Infectious Diseases and Therapy

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PEER REVIEWED SLIDE DECK

The Burden and Long-term Respiratory Morbidity Associated with Respiratory Syncytial Virus Infection in Early Childhood

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Abbreviations

- CHD: Congenital heart disease
- COPD: Chronic obstructive pulmonary disease
- HRQoL: Health-related quality of life
- LRTI: Lower respiratory tract infection
- QoL: Quality of life
- RNA: Ribonucleic acid
- RSV: Respiratory syncytial virus
- RSVH: Respiratory syncytial virus hospitalization
- SOE: Strength of evidence
- wGA: Weeks' gestational age

REGAL 5: Burden and long-term respiratory morbidity associated with RSV in early childhood

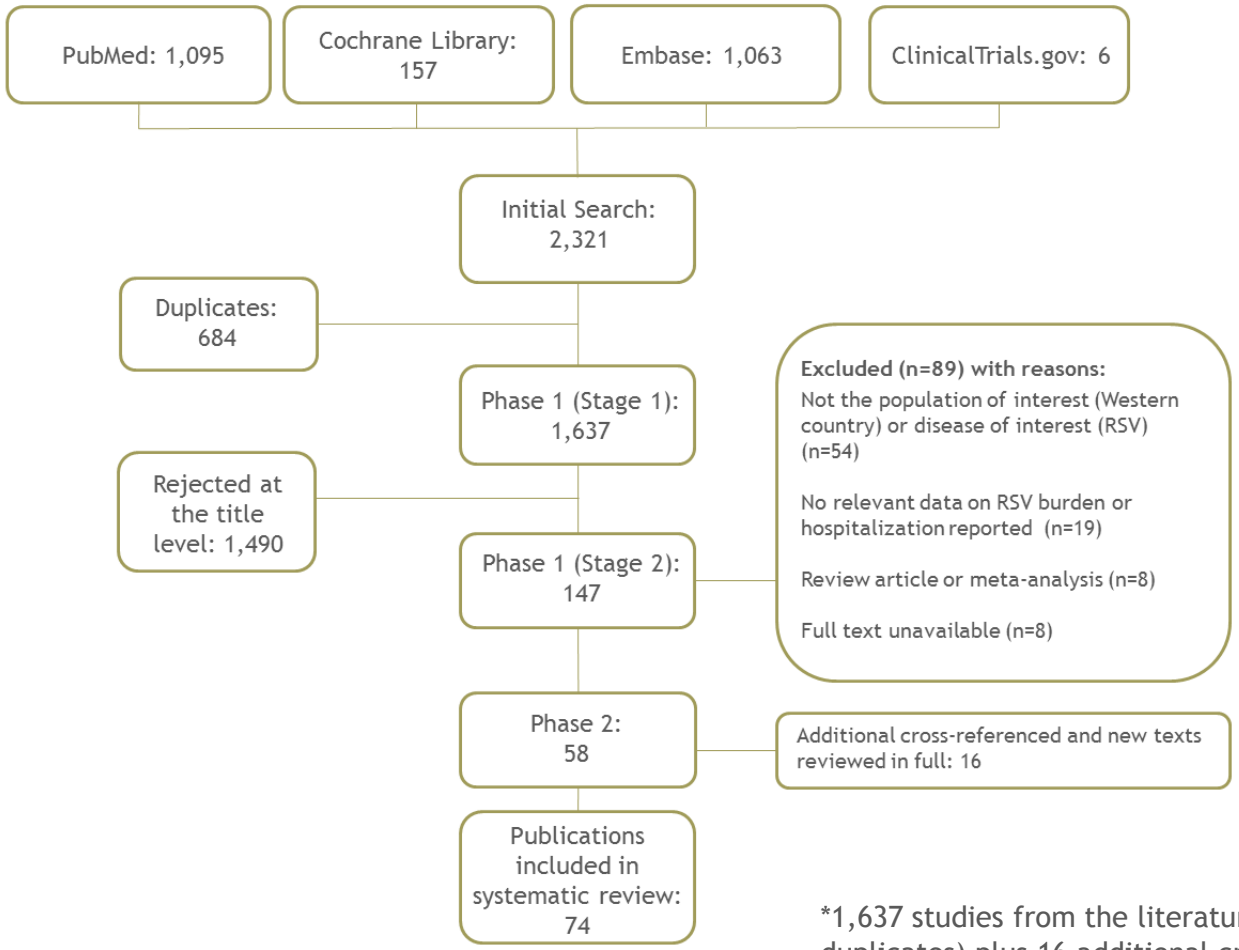
- The methodology followed that of the predetermined protocol outlined in REGAL 1. The target population consisted of:
  - Children hospitalized for RSV LRTI in early childhood (first 2–3 years of life) followed for subsequent development of recurrent wheeze/asthma

- Outcomes of interest for this review included:
  - Asthma, recurrent wheeze and allergic sensitization rates after RSV in early life
  - Lung function after RSV LRTI in early life
  - Relationship between RSV LRTI and subsequent development of clinical allergy or allergic sensitization
  - Factors associated with development of recurrent wheeze/asthma after RSV LRTI in early life

'What is the nature, incidence and impact on long-term respiratory morbidity after RSV LRTI in early life in Western countries, specifically early and late wheeze?'

Systematic review

- 1,653 studies* were identified of which 74 were included



*1,637 studies from the literature search (excluding duplicates) plus 16 additional cross-references

Defining asthma and recurrent wheezing

- A formal diagnosis of asthma was defined using diagnostic tools:

Diagnostic Tool	Identification code
International Statistical Classification of Diseases and Related Health Problems	Asthma: J45
International Classification of Primary Care	Asthma: R96 Wheezing: R03

- The recommended definition of asthma for future studies included:
  - A history of asthma diagnosed by a physician, plus asthma symptoms or medication use in the previous 12 months

- Recurrent wheeze was defined as ≥3 wheezing episodes in the previous 12 months, preferably reported by a physician or patient

RSV LRTI in early life was a significant risk factor for subsequent recurrent wheeze/asthma in later life (high SOE)

- RSV LRTI was associated with reduced lung function and increased airway reactivity at school age and possibly beyond
- RSV LRTI in childhood was identified as an important risk factor for asthma in early adulthood
  - Risk of asthma after bronchiolitis may be associated with severity of the first episode
- RSV-associated wheezing may be a transient event, diminishing or disappearing in early adolescence

Recurrent wheezing rates of

4-47%*

Asthma rates of

8-76%*

*19 Level 1 studies; 4 Level 2 studies

were reported following RSV LRTI in early childhood (<3 years)

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RSV LRTI in early life may be a significant risk factor for subsequent allergy in later life

- Four studies (moderate SOE) identified RSV LRTI as a significant independent risk factor for allergic sensitization
  - RSVH was shown to be significantly associated with development of allergic sensitization up to 13 years of age
  - RSV LRTI was reported to be the single most important risk factor for sensitization (OR, 20.66; 95% CI, 3.53-120.75)
  - Presence of asthma, bronchial reactivity, and lung function abnormalities after RSV infection in infancy have been reported to be clearly associated with atopy
- Four other studies (moderate SOE) found no association between RSV LRTI in early life and subsequent atopy

There was conflicting evidence associated with RSV LRTI in early life and subsequent allergy and/or allergic sensitization

Long-term respiratory morbidity following RSV-LRTI was higher in specific high-risk groups

Premature birth

- Infants born prematurely were at risk of RSV-related sequelae, including the development of recurrent wheezing (moderate SOE)
- Chronic respiratory morbidity has been shown to occur in preterm infants born between 32-35 wGA, regardless of whether the infection required hospitalization
- Prevalence of recurrent wheezing was reported to decrease over time from 5.6% during the second year of life to 4.7% during the fifth year of life

Preterm infants were at increased risk of developing recurrent wheeze/asthma following RSVH

Underlying disease

- Children with CHD and Down syndrome may be at risk of long-term respiratory morbidity based on limited data (low SOE):
  - 59% of children with CHD hospitalized for RSV LRTI in infancy were diagnosed with chronic respiratory morbidity at 10 years of age versus 31.5% of children with CHD without RSV LRTI hospitalization
  - Physician-diagnosed wheeze was more common in children with Down syndrome hospitalized for RSV LRTI versus healthy controls (31% vs 8%; P=0.004)

- Abnormal lung function, airway hyper-responsiveness, or abnormal immunologic status could play a role in development of long-term airway morbidity in children with Down syndrome, irrespective of RSV status

Infants with CHD and Down syndrome may have increased risk of developing recurrent wheeze/asthma following RSVH

Risk factors

Independent factors associated with the development of asthma in children with a history of RSV LRTI in early life (low SOE)

- Male sex
- Breast-feeding <3 months
- Living in a home environment with moisture damage and/or tobacco smoke from ≥2 residents*
- Sensitization to at least one aeroallergen

*Mechanisms underlying the interaction between RSV in infancy and active smoking as determinants of asthma in early adult life were unknown

Several independent risk factors were associated with later asthma in children with a history of RSV LRTI in early life

Genetic factors

- Not all children exposed to RSV experienced subsequent wheezing, indicating that genetic factors may play a role

Genetic factors associated with wheezing after RSV LRTI (high SOE)

- Production of *IL10* by monocytes
- Genetic variation in adaptive immunity genes, particularly the IL10 family member genes *IL19* and *IL20*
- **Late wheeze**
  - *IL-13 Gln* allele
- **Wheeze**
  - *IL8* polymorphism
- **Asthma**
  - Rare nonsynonymous variants, *ADRB2*, *FLG*, *NCAM1*, *NOS1*

Genetics may be a factor in the development of recurrent wheeze/asthma in children with RSV LRTI in early life

Altered immunology

Proportion of plasmacytoid dendritic cells (low SOE)

- Plasma dendritic cells may play a role in protection against allergic disease
- Deficiency of plasmacytoid dendritic cells were seen in peripheral blood of children with asthma and a history of RSV LRTI
- Higher proportion of nasal plasmacytoid dendritic cells were seen in children with recurrent wheeze and a history of RSV, possibly reflecting a heightened antiviral airway response

Increased viral load (low SOE)

- Significant correlations were seen between RSV-RNA load and higher interferon-λ1/2/3 levels in children with a history of RSVH diagnosed with recurrent wheezing

Altered immunology may be a relevant factor in RSV LRTI-related respiratory morbidity

Eosinophilia (low SOE)

- Eosinophilia at the time of bronchiolitis was associated with a higher risk of developing persistent wheezing in later childhood
- Several studies reported higher eosinophilia values in infants with RSV LRTI who had persistent wheezing later in life versus those who did not develop wheezing

Maternal antibodies (low SOE)

- 1 study reported that the concentration of maternally-derived RSV-neutralizing antibodies in cord blood was associated with decreased risk of RSVH in healthy infants <6 months of age, but increased risk of recurrent wheeze in children both with and without RSVH

Eosinophilia during RSV LRTI in early life and/or high levels of maternally-derived RSV antibodies were associated with development of long-term respiratory morbidity

Quality of life and healthcare utilization was significantly impacted by long-term respiratory morbidity after RSV (high SOE)

- Former RSV LRTI patients had a lower respiratory HRQoL for symptoms, activity, and impact at 28-31 years of age versus controls
- Post-bronchiolitis wheezing was associated with lower HRQoL at 3 years of age
  - Infants hospitalized for acute bronchiolitis also had reduced QoL in later life
- Children with RSVH in the first 2 years of life had more outpatient attendances, greater related cost of care between 5-7 years and worse lung function than children not admitted in the first 2 years

RSV LRTI was associated with subsequent decreased quality of life and increased healthcare utilization

Key Statements/Findings	Level of Evidence
There is increasing evidence that RSV LRTI in early life is a significant risk factor for subsequent recurrent wheezing/asthma, persisting at least through early childhood • Recurrent wheezing rates of 4–47% and asthma rates of 8–76% have been reported in studies with up to 25 years follow-up (mean follow-up 6–8 years)	1
RSV LRTI in early life is associated with reduced lung function and increased airway reactivity • Abnormalities reported for spirometric airway function include reduced FEV_1, FEV_1/FVC, and FEF_{25-75}	1
RSV-related respiratory morbidity may be related to a combination of viral insult, pre-existing abnormal lung function and/or factors predisposing for wheezing/asthma such as: • Genetics (e.g. increased production of IL10) • Altered immunology (e.g., altered plasmacytoid dendritic cell levels) • Eosinophilia • Transfer of maternally-derived RSV antibodies • Other risk factors (e.g., tobacco smoke exposure)	1

Key Statements/Findings	Level of Evidence
There is conflicting evidence on the association between RSV LRTI in early life and subsequent development of allergy and/or allergic sensitization	1
RSV LRTI is associated with decreased quality of life and increased healthcare costs, although data are limited	1

RSV LRTI infection in early life was associated with wheezing and/or asthma in later childhood

Further development

- Key areas of research
  - Further prospective, follow-up studies are needed to clarify the risk factors and long-term respiratory outcome of children hospitalized for severe RSV LRTI (including specific populations such as those with CHD, and the potential link with COPD/emphysema)

- Future research should aim to elucidate the pathophysiological mechanisms through which RSV LRTI causes recurrent wheezing/ asthma

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