
REGAL: RSV Evidence - a Geographical Archive of the Literature: Research Protocol

1. Background

Respiratory syncytial virus (RSV) is the most important cause of lower respiratory tract infection (LRTI) in infants and young children, and a major public health burden worldwide.^{1,2} Meta-analysis suggests that up to 200,000 children aged <5 years die from RSV-related infections annually, nearly all in developing countries. In 2005, 33.8 million new RSV-associated acute LRTIs occurred worldwide among children aged <5 years, with at least 3.4 million episodes necessitating hospital admission.¹ Children with RSV infections are also exposed to a variety of other respiratory viruses with a similar seasonal pattern, mainly during winter months, such as influenza and rhinovirus.^{3,4}

The burden of disease and healthcare costs for medical intervention (inpatient stay, intensive care unit [ICU] admissions, mechanical ventilation) for those infants hospitalised for severe RSV infections are considerable.^{5,6,7,8} Comorbid conditions especially prematurity, congenital heart disease (CHD), chronic lung disease (CLD), and Down syndrome seem to increase the risk of disease severity and hospital admission.^{9,10,11}

Prophylaxis with palivizumab, a monoclonal antibody given in a series of doses during the RSV season, has been shown to reduce the incidence of hospitalisation related to severe RSV infection in high-risk infants.¹² In addition to reducing the acute morbidity, there also may be potential benefits from prevention of long-term RSV sequelae, such as recurrent wheezing and asthma.^{13,14} Despite its proven efficacy, the high cost associated with palivizumab prophylaxis has limited its widespread use.¹⁵ Some aspects of the updated American Academy of Pediatrics (AAP) guidance,¹⁵ including restricted eligibility in infants born ≤ 29 weeks' gestational age (wGA) who have no additional risk factors for severe RSV disease, as well as the definition of high-risk, have met with controversy. Furthermore, there is continuing debate about the cost-effectiveness of palivizumab and the relative importance of known risk factors for RSV hospitalisation (RSVH), including preterm infants born at 33-35 wGA, who comprise the majority of premature births.

2. Review questions

The primary objective of this systematic review will be to address the following seven questions, utilising the evidence-base accumulated over the past 20 years:

- What is the epidemiology and disease burden of severe RSV LRTI in western countries, and what are the associated risk factors for RSVH?
- What is the predisposition and associated morbidity, long-term sequelae and mortality of infants with underlying CLD/bronchopulmonary dysplasia (BPD) to severe RSV infection in western countries, and how effective is palivizumab in reducing the incidence of RSVH in these infants?
- What is the predisposition and associated morbidity, long-term sequelae and mortality of infants with underlying CHD to severe RSV infection in western countries, and how effective is palivizumab in reducing the incidence of RSVH in these infants?
- What is the predisposition and associated morbidity, long-term sequelae and mortality of preterm infants (<37 wGA) without CLD/BPD/CHD, overall and split by gestational age segments, to severe RSV infection, and what are the risk factors associated with RSVH? In addition, how effective is palivizumab in reducing the incidence of RSVH in these infants?
- What is the nature, incidence and impact of long-term respiratory morbidity associated with RSVH in infancy in western countries, specifically early and late wheeze, and how effective is palivizumab in reducing such long-term respiratory morbidity?
- What is the predisposition of infants with Down syndrome to severe RSV infection and related hospitalisation and how effective is palivizumab in reducing the incidence of RSVH in these infants?
- What other groups of infants with underlying medical conditions or chronic diseases are at high risk of RSVH and associated morbidity, and can the use of palivizumab prophylaxis be justified in these special populations?

- What is the quantity and quality of the published evidence for the cost-effectiveness of palivizumab prophylaxis in the prevention of RSVH in different subgroups of children who are at high risk of serious morbidity from RSV infection?

The secondary objective of this systematic review will address the following question:

- What is the emerging evidence for the genetic susceptibility of certain infants to severe RSV infection and what are the recent advances and future perspectives for the prevention of RSV?

3. Search terms

Search terms will include:

- Respiratory syncytial virus, RSV, bronchiolitis
- Prevalence, incidence, epidemiology
- Congenital heart disease
- Bronchopulmonary dysplasia, chronic lung disease
- Hospitalisation, inpatient, emergency
- Mortality, fatality, death
- Risk, risk factor
- Immunotherapy, immunoprophylaxis, prophylaxis, prevention
- Palivizumab, Synagis
- Efficacy, effect
- Prematurity, preterm, infant-newborn, neonate, child/children, child, preschool, adolescent, adult
- Wheezing, asthma, respiratory
- Economics, pharmacoeconomics, cost-effectiveness, cost benefit, cost of illness, cost utility, healthcare costs

4. Searches

The following electronic databases will be searched from January 1995 through to current date:

- PubMed (Medline)
- Embase
- The Cochrane Library
- Clinicaltrials.gov

The search results will be supplemented by review of the bibliographies of key articles for additional studies and inclusion of relevant abstracts presented at key meetings, as well as expert input, to help ensure the capture of all pertinent data.

No language limits will be set on database searches, with the caveat that English translations of at least the abstract must be available.

5. Types of study to be included

The following study types will be included to meet the primary and secondary objectives:

- Randomised, controlled clinical trials
- Non-randomised, controlled clinical trials
- Crossover trials
- Single arm studies
- Registries/medical databases
- Cohort studies (prospective/retrospective)
- Case-control studies (prospective/retrospective)
- Case series

6. Condition or domain being studied

RSV infection in children.

7. Participants/population

The following populations will be considered for the primary objective:

- RSV infection in term or preterm infants with or without CLD (BPD) or CHD, or other high-risk comorbid conditions (e.g. anatomic pulmonary abnormalities, neuromuscular disorders, Down syndrome, immunodeficiencies and cystic fibrosis)
- Infants receiving or not receiving RSV prophylaxis
- Infants born <37 wGA

8. Interventions/exposures

In studies evaluating the reduction in RSVH rates and associated morbidity, long-term sequelae and mortality of preterm infants (with and without CLD) and with CHD, the intervention of interest is prophylaxis with palivizumab.

9. Comparators/control

For studies investigating the efficacy of palivizumab prophylaxis, a suitable control population should be available as a comparator, ideally a placebo group, but, if not, an untreated group (either contemporaneously collected or historical).

10. Context

Studies conducted in the healthcare setting (hospital and community).

11. Outcomes

- Risk factors (including biological, environmental and social) for severe RSV infection requiring hospital admission
- Incidence rate of severe RSV infection requiring medical treatment (during first or subsequent years of life) including emergency room visits or paediatric visits
- Hospitalisation rates due to severe RSV infection
- Length of stay (days) in hospital due to severe RSV infection
- RSVH-related outcomes, including
 - o Admission to ICU due to severe RSV infection
 - o Length of stay (days) in ICU due to severe RSV infection
 - o Rate of mechanical ventilation use in ICU due to severe RSV infection
 - o Length of mechanical ventilation use (days) in ICU due to severe RSV infection
 - o Length of non-invasive ventilation
 - o Length of oxygen use on its own
- Recurrent wheezing and childhood asthma and possibly other long-term outcomes up to adulthood (≤ 18 years) following severe RSV infection in infancy (nature, incidence, outcomes)
- Mortality due to severe RSV infection
- Effectiveness of palivizumab at reducing RSVH rates and associated morbidity, long-term sequelae and mortality in different subgroups of children with or without CLD or CHD who are at high risk of serious morbidity from RSV infection
- Cost-effectiveness of immunoprophylaxis of RSV using palivizumab in different subgroups of children with or without CLD or CHD who are at high risk of serious morbidity from RSV infection
- Genetic phenotypes and polymorphisms etc. predisposing certain children to severe RSV infection

- Future developments, novel/new therapies and targets for reducing RSVH and long-term sequelae

12. Data extraction

Studies will be selected for inclusion for review using a two-phase approach:

Phase 1 - the abstracts of potentially relevant citations identified from the electronic searches will be assessed separately by two experienced reviewers to confirm relevance and inclusion in the study according to the inclusion criteria

Phase 2 - the full texts over those citations identified as relevant in Phase 1 will be assessed separately by two experienced reviewers to confirm relevance and inclusion in the study according to the inclusion criteria. If a consensus cannot be reached on a citation, a third senior researcher will make the decision.

During the screening of full text articles (i.e. Phase 2 screening), reviewers will classify the articles into groups to answer the eight research questions: (1) epidemiology of RSVH and associated risk factors, (2) incidence and associated morbidity and mortality of severe RSV infection in infants with underlying CLD/BPD, (3) incidence and associated morbidity and mortality of severe RSV infection in infants with underlying CHD (4) incidence and associated morbidity and mortality of severe RSV infection in preterm infants (<37 wGA) without CLD/BPD and efficacy of palivizumab prophylaxis, (5) long-term respiratory outcomes related to severe RSV infection and efficacy of palivizumab prophylaxis, (6) Risk of RSVH in other groups of infants with underlying medical conditions or chronic diseases and justification for palivizumab prophylaxis, (7) cost-effectiveness of palivizumab prophylaxis, and (8) future perspectives in RSV prevention.

A PRISMA diagram will be used to summarise the exclusions and the reasons for exclusion during Phases 1 and 2.

Data will be extracted from the full-text of all relevant articles identified in Phase 2 by one reviewer, and quality checked by a second reviewer. Key information for every included study will be inserted into an agreed data extraction template. A risk of bias assessment will be included for each article (see below). The completed data extraction templates will be compiled into detailed evidence tables for each study question.

13. Quality assessment

Bias

Each study will receive a risk of bias assessment. For observational studies, the RTI Item Bank¹⁶ will be applied. For randomised clinical trials, the Cochrane Collaboration risk of bias tool will be applied.¹⁷

Strength

Each study will be graded on the strength of evidence using recommendations from the Oxford Centre for Evidence-Based Medicine (Appendix 1).^{18,19}

Quality

A quality assessment for each citation will be carried out using the five-point Jadad Scale (Appendix 2).²⁰

14. Strategy for data synthesis

The accompanying review will provide a narrative synthesis of the data retrieved in the literature searches, organised into chapters to reflect the research questions. All conclusions will have a level of evidence assigned to them. Strengths and weaknesses of the existing data will be discussed. If sufficient data for a meta-analysis exists, this will be noted in the report. Potential areas for future research will also be identified.

15. Analysis of subgroups

Subgroups of infants, such as those born prematurely or with CLD and CHD etc., will be analysed separately in order to answer the research questions.

Appendix 1: Oxford Centre for Evidence-Based Medicine Strength of Evidence Scale (taken from <http://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-2.1.pdf>)¹⁹

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	SR of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	SR of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or “poor or non-independent Reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	SR of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	SR of randomized trials or <i>n</i> -of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	SR of randomized trials, systematic review of nested case-control studies, <i>n</i> -of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	SR of randomized trials or <i>n</i> -of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	SR of randomized trials	Randomized trial	Non-randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

SR: Systematic review

* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

** As always, a systematic review is generally better than an individual study.

Grades of Recommendation (taken from <http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>)¹⁸

A	consistent level 1 studies
B	consistent level 2 or 3 studies <i>or</i> extrapolations from level 1 studies
C	level 4 studies <i>or</i> extrapolations from level 2 or 3 studies
D	level 5 evidence <i>or</i> troublingly inconsistent or inconclusive studies of any level

“Extrapolations” are where data is used in a situation that has potentially clinically important differences than the original study situation.

Appendix 2: Jadad Score²⁰

Item	Maximum points	Description	Examples
Randomisation	2	<p>1 point if randomisation is mentioned</p> <p>1 additional point if the method of randomisation is appropriate</p> <p>Deduct 1 point if the method of randomisation is inappropriate (minimum 0)</p>	<p>“The patients were randomly assigned into two groups”</p> <p>The randomisation was accomplished using a computer-generated random number list, coin toss or well-shuffled envelopes</p> <p>The group assignment was accomplished by alternate assignment, by birthday, hospital number or day of the week</p>
Blinding	2	<p>1 point if blinding is mentioned</p> <p>1 additional point if the method of blinding is appropriate</p> <p>Deduct 1 point if the method of blinding is inappropriate (minimum 0)</p>	<p>“The trial was conducted in a double-blind fashion”</p> <p>Use of identical tablets or injectables, identical vials</p> <p>Use of tablets with similar looks but different taste</p> <p>Incomplete masking</p>
An account of all patients	1	<p>The fate of all patients in the trial is known. If there are no data the reason is stated</p>	<p>“There were 40 patients randomised but the data from 1 patient in the treatment group and 2 in the control were eliminated because of a break in protocol”</p>

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