Defining the Incidence and Associated Morbidity and Mortality of Severe Respiratory Syncytial Virus Infection Among Children with Chronic Diseases

Paolo Manzoni • Josep Figueras-Aloy • Eric A. F. Simões • Paul A. Checchia • Brigitte Fauroux • Louis Bont • Bosco Paes • Xavier Carbonell-Estrany

Infect Dis Ther. 2017 Sep;6(3):383-411

This slide deck represents the opinions of the authors. Sponsorship for this project was funded by AbbVie. Medical writing assistance for this study was provided by Strategen Ltd. For a full list of acknowledgments and conflicts of interest for all authors of this article, please see the full text online.
Copyright © The Authors 2017. Creative Commons Attribution Noncommercial License (CC BY-NC).

Abbreviations

- BMT: Bone marrow transplant
- CHD: Congenital heart disease
- CI: Confidence interval
- CLD: Chronic lung disease
- GMR: Geometric mean ratio
- HIV: Human immunodeficiency virus
- HSCT: Hematopoietic stem cell transplantation
- ICU: Intensive care unit
- IRR: Incidence rate ratio
- LOS: Length of stay
- MV: Mechanical ventilation
- NS: Not significant
- PICU: Pediatric intensive care unit
- RR: Rate ratio
- RSV: Respiratory syncytial virus
- RSVH: Respiratory syncytial virus hospitalization
- SCID: Severe combined immunodeficiency
- SOE: Strength of evidence
- SOT: Solid-organ transplant

REGAL 6: Associated morbidity and mortality of RSV in infants with chronic diseases

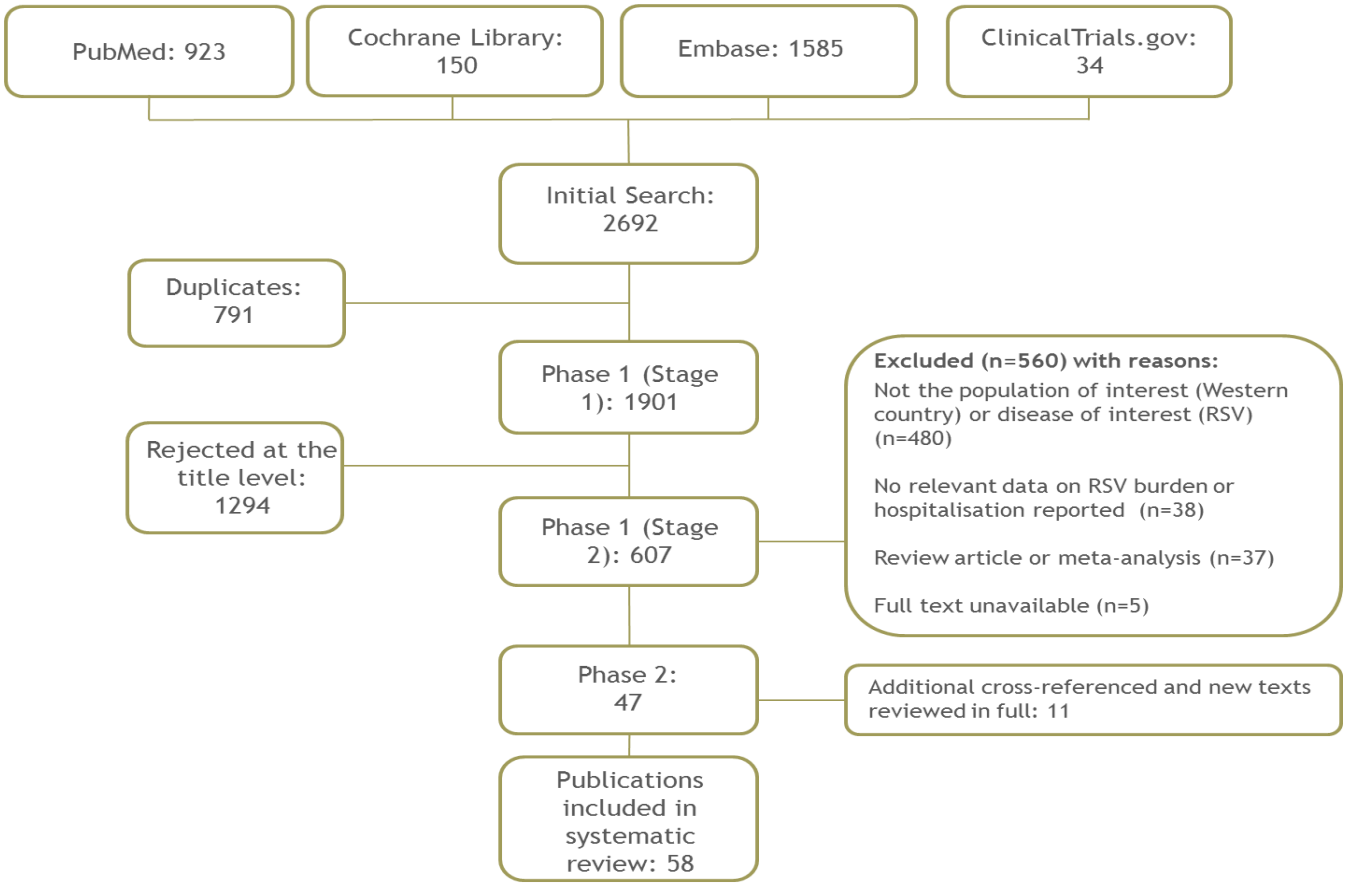
- The methodology followed that of the predetermined protocol outlined in REGAL 1. The target population consisted of:
  - Children aged ≤18 years with:
    - Down syndrome with or without CHD
    - Immunodeficiency
    - Neuromuscular impairment
    - Cystic fibrosis
    - Congenital airway anomalies
    - Other rare congenital and metabolic disorders
- Outcomes of interest for this review included:
  - Incidence of RSV
  - RSVH
  - Hospital LOS
  - PICU admission and LOS
  - Oxygen requirement
  - Need for and duration of MV and/or non-invasive ventilation
  - Case-fatality rates
  - Risk factors for severe RSVH

'What is the predisposition of children with underlying medical conditions or chronic diseases (other than CLD and CHD) to severe RSV infection and related hospitalization?'

Manzoni P, et al. Infect Dis Ther. 2017

Systematic review

- 1,912 studies* were identified of which 58 were included



*1,901 studies from the literature search (excluding duplicates) plus 11 additional cross-references

Infants with Down syndrome were at increased risk of severe RSV (high SOE)

RSVH incidence rates ranged from

36-195 /1000*

53.6-79.5%

Received supplemental oxygen

ICU admission was required in

14.3%

3.6-28.6%

Received intubation and/or MV

With a hospital LOS of

3-10 days

*Children <3 yrs with Down syndrome (with or without associated RSV risk factors). Children with Down syndrome had increased RSVH risk in the absence of co-existing risk factors versus matched infants without Down syndrome

Down syndrome was a significant risk factor for severe RSV infection leading to high morbidity

Manzoni P, et al. Infect Dis Ther. 2017

Immunocompromised children were at high risk of severe RSV infection (high SOE)

RSVH incidence rates ranged from

11-187 /1000*

6-44%

Received supplemental oxygen

ICU admission was required in

2-29%

0-21%

Received intubation and/or MV

With a hospital LOS of

6-10 days

*Rate of infection may depend on the underlying cause of immune suppression

Immunocompromised children experienced significant morbidity due to RSV infection

Manzoni P, et al. Infect Dis Ther. 2017

Cystic fibrosis was identified as a significant risk factor for severe RSV infection (low SOE)

- Studies reported an RSVH rate for children with cystic fibrosis of 64-181 per 1000 children; patients experienced 2-11 days of RSVH
- A decline in lung function caused by RSV LRTI among children (<2 years) with cystic fibrosis may persist for several months after resolution of infection
- Morbidity associated with RSV in children with lung diseases such as cystic fibrosis was similar to children with CLD
- Pre-clinical data indicated that RSV could facilitate lung disease caused by *Pseudomonas aeruginosa* in children with cystic fibrosis

Children with cystic fibrosis were at high risk for severe RSV infection and associated morbidity

Manzoni P, et al. Infect Dis Ther. 2017

Chronic congenital conditions increased vulnerability of infants to severe RSV infection

Congenital Condition	RSV/Total (%)	IRR (95% CI; P value	GMR for LOS (95% CI); P value
Malformations of respiratory system			
Cleft lip and plate	50/855 (6.4)	1.5 (1.1-2.0); 0.004	1.0 (0.8-1.3); NS
Malformations of the larynx, trachea and bronchi	41/440 (9.3)	1.5 (1.1-2.1); 0.009	1.1 (0.8-1.5); NS
Malformations of the lungs	7/51 (13.7)	2.2 (1.0-4.8); 0.049	1.5 (0.7-3.2); NS
Other conditions with respiratory symptoms			
Esophageal atresia	26/115 (22.6)	2.8 (1.6-4.9); <0.001	1.8 (1.1-3.1); 0.022
Neuromuscular disease			
Encephalocele	58/542 (10.7)	1.5 (1.1-2.1); 0.005	1.1 (0.8-1.4); NS
Spina bifida and spinal cord malformations	17/172 (9.9)	2.2 (1.3-3.6); 0.002	2.1 (1.3-3.3); 0.003
Muscular dystrophy	13/82 (15.9)	2.5 (1.4-4.6); 0.003	1.5 (0.9-2.4); NS
Cerebral palsy	93/905 (10.3)	1.6 (1.3-2.0); <0.001	1.3 (1.1-1.6); 0.005
Congenital diseases, chromosomal abnormalities, and others			
Urinary system malformations	82/1232 (6.7)	1.5 (1.2-1.9); <0.001	1.0 (0.8-1.2); NS
Other chromosomal abnormalities	4/17 (23.5)	5.1 (1.7-15.5); 0.004	1.6 (0.7-3.8); NS
GI tract, liver, biliary system, pancreas and abdominal wall malformations	94/1078 (8.7)	1.6 (1.3-2.0); <0.001	1.2 (1.0-1.5); NS
Congenital immunodeficiencies	26/122 (21.3)	2.4 (1.6-3.5); <0.001	1.2 (0.9-1.8); NS
Inborn errors of metabolism	29/276 (10.5)	2.4 (1.6-3.5); <0.001	1.1 (0.8-1.5); NS

Manzoni P, et al. Infect Dis Ther. 2017

Chronic acquired conditions increased vulnerability of infants to severe RSV infection

Acquired Condition	RSV/Total (%)	IRR (95% CI; P value	GMR for LOS (95% CI); P value
Intestinal lung disease	3/11 (27.3)	6.5 (1.7-23.9); 0.005	1.3 (0.4-4.1); NS
Gastroesophageal reflux	40/610 (6.6)	1.5 (1.1-2.1); 0.019	1.0 (0.7-1.3); NS
Epilepsy	75/713 (10.5)	2.6 (2.1-3.4); <0.001	1.6 (1.3-2.0); <0.001
Acquired heart disease	53/427 (12.4)	2.0 (1.5-2.7); <0.001	1.1 (0.8-1.4); NS
Liver disease	9/48 (18.7)	4.0 (2.0-8.2); <0.001	1.0 (0.6-1.9); NS

Neurological and neuromuscular disorders, congenital malformations and other chronic conditions were risk factors for severe RSV infection

Manzoni P, et al. Infect Dis Ther. 2017

RSV-attributable mortality rates varied in children with underlying conditions

Reported case-fatality rates

- 0-14.3%* in children with Down syndrome (not reported in many studies)
- 0% in children with cystic fibrosis (not reported in most studies)
- <10% in immunocompromised children and young adults
- As high as 19% in children undergoing BMT
- As high as 40% were reported in SOT recipients

*14.3% = 1 child with Down syndrome and CHD in a cohort of 7 children with Down syndrome

A meta-analysis indicated that RSVH-associated mortality in children with chronic conditions was uncommon, with 3-4 deaths per 10,000 admissions+

+Neuromuscular (20-26%); congenital/genetic (13-19%); medically fragile or ≥2 complex chronic conditions (~40%)

Concluding statements

Key Findings	SOE*
Down syndrome • Down syndrome is a significant risk factor for RSVH in early (<3 years) childhood (RR: 2.5–12.6), even when excluding co-existing risk factors for severe RSV disease, such as CHD and prematurity (RR: 3.5–10.5) • RSVH rate of 70–195 per 1000 children • Average LOS of 3–10 days • Irrespective of other risk factors, increased severity of disease, longer LOS, and greater risk of respiratory support, including intubation and/or MV, vs. otherwise healthy children	Moderate
Immunocompromised children (including HSCT/BMT recipients, SOT recipients, cancer patients on chemotherapy, children with SCID/DiGeorge syndrome, and those with HIV) • RSVH rate of 11–187 per 1000 children and young adults • Hospital LOS ranged from 6–10 days with ≤29% admitted to ICU and ≤21% requiring intubation and/or MV • Independent predictors of prolonged LOS: nosocomial RSV infection (P<0.001); presence of HSCT, SOT or congenital immunodeficiencies (P=0.008)	Low

*high = supported by Level 1 evidence; Moderate: supported by limited Level 1 and/or Level 2 evidence; Low: supported by limited Level 2 and/or Level 3 evidence

Manzoni P, et al. Infect Dis Ther. 2017

Concluding statements

Key Findings	SOE*
Cystic fibrosis • Cystic fibrosis is a significant risk factor for RSVH in early (<2 years) childhood (RR: 2.5–4.3) • RSVH rate of 64–181 per 1000 children • Hospital LOS of 2–11 days • Morbidity (LOS, ICU, MV) associated with RSV in children with underlying lung diseases (including cystic fibrosis) is similar to those with CLD	Low
Neurological and neuromuscular disorders, congenital malformations, and other chronic conditions • Neurological and neuromuscular conditions (including spina bifida, cerebral palsy, and muscular dystrophy) are associated with a significantly ($P<0.05$) increased risk of RSVH and morbidity • A number of congenital malformations and chronic conditions are also associated with a significantly ($P<0.05$) increased risk of RSVH	Low

*high = supported by Level 1 evidence; Moderate: supported by limited Level 1 and/or Level 2 evidence; Low: supported by limited Level 2 and/or Level 3 evidence

Manzoni P, et al. Infect Dis Ther. 2017

Concluding statements

Key Findings	SOE*
RSV-attributable mortality • Immunocompromised children: case fatality rates of 0–40% (7/18 studies reported a rate of 0%) • Underlying medical conditions: case fatality rates <1%, with pre-existing disease (RR 2.4, 95% CI 2.0–2.8) a significant risk factor for mortality	Low

Key areas for research

- Larger prospective studies are required to fully define the risk and outcomes of RSV infection in children with chronic diseases
- More data are needed on fatality rates in children with underlying medical conditions and chronic disease to determine the true burden of RSV disease

Severe RSV infection in young children with chronic conditions/diseases posed a significant health burden

*high = supported by Level 1 evidence; Moderate: supported by limited Level 1 and/or Level 2 evidence; Low: supported by limited Level 2 and/or Level 3 evidence

Acknowledgments

- Sponsorship and article processing charges for this study were funded by AbbVie. Dr Joanne Smith, Julie Blake and Dr Barry Rodgers-Gray, from Strategen Limited, undertook the systematic review following protocol approval by the authors. AbbVie provided funding to Strategen to undertake the systematic review.
- Julie Blake and Dr Barry Rodgers-Gray provided editorial assistance in the preparation of this manuscript. Support for this assistance was funded by AbbVie.
- AbbVie had the opportunity to review and comment on the completed manuscript but final editorial control rested fully with the authors.
- All named authors met the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, took responsibility for the integrity of the work as a whole, and gave final approval for the published version of the manuscript.

Disclosures

The institute of Louis Bont received money for investigator initiated studies by MeMed, AstraZeneca, AbbVie, and Janssen. The institute of Louis Bont received money for consultancy by AstraZeneca, AbbVie, MedImmune, Janssen, Gilead and Novavax. Paul Checchia has acted as an expert advisor and speaker for AbbVie and has received honoraria in this regard. He has also received research grant funding from AstraZeneca. Brigitte Fauroux has received compensation as a neonatology board member from AbbVie. Josep Figueras-Aloy has acted as an expert advisor and speaker for AbbVie and has received honoraria in this regard. Paolo Manzoni has acted as a speaker for AbbVie and as an expert advisor for AbbVie, TEVA, Medimmune, AstraZeneca, Janssen, and has received honoraria in this regard. Bosco Paes has received research funding from AbbVie Corporation and compensation as an advisor or lecturer from AbbVie and MedImmune. Eric Simões has received grant funding to his institution from Medimmune, Glaxo Smith Kline Inc, and received consultancy fees to the institution, from AbbVie. Xavier Carbonell-Estrany has acted as an expert advisor and speaker for AbbVie and has received honoraria in this regard.

Copyright

Copyright © The Authors 2017.
This slide deck is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and the source are credited.