

Defining the Risk and Associated Morbidity and Mortality of Severe Respiratory Syncytial Virus Infection Among Preterm Infants Without Chronic Lung Disease or Congenital Heart Disease

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Abbreviations

- BPD: Bronchopulmonary dysplasia
- CHD: Congenital heart disease
- CLD: Chronic lung disease
- ICU: Intensive care unit
- LOS: Length of stay
- MV: Mechanical ventilation
- NICU: Neonatal intensive care unit
- OR: Odds ratio
- RSV: Respiratory syncytial virus
- RSVH: Respiratory syncytial virus hospitalization
- SOE: Strength of Evidence
- wGA: weeks' gestational age

REGAL 2: Associated morbidity and mortality of RSV in preterm infants without CLD/CHD

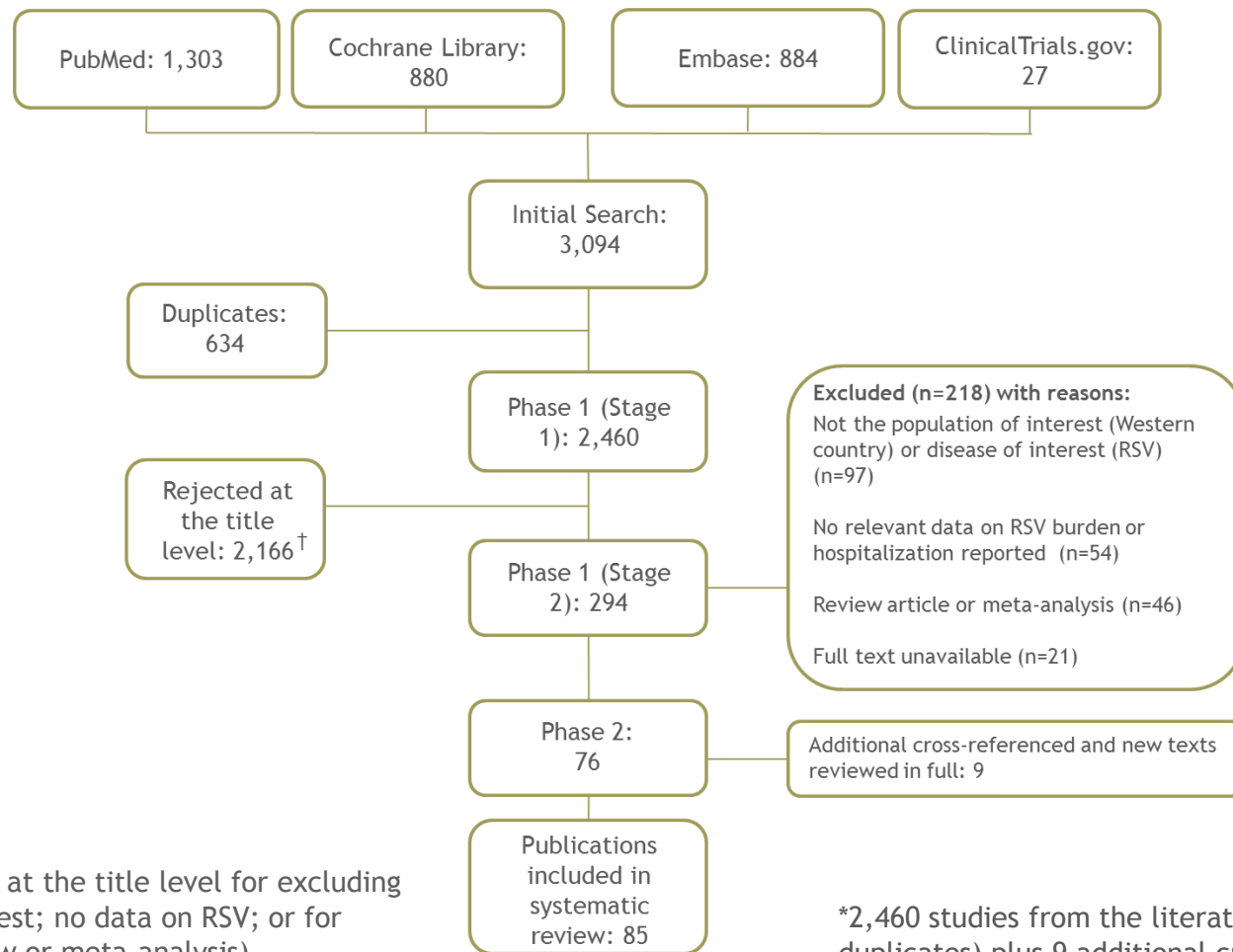
- The methodology followed that of the predetermined protocol outlined in REGAL 1. The target population consisted of:
 - Children (≤ 18 years of age) born preterm (< 37 wGA) without CLD or CHD
- Short-term outcomes of interest for this review included:
 - RSVH (< 28 - 37 wGA)
 - Hospital LOS (29 - < 37 wGA)
 - ICU admission and LOS (29 - < 37 wGA)
 - Oxygen requirement (29 - < 37 wGA)
 - Need for and duration of MV and/or non-invasive ventilation (29 - < 37 wGA)
 - Case-fatality rates (29 - < 37 wGA)
 - Risk factors for severe RSVH (23 - 35 wGA)

‘What is the predisposition and associated morbidity, long-term sequelae and mortality of preterm infants (< 37 wGA) without CLD/BPD or CHD, overall, and split by gestational age segments, to severe RSV infection?’

‘What are the risk factors associated with RSVH?’

Systematic review

- 2,469 studies* were identified of which 85 were included

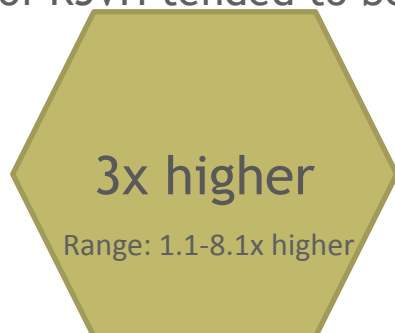


†Studies were rejected at the title level for excluding the population of interest; no data on RSV; or for article type (e.g. review or meta-analysis)

*2,460 studies from the literature search (excluding duplicates) plus 9 additional cross-references

Preterm infants were at greater risk of RSVH than term infants (high SOE)

Overall, comparative rates of RSVH tended to be



in preterm (≤ 36 wGA) than full term infants (≥ 38 wGA)

Overall reported RSVH rates for preterm infants (≤ 37 wGA) ≤ 2 years



vs. ~10 to 20/1000/year in full term infants (≥ 38 wGA) ≤ 2 years

The highest rates of RSVH were reported in infants with lower wGA

Gestational age-specific complications increased hospital resource utilization in preterm infants with RSVH (range 29-<37 wGA) (high SOE)

Median of

2-17
days

in hospital

0.0-
75.0%

were admitted
to ICU

Median ICU LOS was

0-6
days

54.5-
73.4%

received oxygen

MV was given in

3.4-
38.7%

of patients*

*A non-invasive
ventilation rate of 15.2%
was recorded in 1 study

Preterm infants with RSVH had high morbidity and high rate of health care resource utilization

There were limited data on specific RSV-related mortality in preterm infants

- Overall case-fatality rates ranged from 0-5.7%
- Two studies were identified that addressed RSV-related mortality in preterm infants:
 - One study reported that low birth weight and/or prematurity (≤ 35 wGA) independently increased risk of post-neonatal RSV-associated death
 - Case-fatality rate of 43/100,000 for ≤ 35 wGA infants without comorbidities born weighing < 2500 g versus 20.3/100,000 for ≥ 37 infants without comorbidities weighing < 2500 g
 - An overall mortality rate of 8.1% (196/2415) was found in RSVH infants (32-35 wGA) versus 1.6% (320/20,254) in healthy matched controls (OR: 5.5; 95% CI: 4.6-6.6, $P = 0.001$)

RSV may increase mortality rate in preterm infants

Identification of infants requiring RSV immunoprophylaxis to reduce hospitalization in 23-35 wGA infants

Factors associated with increased RSV risk in 23-32 wGA infants

- Asthma hospitalization
- Siblings

Additional factors associated with increased RSV risk in 29-35 wGA infants*

- Neurologic problems
- Male sex
- Discharge from October to December/ chronologic age <3 months at RSV season onset
- Lower gestational age
- Exposure to tobacco smoke
- Day care

*Breastfeeding was found to have a protective effect in infants born ≤ 33 wGA. Data on the specific protective effect of breastfeeding in 32/33-35 wGA infants were conflicting

Several independent RSVH risk factors were identified in 32/33-35 wGA infants (high SOE)

Category	Independent factors affecting preterm risk of RSVH
Exposure	<ul style="list-style-type: none">• Proximity of birth to RSV season• Living with school age siblings• Crowding at home• Day care attendance
Social	<ul style="list-style-type: none">• Maternal smoking during pregnancy• Exposure to smoke• Reduced breast feeding
Biological	<ul style="list-style-type: none">• Small for gestational age• Male sex• Young maternal age• Low maternal education
Medical	<ul style="list-style-type: none">• Familial wheezing and atopy• Neonatal respiratory support• Short hospital stay at birth

The presence of ≥ 1 risk factor may increase an infant's susceptibility to RSVH

Identification of infants requiring RSV immunoprophylaxis to reduce hospitalization in 32-35 wGA infants

- Predictive models have been developed to predict preterm infants (32/33-35 wGA) at high risk of RSVH (high SOE)
- Several predictive models identified preterm infants more at risk of RSVH using between **4 and 7** risk factors
- Areas under the receiver operating characteristics (ROC) curves presented **fair to good accuracy** ranging from 0.687 to 0.791 for six different models
- Age at the start of the **RSV season**, the presence of **siblings** and **day care attendance** were the most predictive variables for RSVH

Key Statements/Findings	Level of Evidence
Studies have shown that preterm infants, particularly those born at lower gestational ages, are at high risk for RSVH and tended to have higher rates of hospitalization for RSV compared with otherwise healthy term infants	1
RSVH rates for preterm infants ranged from ~5 per 1000 children to >100 per 1000, with the highest rates shown in the lowest gestational age infants	1
Compared to otherwise healthy/term infants, premature infants have longer median hospital stays; increased complication rates and increased risk for ICU admission	1
A number of independent risk factors associated with RSVH in preterm infants have been reported including exposure (e.g. proximity of birth to the RSV season, living with school-age siblings), social factors (e.g. maternal smoking during pregnancy or environmental smoking, reduced breast feeding), and biological factors (e.g. male sex, familial asthma)	1
Predictive models for RSVH in 32-35 wGA infants have been developed using 4 or 7 risk factors with areas under the ROC curves ranging from 0.687 to 0.791 (fair to good predictive accuracy)	1

Preterm infants (<37 wGA) were at significant risk for severe RSV disease, which was associated with substantial morbidity

Further development

- Key areas for research:
 - Identification of gestational age-specific prevalence and burden of RSV to confirm the vulnerability of these children
 - Prospective studies to explore the changing risk of RSVH during the first year of life in preterm infants
- Gestation-specific data are important for the planning of healthcare utilization and the use of prophylactic agents

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