: A rapid review

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Abstract

Respiratory syncytial virus (RSV) infections are common among young children and represent a significant burden to patients, their families and the Canadian health system. Here we conduct a rapid review of the burden of RSV illness in children 24 months of age or younger. Four databases (Medline, Embase, Cochrane Database of Clinical Trials, ClinicalTrials.gov from 2014 to 2018), grey literature and reference lists were reviewed for studies on the following: children with or without a risk factor, without prophylaxis and with lab-confirmed RSV infection. Of 29 studies identified, 10 provided within-study comparisons and few examined clinical conditions besides prematurity. For infants of 33–36 weeks gestation (wGA) versus term infants, there was low-to-moderate certainty evidence for an increase in RSV-hospitalizations (n=599,535 infants; RR 2.05 [95% CI 1.89–2.22]; 1.3 more per 100 [1.1–1.5 more]) and hospital length of stay (n=7,597 infants; mean difference 1.00 day [95% CI 0.88–1.12]). There was low-to-moderate certainty evidence of little-to-no difference for infants born at 29–32 versus 33–36 wGA for hospitalization (n=12,812 infants; RR 1.20 [95% CI 0.92–1.56]). There was low certainty evidence of increased mechanical ventilation for hospitalized infants born at 29–32 versus 33–35 wGA (n=212 infants; RR 1.58, 95% CI 0.94–2.65). Among infants born at 32–35 wGA, hospitalization for RSV in infancy may be associated with increased wheeze and asthma-medication use across six-year follow-up (RR range 1.3–1.7). Children with versus without Down syndrome may have increased hospital length of stay (n=7,206 children; mean difference 3.00 days, 95% CI 1.95–4.05; low certainty). Evidence for other within-study comparisons was of very low certainty. In summary, prematurity is associated with greater risk for RSV-hospitalization and longer hospital length of stay, and Down syndrome may be associated with longer hospital stay for RSV. Respiratory syncytial virus-hospitalization in infancy may be associated with greater wheeze and asthma-medication use in early childhood. Lack of a comparison group was a major limitation for many studies.

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Introduction

Respiratory syncytial virus (RSV) infections are common among young children (1,2), presenting as bronchiolitis, pneumonia, or other respiratory morbidity (3). Hospitalization due to RSV is a significant burden for patients, families and the Canadian health system (4).

Increased risk for RSV-hospitalization has been associated with age younger than one year (3,5), prematurity (6), chronic lung disease (7), congenital heart disease (8), other chronic conditions including cystic fibrosis, immunodeficiency (9–12) and residence in Indigenous, northern or remote communities (13). These populations may also have higher rates of admission to intensive care units (ICU), requirements for respiratory support, and higher mortality attributable to RSV (9). RSV-hospitalization in the first two years of life has also been associated with wheezing in childhood (14–16).

While no active vaccines exist for RSV prophylaxis, the monoclonal antibody palivizumab (Synagis®, AstraZeneca) has demonstrated effectiveness in preventing RSV-hospitalization among some high risk populations (17,18). However, while efficacy of palivizumab (PVZ) in clinical trials appears to be high for children with some underlying clinical conditions, real-world evidence from observational studies is less certain (2), with wide variations in effectiveness. Due to the high numbers needed to treat in order to prevent hospitalization and the relatively high cost of PVZ, most jurisdictions use the intervention sparingly for select groups at highest risk of severe disease. Additionally, RSV vaccine development has been well under way, with some vaccine candidates undergoing phase 3 clinical trials (19). There is currently no global consensus on RSV risk groups and variable policies exist even within Canada.

The objective of this rapid review is to address the following question: What is the burden of RSV illness including long-term sequelae among children 24 months of age and younger without prophylaxis, and with or without risk factors for severe RSV disease, and for immunocompromised children younger than 18 years of age?

Findings from the review will help inform updated recommendations of Canada's National Advisory Committee on Immunization on the use of PVZ prophylaxis to prevent severe consequences of RSV infection. This evidence base will also be relevant for future deliberations on program design for anticipated RSV vaccines and newer monoclonal antibodies (19).

Methods

This review was guided by methods for reviews of interventions (20), overall prognosis (21), and risk of future event (prognosis) (22); a protocol was developed a priori (**Supplement 1**), and reviewed and approved by the National Advisory Committee on Immunization RSV Working Group. In light of the restricted literature search timeframe of interest to the review commissioners, we refer to the undertaken work as a rapid review.

Literature search

Searches were conducted on September 6, 2018, in Medline, Embase, Cochrane Database of Clinical Trials, ClinicalTrials.gov, and websites of international public health authorities (**Supplement 2**). Limits were applied for date of publication (January 1, 2014 to September 6, 2018) and language (English or French). The date limit was aimed at capturing outcomes just before and after significant changes in clinical practice stemming from the revised recommendations for PVZ prophylaxis by the American Academy of Pediatrics (23) as well as the Canadian Paediatric Society (2).

Study selection and eligibility criteria

Two reviewers independently screened titles and abstracts followed by full texts. Discrepancies were resolved by discussions.

Studies conducted in Organisation for Economic Co-operation and Development (OECD) countries, including observational studies and placebo groups of controlled trials were eligible for inclusion. Studies reporting on children 24 months of age and younger, with or without a risk factor of interest, or immunocompromised children 18 years of age and younger without PVZ prophylaxis and with lab-confirmed RSV infection were eligible. Children without RSV infection were eligible as a comparator group for long-term outcomes. Short-term outcomes included RSV-hospitalization, hospital length of stay, ICU admission and length of stay, oxygen support and duration, mechanical ventilation and duration, extracorporeal membrane oxygenation and duration, case fatality (death due to RSV), and complications from RSV infection (e.g. secondary infection). Long-term outcomes (minimum one-year follow-up) included self-reported, parent-reported or physician-diagnosed recurrent wheeze, atopic asthma, deterioration of pulmonary or cardiac function, and impaired growth or development. Detailed inclusion and exclusion criteria are in **Supplement 3**.

Data extraction, synthesis/analysis and risk of bias assessment

One reviewer extracted data with second-reviewer verification.

For dichotomous outcomes, we extracted the number of events and the number analysed in each eligible group, or relative measures (e.g. odds ratio) if crude events were not reported. For continuous outcomes, mean values for each time-point, and change scores, including standard deviations or measures of variability were extracted. Risk ratio (RR) with 95% confidence interval (CI) and mean difference (MD) were used for comparisons between groups.

Our primary interest was using data from studies that reported on two or more groups, either having different risk factors, or a risk group versus healthy term infants (within-study/direct comparisons). For similar comparisons reported by more than one study, data 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 short-term outcomes in risk groups and healthy term infants reported by different studies (between-study/indirect comparisons). We used the double-arc sine transformation to pool single-group proportions across multiple studies. When no comparison was made, we report event proportions for the single group in these studies.

For outcomes where estimates were statistically significant, we calculated the absolute risk difference (24).

Analyses were performed using Excel, Review Manager (version 5.3) and STATA (version 14.2).

Two reviewers independently assessed the risk of bias for each study, using a modified tool based on the Quality Assessment Tool for Observational Cohort and Cross-sectional Studies and the Quality In Prognosis Studies (QUIPS) tool (**Supplement 4**). Disagreements were resolved via consensus or third-reviewer consultation.

Certainty of evidence

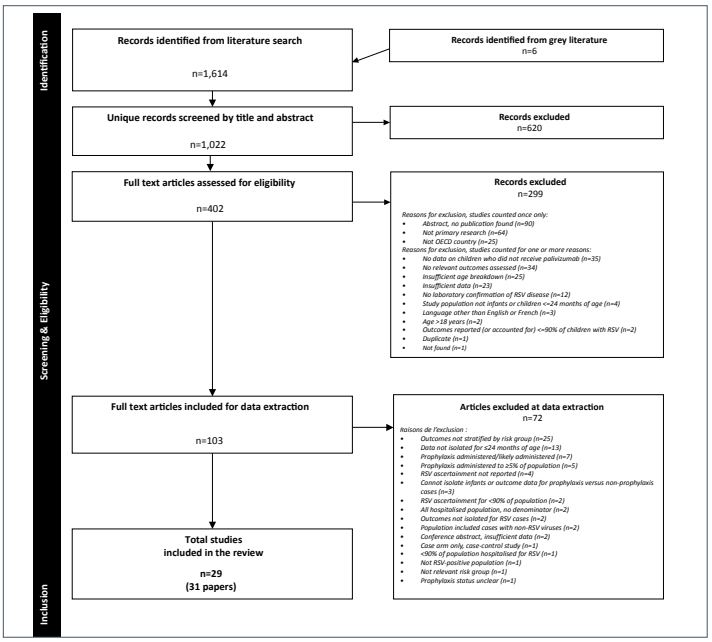
Two reviewers independently assessed the certainty of evidence for each outcome (as high, moderate, low, or very low) from within-study comparisons (direct evidence), with disagreements resolved through consensus. The approach followed principles of the Grading of Recommendations Assessment, Development and Evaluation working group and considerations for a body of evidence that examines risk of future events (prognosis) (**Supplement 5**) (21).

Results

Study selection and characteristics

Twenty-nine cohort studies were included (**Figure 1, Table 1**, and **Supplements 6 and 7**) (13,25–52); of these, 10 reported at least one within-study comparison (26–28,31,32,36,37,42,50,52). Twelve studies were conducted in the United States (25,26,33,34,36,38,42,45–47,49,50), three each, in Canada (13,29,48) and the Netherlands (30,43,52), two each, in Finland (27,28), France (35,37) and Japan (40,41) and one each in Chile (44), Denmark (31), Ireland (39), Spain (32) and multiple countries (51). Thirteen (13,25,26,29–32,37,43,45,46,51,52) studies had some form of industry funding. Three papers reported on the same study: primary publication by Ambrose *et al.* (25), with associated publications by Franklin *et al.* (53) and Simões *et al.* (54).

Figure 1: Flow diagram of study selection



Abbreviations: OECD, Organisation for Economic Co-operation and Development; RSV, respiratory syncytial virus

Table 1: Summary of included studies

Study design & setting (no. of studies)	Risk groups (no. of studies[a])	RSV infection (no. of studies)	Short-term outcomes (no. of studies[a])	Long-term outcomes and follow-up (no. of studies[a])	Risk of bias by outcome (no. of studies[a])
Study design: • Prospective cohort (n=15) • Retrospective cohort (n=12) • Retrospective follow-up of prospective cohort (n=1) • Retrospective cohort with non-concurrent control (n=1) Country: • United States (n=12) • Canada (n=3) • Netherlands (n=3) • Finland (n=2) • Japan (n=2) • France (n=2) • Chile (n=1) • Denmark (n=1) • Ireland (n=1) • Spain (n=1) • International, multi-site (n=1)	At-risk: • Premature (n=11) • CF (n=2) • CCLD (n=1) • chILD (n=1) • Down syndrome (n=1) • HS-CHD (n=1) • Remote geographic (n=2) • Leukemia (AML & ALL) (n=1) • Liver transplant recipient (n=1) • Sickle cell disease (n=1) Not-at-risk: • Healthy term infants (n=11)	Age at RSV: • First RSV season (n=1) • <6 mo at infection (n=1) • ≤6 mo at study enrolment or start of RSV season (n=4) • <10 mo at infection (n=1) • ≤12 mo at RSV season (n=1) • ≤12 mo at hospitalization (n=8) • ≤12 mo at end of insurance enrollment, study period or first year of life (n=1) • ≤24 mo at hospitalization (n=8) • <3 y of age (n=1) • <18 y of age (n=1) • <18 y, ≤24 mo post-transplantation (n=1) Birth cohort with FU to 6 y of age (n=1)	Incidence of RSV-hospitalization (n=23) Hospital LOS (n=16) ICU admission (n=13) ICU LOS (n=5) Oxygen therapy (n=6) Oxygen therapy duration (n=5) MV (n=15) MV duration (n=4) Case fatality (n=7)	Wheeze: • At 1 y FU (n=1) • Across 2–6 y of age (n=1) • At 6 y of age (n=1) Asthma: • Across 2–6 y of age (n=1) • At 7 y of age (n=1) • At 17–20 y of age (n=1) • At 28–31 y of age (n=1) Lung function: • At 6 y of age (n=1) • At 17–20 y of age (n=1) • At 28–31 y of age (n=1)	Incidence of RSV-hospitalization: • High (n=10) • Moderate (n=11) Short-term outcomes: • High (n=2) • Moderate (n=9) • Low (n=10) Long-term outcomes: • Moderate (n=5) • Low (n=1)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CCLD, congenital cystic lung disease; CF, cystic fibrosis; chILD, childhood interstitial lung disease; FU, follow-up; HS-CHD, hemodynamically significant congenital heart disease; ICU, intensive care unit; LOS, length of stay; mo, month(s); MV, mechanical ventilation; no., number; RSV, respiratory syncytial virus; y, year(s)

[a] Study may contribute to more than one risk group, outcome and/or follow-up duration

Eighteen studies (25,26,29,30,33–37,39–43,45,48,50,51) included children either not given or not considered for PVZ prophylaxis prior to RSV-hospitalization; four studies (13,32,46,47) reported prophylaxis among less than 5% of the applicable population with RSV, and seven studies (27,28,31,38,44,49,52) were considered by clinical judgement to not have included children who received prophylaxis. One study included some children who may have received prophylaxis (34).

We included three studies of children with RSV older than 24 months of age to capture evidence for immunocompromised populations: children three years old or younger with Down syndrome with or without known risk factors for RSV (50), and younger than 18 years old with liver transplantation (38) and sickle cell disease (49).

Studies of at-risk populations reporting short-term outcomes included the following: infants with premature birth (eleven studies) (25,26,30,32,36,37,42,43,47,48,51); cystic fibrosis (two studies) (29,39); one study each for congenital cystic lung disease (40), childhood interstitial lung disease (35), Down syndrome (50), sickle cell disease (49), acute leukemia (41) and prior liver transplant (38); and children residing in remote geographic locations (two studies) (13,46).

Seven studies reporting short-term outcomes included data on healthy term infants hospitalized for RSV (33,37,42,44,45,50,52).

Six studies reported on long-term outcomes: healthy term infants with versus without RSV in infancy (27,28,31,52), premature infants with versus without RSV-hospitalization in infancy (32), and premature versus term infants hospitalized for RSV in their first RSV season (37).

Risk of bias

Risk of bias ratings are in Table 1 and Supplements 4 and 6. Studies that reported incidence of RSV-hospitalization were at moderate-to-high risk of bias, mainly due to lack of blinding to childrens' risk status by healthcare providers that may have influenced admission to hospital. For other short-term outcomes, studies were mostly at moderate risk of bias (25,26,29,33,35,39,45–47). Two studies were at high risk of bias due to concerns in more than one domain (41,44). Nearly all reported long-term outcomes (27,28,32,37,52) were at moderate risk of bias, arising from lack of blinding for patient or parent-reported outcomes and/or potential selection biases.

Short-term outcomes from within-study comparisons

Table 2 summarizes evidence for short-term outcomes from within-study comparisons. Here we do not report further on findings having very low certainty of evidence.

Different degrees of prematurity: One study found little-to-no difference in RSV-hospitalization during their first RSV season for infants born at 29–32 compared with 33–36 weeks' gestation (wGA) (36). This study found little-to-no difference for hospital stay of less than one day versus one day or more between infants born at 29–32 or 33–36 wGA (36).

Another study of infants born at 29–32 versus 33–35 wGA who were hospitalized for RSV in the first year of life found little-to-no difference for ICU admission, but longer (although not statistically significant) ICU length of stay among the infants born at 29–32 wGA (26). There was a greater need for mechanical ventilation for hospitalized infants born at 29–32 wGA versus 33–35 wGA (26).

There were no studies of premature infants born before 29 wGA.

Premature versus term infants: One study found that being born late-premature (33–36 wGA) versus at term was associated with increased RSV-hospitalization in the first two years of life (42). The same study found slightly longer hospitalization for the preterm group (42).

Down syndrome: One study comparing children with Down syndrome without additional risk factors for RSV versus healthy children, all followed to three years of age, reported a higher hospitalization rate in those with Down syndrome (50). There was a discrepancy between the text and tables for RSV-hospitalization rates in these groups that could not be resolved due to unsuccessful attempts to contact the study authors (50). This study also found that RSV was associated with longer hospital length of stay among children with Down syndrome without other risk factors versus children without Down syndrome (50). For all cases of Down syndrome, including those with known risk factors for RSV, the authors conclude that Down syndrome is independently associated, after adjusting for known risk factors for RSV disease, with an increased risk for RSV-hospitalization (50). Of note, data on children younger than 24 months of age without risk factors were not isolated from those with additional risk factors, and therefore, were not used in our analysis.

Select short-term outcome comparisons: Other data

Supplement 8 contains single risk group data and pooled analyses (when appropriate). Data for between-study comparisons are in **Supplement 9**. Findings for select outcomes are reported below; data on other short-term outcomes are in Supplement 8.

Single group proportions for RSV-hospitalizations were 5.1% in the first six months of life and 3.3% in the first two years of life for infants 29 to younger than 33 wGA (36,37) and 32/33 to 35

Table 2: Summary of evidence for short-term outcomes among within-study population comparisons

Outcome	Comparator 1	Comparator 2	Study design (no. of studies); Sample size	Absolute difference (95% CI)		Relative risk (95% CI)	Certainty of evidence	Conclusion
				Comparator 2 risk	Absolute risk difference[a]			
RSV-hospitalization								
At-risk population	Prematurity: 29–32 wGA	Prematurity: 33–36 wGA	RC[36] (n=1); 12,812	4.2 per 100	NS	RR 1.20 (0.92, 1.56)	Moderate to low[b,c,d]	**Little to no difference** For RSV-hospitalization in their first RSV season among infants born premature at 29–32 wGA vs. 33–36 wGA
At-risk vs. not-at-risk population	Prematurity: 33–36 wGA	Term: ≥37 wGA	RC[42] (n=1); 599,535	1.2 per 100	1.3 more per 100 (1.1 to 1.5 more)	RR 2.05 (1.89, 2.22)	Moderate to low[b,c,d]	**Increase** RSV-hospitalization by age <24 months among infants born premature (33–36 wGA) vs. at term Among this group, infants born at 33–34 wGA had highest incidence density for RSV hospitalization at 6–12 months of age (adjusted hazard ratio [aHR] 1.74 [1.17–2.58], $p<0.05$) and 12–24 months of age (aHR 1.96 [1.26–3.05], $p<0.05$) compared to term infants
At-risk vs. not-at-risk population	Prematurity: <33 wGA	Term: 39–41 wGA	RFUPC[37] (n=1); 443	1.5 per 100	4.3 more per 100 (0.2 to 18 more)	RR 3.88 (1.13, 13.30)	Very low[b,c,e]	**Very uncertain** For RSV-hospitalization in their first RSV season among infants born at <33 wGA vs. at term
Hospital length of stay, mean days								
At-risk population	Prematurity: 29–32 wGA	Prematurity: 33–35 wGA	PC[26] (n=1); 212	MD 4.00 (1.54, 6.46)		N/A	Very low[b,c,e]	**Very uncertain** For hospital length of stay among infants born premature at 29–32 wGA vs. 33–35 wGA and hospitalized for RSV at <12 months
At-risk vs. not-at-risk population	Prematurity: 33–36 wGA	Term: ≥37 wGA	RC[42] (n=1); 7,597	MD 1.00 (0.88, 1.12)		N/A	Moderate to low[b,c,d]	**Small increase** For hospital length of stay among infants born premature at 33–36 wGA vs. at term and hospitalized for RSV at <24 months
At-risk vs. not-at-risk population	Down syndrome	No Down syndrome	RC[50] (n=1); 7,206	MD 3.00 (1.95, 4.05)		N/A	Low[b,c]	**Small increase** For hospital length of stay for RSV among infants with vs. without Down syndrome and hospitalized for RSV at <3 years
Hospital length of stay, <1 day vs. ≥1 day								
At-risk population	Prematurity: 29–32 wGA	Prematurity: 33–36 wGA	RC[36] (n=1); 542	13.9 per 100	NS	<1 day: RR 0.86 (0.41, 1.78)	Low[c,e]	**Little to no difference** For hospital length of stay <1 day among infants born premature at 29–32 wGA vs. 33–35 wGA and hospitalized in their first RSV season
At-risk population	Prematurity: 29–32 wGA	Prematurity: 33–36 wGA	RC[36] (n=1); 542	86.1 per 100	NS	≥1 day: RR 1.02 (0.93, 1.13)	Low[c,e]	**Little to no difference** For hospital length of stay ≥1 day among infants born premature at 29–32 wGA vs. 33–36 wGA and hospitalized in their first RSV season

Table 2: Summary of evidence for short-term outcomes among within-study population comparisons (*continued*)

Outcome	Comparator 1	Comparator 2	Study design (no. of studies); Sample size	Absolute difference (95% CI)		Relative risk (95% CI)	Certainty of evidence	Conclusion
				Comparator 2 risk	Absolute risk difference[a]			
ICU admission, among RSV-hospitalized population								
At-risk population	Prematurity: 29–32 wGA	Prematurity: 33–35 wGA	PC[26] (n=1); 212	50.4 per 100	NS	RR 1.03 (0.79, 1.34)	Low to very low[b,c,d,e]	**Little to no difference/very uncertain** For ICU admission among infants born premature at 29–32 wGA vs. 33–35 wGA and hospitalized for RSV at <12 months
ICU length of stay, mean days								
At-risk population	Prematurity: 29–32 wGA	Prematurity: 33–35 wGA	PC[26] (n=1); 169	MD 2.00 (-0.28, 4.28)		N/A	Low to very low[b,c,d,e]	**Small increase/very uncertain** For ICU length of stay among infants born premature at 29–32 wGA or at 33–35 wGA and hospitalized for RSV at <12 months
Mechanical ventilation, among RSV-hospitalized population								
At-risk population	Prematurity: 29–32 wGA	Prematurity: 33–35 wGA	PC[26] (n=1); 212	17.1 per 100	NS	RR 1.58 (0.94, 2.65)	Low[c,e]	**Small increase** For mechanical ventilation among infants born premature at 29–32 wGA vs. 33–35 wGA and hospitalized for RSV at <12 months
Mechanical ventilation, among ICU population								
At-risk population	Prematurity: 29–32 wGA		PC[26] (n=1); 108	33.9 per 100	NS	RR 1.54 (0.99, 2.40)	Very low[c,e,f]	**Very uncertain** For mechanical ventilation therapy among infants born premature at 29–32 wGA vs. 33–35 wGA and admitted to ICU for RSV at <12 months
Mechanical ventilation therapy duration, mean days								
At-risk population	Prematurity: 29–32 wGA	Prematurity: 33–35 wGA	PC[26] (n=1); 45	MD 2.00 (-1.21, 5.21)		N/A	Very low[c,e,f]	**Very uncertain** For duration of mechanical ventilation therapy among infants born premature at 29–32 wGA vs. 33–35 wGA and hospitalized for RSV at <12 months
Case fatality, among RSV-hospitalized population								
At-risk population	Prematurity: 29–32 wGA	Prematurity: 33–35 wGA	PC[26] (n=1); 212	0 per 100	NS	RR 4.13 (0.17, 100.30)	Very low[c,e,f]	**Very uncertain** for death due to RSV among infants born premature at 29–32 wGA vs. 33–35 wGA and hospitalized for RSV at <12 months
Case fatality, among ICU population								
At-risk population	Prematurity: 29–32 wGA	Prematurity: 33–35 wGA	PC[26] (n=1); 108	0 per 100	NS	RR 4.02 (0.17, 96.53)	Very low[c,e,f]	**Very uncertain** For death due to RSV among infants born premature at 29–32 wGA vs. 33–35 wGA and admitted to ICU for RSV at <12 months

Abbreviations: CI, confidence interval; ICU, intensive care unit; MD, mean difference; N/A, not applicable; no., number; NS, not significant (results failed to show a difference between groups); PC, prospective cohort; RC, retrospective cohort; RFUPC, retrospective follow-up of prospective cohort; RR, relative risk; RSV, respiratory syncytial virus; vs., versus; wGA, weeks' gestational age

[a] Absolute risk reductions were calculated when findings were statistically significant; NS denotes when findings were not statistically significant

Certainty of evidence was assessed for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. Starting at high for observational studies (for prognosis evidence) each outcome is rated as high, moderate, low or very low based on downgrading (if any) for one or more of the following domains:

[b] Study limitations, including selective outcome reporting

[c] Inconsistency

[d] Half decrement (-0.5) due to small concern for this domain

[e] Imprecision

[f] Two decrements (-2) due to very serious concerns for this domain

wGA (25,30,32,36,42,43,48,51), respectively; 5.3% two years post-transplantation, 8.3% in the first two years of life, 12.3% in the first two years of life and 30.0% in the first or second RSV season for liver transplant (38), congenital cystic lung disease (40), cystic fibrosis (29,39) and childhood interstitial lung disease (35), respectively. The 95% confidence intervals for the latter three conditions were very wide. The pooled proportion for healthy term infants was 1.2% in the first two years of life (37,42,45,52).

Case fatality rate attributable to RSV for those hospitalized were 1.1 % (n=89), 2.5% (n=80), 4.4% (n=135) and 40.0% (n=10) for infants of 29–32 wGA (26), children residing in remote geographic area (46), children with liver transplant (38) and with leukemia (41), respectively. Most studies reported no attributable deaths. Many studies of clinical conditions contained very small sample sizes.

Complications

One study reported on complications associated with RSV-hospitalization (**Supplement 10**).

Long-term outcome comparisons from within-study comparisons

Tables 3 to 5 summarize evidence for long-term outcomes from within-study comparisons. No study reported on growth or impaired development. Here we do not report on findings having very low certainty evidence.

Table 3: Summary of evidence for wheeze associated with RSV infection among within-study population comparisons

Outcome	Comparator 1	Comparator 2	FU	Study design (no. of studies); Sample size	Absolute difference (95% CI)		Relative risk (95% CI)	Certainty of evidence	Conclusion
					Comparator 2 risk	Absolute risk difference[a]			
Simple wheeze; parent and/or physician-reported									
At-risk with RSV-H vs. at-risk without RSV-H	Prematurity: 32–35 wGA, RSV-H <12 months of age	Prematurity: 32–35 wGA, No RSV-H <12 months of age	During 6th y	PC[32] (n=1); 434	14 per 100	NS	RR 1.16 (0.70, 1.93)	Low[b,c]	**Little to no difference** For parent/physician-reported simple wheeze (episodes <3 within 12 months) during the 6th year among infants born premature (32–35 wGA) with vs. without hospitalization for RSV at <12 months
At-risk with RSV-H vs. at-risk without RSV-H	Prematurity: 32–35 wGA, RSV-H <12 months of age	Prematurity: 32–35 wGA, No RSV-H <12 months of age	Across 2–6 y	PC[32] (n=1); 474	49 per 100	18 more per 100 (7–30 more)	RR 1.36 (1.15, 1.60)	Low[b,c]	**Small increase** For parent/physician-reported simple wheeze (episodes <3 within 12 months) from 2–6 years among infants born premature (32–35 wGA) with vs. without hospitalization for RSV at <12 months
At-risk with RSV-H vs. not-at-risk with RSV-H	Prematurity: <33 wGA & RSV-H	Term: 39–41 wGA & RSV-H	1 y	RFUPC[37] (n=1); 17	67 per 100	NS	RR 0.54 (0.18, 1.55)	Very low[b,c,d]	**Very uncertain** For parent and physician-reported simple wheeze (episodes <3 in 12 months) within one year among premature (<33 wGA) vs. term infants with hospitalization in their first RSV season
Recurrent wheeze; parent and/or physician-reported									
At-risk with RSV-H vs. at-risk without RSV-H	Prematurity: 32–35 wGA, RSV-H <12 months of age	Prematurity: 32–35 wGA, No RSV-H <12 months of age	During 6th y	PC[32] (n=1); 434	10 per 100	NS	RR 1.28 (0.71, 2.32)	Low[b,c]	**Little to no difference** For parent/physician-reported recurrent wheeze (≥3 episodes within 12 months) during the 6th year among infants born premature (32–35 wGA) with vs. without hospitalization for RSV at <12 months
At-risk with RSV-H vs. at-risk without RSV-H	Prematurity: 32–35 wGA, RSV-H <12 months of age	Prematurity: 32–35 wGA, No RSV-H <12 months of age	Across 2–6 y	PC[32] (n=1); 422	27 per 100	19 more per 100 (7–35 more)	RR 1.70 (1.27, 2.29)	Low[b,c]	**Small increase** For parent/physician-reported recurrent wheeze (≥3 episodes within 12 months) from 2–6 years among infants born premature (32–35 wGA) with vs. without hospitalization for RSV at <12 months
At-risk with RSV-H vs. not-at-risk with RSV-H	Prematurity: <33 wGA & RSV-H	Term: 39–41 wGA & RSV-H	1 y	RFUPC[37] (n=1); 17	0 per 100	NS	RR 0.80 (0.04, 16.14)	Very low[b,c,d]	**Very uncertain** For parent and physician-reported recurrent wheeze ≥3 episodes in 12 months) within one year among premature (<33 wGA) vs. term infants with hospitalization in their first RSV season

Table 3: Summary of evidence for wheeze associated with RSV infection among within-study population comparisons (*continued*)

Outcome	Comparator 1	Comparator 2	FU	Study design (no. of studies); Sample size	Absolute difference (95% CI)		Relative risk (95% CI)	Certainty of evidence	Conclusion
					Comparator 2 risk	Absolute risk difference[a]			
Severe wheeze; parent or physician-reported									
At-risk with RSV-H vs. at-risk without RSV-H	Prematurity: 32–35 wGA, RSV-H <12 months of age	Prematurity: 32–35 wGA, No RSV-H <12 months of age	During 6th y	PC[34] (n=1); 434	9 per 100	NS	RR 0.91 (0.44, 1.88)	Low[b,c]	**Little to no difference** For parent/physician-reported severe wheeze (≥1 hospitalization or ≥3 medical attendances or medication for three consecutive months or five cumulative months) during the 6th year among infants born premature (32–35 wGA) with vs. without hospitalization for RSV at <12 months
At-risk with RSV-H vs. at-risk without RSV-H	Prematurity: 32–35 wGA, RSV-H <12 months of age	Prematurity: 32–35 wGA, No RSV-H <12 months of age	Across 2–6 y	PC[34] (n=1); 427	24 per 100	14 more per 100 (3–29 more)	RR 1.59 (1.13, 2.24)	Low[b,c]	**Small increase** For parent/physician-reported severe wheeze (≥1 hospitalization or ≥3 medical attendances or medication for three consecutive months or five cumulative months) from 2–6 years among infants born premature (32–35 wGA) with vs. without hospitalization for RSV at <12 months
At-risk with RSV-H vs. not-at-risk with RSV-H	Prematurity: <33 wGA & RSV-H	Term: 39–41 wGA & RSV-H	1 y	RFUPC[37] (n=1); 17	0 per 100	NS	RD 0.00 (-0.34, 0.34)	Very low[b,c,d]	**Very uncertain** For physician-reported severe wheeze (hospitalization for wheeze in 12 months) within one year among premature (<33 wGA) vs. term infants with hospitalization in their first RSV season
Wheeze duration (days per month post-RSV); parent-reported									
Not-at-risk population	RSV-positive, hospitalized	RSV-positive, non-hospitalized	1 y	PC[52] (n=1); 90	MD 0.70 (-0.94, 2.34)		N/A	Very low[b,c,d]	**Very uncertain** For parent-reported days with wheeze at one year among hospitalized vs. non-hospitalized healthy term infants positive for RSV at <12 months

Abbreviations: CI, confidence interval; FU, follow-up; MD, mean difference; N/A, not applicable; no., number; NS, not significant; PC, prospective cohort; RD, risk difference; RFUPC, retrospective follow-up of prospective cohort; RR, risk ratio; RSV, respiratory syncytial virus; RSV-H, respiratory syncytial virus hospitalization; vs., versus; wGA: weeks' gestational age; y, year(s)

[a] Absolute risk reductions were calculated when findings were statistically significant; NS denotes when findings were not statistically significant

Certainty of evidence was assessed for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. Starting at high for observational studies (for prognosis evidence) each outcome is rated as high, moderate, low or very low based on downgrading (if any) for one or more of the following domains:

[b] Inconsistency

[c] Imprecision

[d] Two decrements (-2) due to very serious concerns for this domain

Table 4: Summary of evidence for asthma associated with RSV infection among within-study population comparisons

Outcome	Comparator 1	Comparator 2	FU	Study design (no. of studies); Sample size	Absolute difference (95% CI)		Relative risk (95% CI)	Certainty of evidence	Conclusion
					Comparator 2 risk	Absolute risk difference[a]			
Asthma; physician-diagnosed									
Not-at-risk population	RSV infection in first year of life	Infection with a respiratory pathogen other than RSV in first year of life	7 y	PC[31] (n=1); 329	12 per 100	15 more per 100 (4–35 more)	RR 2.33 (1.35, 4.05) Adjusted for total number of respiratory episodes: OR 1.26 (0.54, 2.91), *p*=0.59	Very low[b,c,d,e]	**Very uncertain** For physician-diagnosed asthma at seven years of age among healthy infants with RSV vs. a different respiratory pathogen in the first year of life
Not-at-risk population	RSV-H	No RSV-H	28–31 y	PC[28] (n=1); 129	13 per 100	NS	RR 1.82 (0.84, 3.94)	Very low[b,c,e]	**Very uncertain** For physician-diagnosed asthma at 28–31 years of age among term infants with vs. without hospitalization for RSV at age <24 months
Asthma; self-reported									
Not-at-risk population	RSV-H	No RSV-H	17–20 y; 28–31 y	PC[27,28] (n=2); 203	15 per 100	19 more per 100 (0.1–60 more)	RR 2.28 (1.01, 5.12)	Low[b,e]	**Small increase** For self-reported asthma in adulthood (17–31 years of age) among infants with vs. without hospitalization for RSV at age <24 months
Asthma medication (bronchodilator)									
At-risk with RSV-H vs. at-risk without RSV-H	Prematurity: 32–35 wGA, RSV-H	Prematurity: 32–35 wGA, No RSV-H	Across 2–6 y	PC[32] (n=1); 487	17 per 100	8 more per 100 (4–13 more)	RR 1.48 (1.23, 1.77)	Low[c,e]	**Small increase** Parent-reported bronchodilator use from 2–6 years of age among infants born premature (32–35 wGA) with vs. without hospitalization for RSV at <12 months
Not-at-risk population	RSV-H	No RSV-H	28–31 y	PC[28] (n=1); 129	14 per 100	16 more per 100 (1–47 more)	RR 2.17 (1.08, 4.34)	Very low[b,c,e]	**Very uncertain** For self-reported bronchodilator use in adulthood (28–31 years of age) among term infants with vs. without hospitalization for RSV at age <24 months
Asthma medication (inhaled CS)									
At-risk with RSV-H vs. at-risk without RSV-H	Prematurity: 32–35 wGA, RSV-H	Prematurity: 32–35 wGA, No RSV-H	Across 2–6 y	PC[32] (n=1); 487	16 per 100	10 more per 100 (2–22 more)	RR 1.65 (1.13, 2.40)	Low[c,e]	**Small increase** Parent-reported ICS use from 2–6 years of age among infants born premature (32–35 wGA) with hospitalization for RSV at <12 months
Not-at-risk population	RSV-H	No RSV-H	28–31 y	PC[28] (n=1); 129	11 per 100	NS	RR 1.56 (0.62, 3.89)	Very low[b,c,e]	**Very uncertain** For self-reported ICS use in adulthood (28–31 years of age) among term infants with vs. without hospitalization for RSV at age <24 months

Table 4: Summary of evidence for asthma associated with RSV infection among within-study population comparisons (*continued*)

Outcome	Comparator 1	Comparator 2	FU	Study design (no. of studies); Sample size	Absolute difference (95% CI)		Relative risk (95% CI)	Certainty of evidence	Conclusion
					Comparator 2 risk	Absolute risk difference[a]			
Asthma medication (leukotriene antagonist)									
At-risk with RSV-H vs. at-risk without RSV-H	Prematurity: 32–35 wGA, RSV-H	Prematurity: 32–35 wGA, No RSV-H	Across 2–6 y	PC[32] (n=1); 487	6 per 100	10 more per 100 (3–22 more)	RR 2.52 (1.43, 4.42)	Low[c,e]	**Increased** Parent-reported leukotriene antagonist use from 2–6 years of age among infants born premature (32–35 wGA) with vs. without hospitalization for RSV at <12 months

Abbreviations: CI, confidence interval; CS, corticosteroid(s); FU, follow-up; ICS, inhaled corticosteroid(s); no., number; NS, not significant; OR, odds ratio; PC, prospective cohort; RR, risk ratio; RSV, respiratory syncytial virus; RSV-H, respiratory syncytial virus hospitalization; vs.: versus; wGA, weeks' gestational age; y, year(s)

[a] Absolute risk reductions were calculated when findings were statistically significant; NS denotes when findings were not statistically significant

Certainty of evidence was assessed for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. Starting at high for observational studies (for prognosis evidence) each outcome is rated as high, moderate, low or very low based on downgrading (if any) for one or more of the following domains:

[b] Study limitations, including selective outcome reporting

[c] Inconsistency

[d] Indirectness

[e] Imprecision

[f] Half decrement (-0.5) due to small concern for this domain

Table 5: Summary of evidence for lung function associated with RSV infection among within-study population comparisons

Outcome	Comparator 1	Comparator 2	FU	Study design (no. of studies); Sample size	Absolute difference (95% CI)		Relative risk (95% CI)	Certainty of evidence	Conclusion
					Comparator 2 risk	Absolute risk difference[a]			
Lung function: FEV_1 Z-score ranking [-2,-1]									
At-risk with RSV-H vs. at-risk without RSV-H	Prematurity: 32–35 wGA, RSV-H	Prematurity: 32–35 wGA, No RSV-H	During 6th y	PC[32] (n=1); 243	21 per 100	NS	RR 0.83 (0.45, 1.53)	Low[b,c]	**Little to no difference** For forced expiratory volume in one second (Z-score rank of [-2, -1], considered extreme range) during the 6th year of age among children hospitalized with RSV at <12 months
Lung function (FEV_1 pre-BD, mean % of predicted)									
Not-at-risk population	RSV-H	No RSV-H	17–20 y; 28–31 y	PC[27,28] (n=2); 202	MD -7.63 (-11.35, -3.91)		N/A	Low[c,d]	**Small decrease** For forced expiratory volume in one second (mean % of predicted, pre-bronchodilation test) in adulthood (17–31 years of age) among infants with vs. without hospitalization for RSV at age <24 months
Lung function (FEV_1, change in mean % predicted)									
Not-at-risk population	RSV-H	No RSV-H	17–20 y; 28–31 y	PC[27,28] (n=2); 202	MD 0.81 (-0.67, 2.30)		N/A	Low[c,d]	**Little to no difference** For forced expiratory volume in one second (change in mean % predicted, pre vs. post-bronchodilation test) in adulthood (17–31 years of age) among infants with vs. without hospitalization for RSV at age <24 months
Lung function (FVC pre-BD, mean % of predicted)									
Not-at-risk population	RSV-H	No RSV-H	17–20 y; 28–31 y	PC[27,28] (n=2); 202	MD -4.74 (-7.80, -1.67)		N/A	Low[c,d]	**Small decrease** For forced vital capacity (mean % of predicted, pre-bronchodilation test) in adulthood (17–31 years of age) among infants with vs. without hospitalization for RSV at age <24 months

Table 5: Summary of evidence for lung function associated with RSV infection among within-study population comparisons (*continued*)

Outcome	Comparator 1	Comparator 2	FU	Study design (no. of studies); Sample size	Absolute difference (95% CI)		Relative risk (95% CI)	Certainty of evidence	Conclusion
					Comparator 2 risk	Absolute risk difference[a]			
Lung function (FVC, change in mean % predicted)									
Not-at-risk population	RSV-H	No RSV-H	17–20 y	PC[27] (n=1); 74	MD 0.60 (-0.67, 1.87)		N/A	Very low[c,d,e]	**Very uncertain** For forced vital capacity (change in mean % predicted, pre vs. post-bronchodilation test) in adulthood (17–20 years of age) among infants with vs. without hospitalization for RSV at age <24 months
Not-at-risk population	RSV-H	No RSV-H	17–20 y; 28–31 y	PC[27,28] (n=2); 202	MD -3.20 (-9.07, 2.67)		N/A	Very low[b,c,d]	**Very uncertain** For FEV_1/FVC (mean % of predicted, pre-bronchodilation test) in adulthood (17–31 years of age) among infants with vs. without hospitalization for RSV at age <24 months
Lung function (FEV_1/FVC, change in mean % predicted)									
Not-at-risk population	RSV-H	No RSV-H	17–20 y	PC[27] (n=1); 74	MD -0.20 (-2.71, 2.31)		N/A	Very low[b,c,e]	**Very uncertain** For FEV_1/FVC (change in mean % predicted, pre vs. post-bronchodilation test) in adulthood (17–20 years of age) among infants with vs. without hospitalization for RSV at age <24 months
Lung function (FENO, mean ppb)									
Not-at-risk population	RSV-H	No RSV-H	17–20 y; 28–31 y	PC[27,28] (n=2); 202	MD -1.00 (-14.49, 12.49)		N/A	Low[c,d]	**Little to no difference** For fractional exhaled nitric oxide (mean ppb) in adulthood (17–31 years of age) among infants with vs. without hospitalization for RSV at age <24 months
Lung function (MEF50 pre-BD, mean % of predicted)									
Not-at-risk population	RSV-H	No RSV-H	17–20 y	PC[27] (n=1); 74	MD -4.00 (-14.95, 6.95)		N/A	Very low[b,c,d,e]	**Very uncertain** For maximum expiratory flow after 50% of expired FVC (change in mean % predicted, pre-bronchodilation test) in adulthood (17–20 years of age) among infants with vs. without hospitalization for RSV at age <24 months
Lung function (MEF50, change in mean % predicted)									
Not-at-risk population	RSV-H	No RSV-H	17–20 y	PC[27] (n=1); 74	MD 3.70 (-5.42, 12.82)		N/A	Very low[b,c,d,e]	**Very uncertain** For maximum expiratory flow after 50% of expired FVC (change in mean % predicted, pre vs. post-bronchodilation test) in adulthood (17–20 years of age) among infants with vs. without hospitalization for RSV at age <24 months

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; MD, mean difference; MEF50, maximum expiratory flow after 50% of expired FVC; N/A, not applicable; no., number; NS, not significant; PC, prospective cohort; ppb, parts per billion; RR, risk ratio; RSV, respiratory syncytial virus; RSV-H, respiratory syncytial virus hospitalization; vs., versus; wGA, weeks' gestational age; y, year(s)

[a] Absolute risk reductions were calculated when findings were statistically significant; NS denotes when findings were not statistically significant

Certainty of evidence was assessed for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. Starting at high for observational studies (for prognosis evidence) each outcome is rated as high, moderate, low or very low based on downgrading (if any) for one or more of the following domains:

[b] Indirectness

[c] Imprecision

[d] Study limitations, including selective outcome reporting

[e] Two decrements (-2) due to very serious concerns for this domain

Prematurity: One study enrolled premature (32–35 wGA) infants with or without hospitalization for RSV infection before 12 months of age to examine several long-term outcomes (32). Data were collected through telephone calls every four months and annual visits until the 6th year of life. The authors analysed data both across the five years and only within the 6th year. All findings offered low certainty evidence.

Across years two through six, associations were found between RSV-hospitalization and increased risk for parent or physician-reported simple wheeze, recurrent wheeze, severe wheeze and any/all wheeze (32). When examining the 6th year only, there was little-to-no difference in parent or physician-reported simple wheeze, recurrent wheeze, severe wheeze and any/all wheeze (32). This study also compared groups for parent-reported asthma-associated medication use across years two through six. There were associations with increased risk from RSV-hospitalization for use of bronchodilators, inhaled corticosteroids, oral corticosteroids and leukotriene antagonists (32). Through lung function testing using spirometry, there was little-to-no difference in severe respiratory morbidity at six years of age between groups (32).

RSV without risk factors: Pooled data from two studies of children with versus without RSV-hospitalization at younger than 24 months of age found low certainty of an increase in self-reported asthma in adulthood (27,28). Of note, there was no difference in physician-diagnosed asthma (considered more reliable than patient-reported asthma) (28), but certainty of evidence was very low for this outcome. An association was also found between RSV and lower pre-bronchodilation mean percent of predicted forced expiratory volume in one second (FEV_1), but there was little-to-no difference in change in FEV_1 from pre to post-bronchodilation (27,28). The RSV was associated with lower predicted forced vital capacity, but not fractional exhaled nitric oxide (27,28).

Long-term outcome comparisons: Other data

Supplement 11 contains single group data and pooled analyses (when appropriate). We did not conduct analyses for between-study comparator groups, since single studies that contributed to each long-term outcome were represented among within-study comparisons.

Discussion

Summary of findings and limitations

Few studies contributed data for within-study comparisons of outcomes of interest. There was moderate-to-low certainty that RSV is associated with a small increase in hospitalization and length of stay among moderate-to-late preterm (33–36 wGA) compared with term infants. There was moderate-to-low certainty evidence for no significant differences in hospitalizations between infants born at 29–32 wGA versus 33–36 wGA. Low certainty of evidence was found for a slight increase in mechanical ventilation among those born at 29–32 wGA versus 33–35 wGA and hospitalized for RSV prior to 12 months of age. Low certainty evidence was found for increased hospital length of stay among children younger than three years of age with versus without Down syndrome. There was low certainty evidence for increased wheezing and asthma medication use from two to six years of age among RSV-hospitalized versus non-hospitalized premature (32–35 wGA) infants, although there was little-to-no difference for these outcomes in the 6th year of follow-up. Low certainty evidence was found for decreased lung function measurements before bronchodilation but changes in measurements after bronchodilation did not differ between groups. Very low certainty evidence was found for other long-term outcomes comparing different risk groups.

Single studies contributed data for most outcomes, where populations with rare conditions (e.g. cystic fibrosis) often represent small/under-powered sample sizes, precluding investigation of heterogeneity among studies for important population and RSV characteristics, or consistency in findings. The paucity of studies on clinical conditions other than prematurity is a limitation of the evidence base. We also did not find studies of premature infants born before 29–30 weeks gestation, or of children with chronic lung disease of prematurity or congenital heart disease, groups for whom prophylaxis is now recommended in the United States and in Canada (2,23).

Retrospective study designs utilizing older data (i.e. pre-2014) were included, and may reflect different practices (e.g. prophylaxis, RSV-testing, standard of care) over time and across countries and settings. Detection of RSV infection may be impacted by variation in testing methods, including types of tests and indications for testing, and seasonal and geographic variability. Among tested individuals, the proportion of patients with viral or bacterial co-infections may be an important confounder in etiology of outcome severity. Lack of blinding of healthcare providers to risk status may influence rates of hospitalization and possibly other care parameters, particularly among children with known RSV risk factors.

Comparison with other reviews

A series of systematic reviews of publications from 1995 to 2015 found that RSV-hospitalization is associated with significant morbidity among children younger than 18 years old in Western countries (Canada, United States, Europe), particularly for young children with prematurity, chronic lung disease of prematurity and congenital heart disease (6–9). Whereas the current work focused on children younger than two years of age with a single risk factor, these reviews also included studies of children up to 18 years of age. Our review scope searched comparatively more recent publications (2014–2018) and covered a broader geographic area by including high-income (OECD) countries.

Future research

Based on current evidence, there is a need for studies to focus on the burden of RSV disease among children with underlying chronic conditions, for some of which data on risk are contradictory or non-existing. Assessments of current RSV surveillance activities in Canada have identified data gaps for particular populations, including children with underlying medical conditions and those living in Indigenous, northern or remote communities (19). Gaps will need to be filled in preparation for monitoring of RSV vaccine effectiveness in the future.

Conclusion

Prematurity is associated with increased risk for RSV-hospitalization in infancy and increased hospital length of stay, and may be associated with increased wheeze and asthma-medication use at up to six years of age. Down syndrome may be associated with longer hospital length of stay. We are very uncertain about evidence from other within-study comparisons. Very few studies included a comparison group.

Authors' statement

AW — Conceptualization, methodology, analysis, writing–original draft, review and editing
JP — Conceptualization, methodology, analysis, writing–review and editing
DLM — Conceptualization, methodology, analysis, writing–review and editing
SG — Analysis, writing–review and editing
BV — Analysis, writing–review and editing
MPD — Conceptualization, methodology, analysis
AS — Conceptualization, methodology, analysis, writing–review and editing
MT — Conceptualization, methodology, writing–review and editing
LH — Conceptualization, methodology, writing–review and editing

Competing interests

AW, JP, SG, BV, MPD and LH report grants from the Public Health Agency of Canada during the conduct of the study.

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Supplemental material

These documents can be accessed on the Supplemental material file.
Supplement 1: Methods
Supplement 2: Search strategy
Supplement 3: Inclusion/exclusion criteria
Supplement 4: Methodological quality assessments
Supplement 5: Certainty of evidence assessments
Supplement 6: Characteristics of included studies
Supplement 7: Outcomes of included studies
Supplement 8: Single group proportions for short-term outcomes
Supplement 9: Summary of evidence for short-term outcomes—between-study
Supplement 10: Complications
Supplement 11: Single group proportions for long-term outcomes

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