REGAL: <u>R</u>SV <u>E</u>vidence - a <u>G</u>eographical <u>A</u>rchive of the <u>L</u>iterature: 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 Bank[16] 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]

Quality

A quality assessment for each citation will be carried out using the five-point Jadad Scale (Appendix 2).[19]

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/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/)

Level	Therapy / Prevention, Aetiology / Harm	Prognosis	Diagnosis	Differential diagnosis / symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR" validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR" with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval"¡)	Individual inception cohort study with > 80% follow-up; CDR" validated in a single population	Validating** cohort study with good""" reference standards; or CDR" tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts" "	All or none case-series	Absolute better-value or worse-value analyses " " " "
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR" or validated on split-sample§§§ only	Exploratory** cohort study with good" " " reference standards; CDR" after derivation, or validated only on split-sample§§§ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations

4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

SR: Systematic review; RCT: Randomised controlled trial

Notes

Users can add a minus-sign "-" to denote the level of that fails to provide a conclusive answer because:

- *EITHER* a single result with a wide Confidence Interval

- *OR* a Systematic Review with troublesome heterogeneity.

Such evidence is inconclusive, and therefore can only generate Grade D recommendations.

*	By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.
"	Clinical Decision Rule. (These are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category.)
"¡	See note above for advice on how to understand, rate and use trials or other studies with wide confidence intervals.
§	Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.
§§	By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.
§§§	Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.
" "	An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis.
"¡"¡	Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and benefits.
" " "	Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of

	a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.
„ „ „ „	Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and the equally or more expensive.
**	Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.
***	By poor quality prognostic cohort study we mean one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors.
****	Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (for example 1-6 months acute, 1 – 5 years chronic)

Grades of Recommendation

A	consistent level 1 studies
B	consistent level 2 or 3 studies *or* extrapolations from level 1 studies
C	level 4 studies *or* extrapolations from level 2 or 3 studies
D	level 5 evidence *or* 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 Score[19]

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

References

1. Nair H, Nokes DJ, Gessner BD, et al. Global burden of acute lower respiratory infections due to respiratory yncytial virus in young children: a systematic review and meta-analysis. *Lancet* 2010;375:1545-1555.

2. Jain S, Williams DJ, Arnold SR, et al. Community-acquired pneumonia requiring hospitalization among US children. *N Engl J Med* 2015;372:835-845.

3. Calvo C, García-García ML, Pozo F, et al. Respiratory syncytial virus coinfections with rhinovirus and human bocavirus in hospitalized children. *Medicine (Baltimore)* 2015;94:e1788**.**

4. Tanner H, Boxall E, Osman H. Respiratory viral infections during the 2009–2010 winter season in Central England, UK: incidence and patterns of multiple virus coinfections. *Eur J Clin Microbiol Infect Dis* 2012;3:3001–3006.

5. Shefali-Patel D, Paris MA, Watson F, et al. RSV hospitalisation and healthcare utilisation in moderately prematurely born infants. *Eur J Pediatr* 2012;171:1055–1061.

6. Greenough A, Alexander J, Burgess S, et al. Health care utilisation of prematurely born, preschool children related to hospitalisation for RSV infection. *Arch Dis Child* 2004;89:673–678.

7. Forbes ML, Hall CB, Jackson A, et al. Comparative costs of hospitalisation among infants at high risk for respiratory syncytial virus lower respiratory tract infection during the first year of life. *J Med Econ* 2010;13:136-141.

8. Palmer L, Hall CB, Katkin JP, et al. Respiratory outcomes, utilization and cost 12 months following a respiratory syncytial virus diagnosis among commercially insured late-preterm infants. *Curr Med Res Opin* 2011;27:403-412.

9. Langley GF, Anderson LJ. Epidemiology and prevention of respiratory syncytial virus infections among infants and young children. *Paediatr Infect Dis J* 2011;30: 510–517.

10. Welliver RC. Review of epidemiology and clinical risk factors for severe respiratory syncytial virus (RSV) infection. *J Paediatr* 2003;143:S112–S117.

11. Murray J, Bottle A, Sharland M, et al. Risk factors for hospital admission with RSV bronchiolitis in England: a population-based birth cohort study. *PLoS One* 2014;9:e89186.

12. The IMpact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics* 1998;102:531-537.

13. Blanken MO, Rovers MM, Molenaar JM, et al. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. *New Engl J Med* 2013;368:1791-1799.

14. Yoshihara S, Kusuda S, Mochizuki H, et al. Effect of palivizumab prophylaxis on subsequent recurrent wheezing in preterm infants. *Pediatrics* 2013;132:811-818.

15. American Academy of Pediatrics Committee on Infectious Diseases; American Academy of Pediatrics Bronchiolitis Guidelines Committee. Updated guidance for palivizumab prophylaxis among infants and

young children at increased risk of hospitalization for respiratory syncytial virus infection. *Pediatrics* 2014;134:e620-638.

[16] Viswanathan M, Berkman ND, Dryden DM, et al. Assessing Risk of Bias and Confounding in Observational Studies of Interventions or Exposures: Further Development of the RTI Item Bank. Methods Research Report. (Prepared by RTI–UNC Evidence-based Practice Center under Contract No. 290-2007-10056-I). AHRQ Publication No. 13-EHC106-EF. Rockville, MD: Agency for Healthcare Research and Quality; August 2013. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm [Accessed November 2015]

[17] Higgins JPT, Altman DG (editors). Chapter 8: Assessing risk of bias in included studies. In Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.0.1 [updated September 2008]. The Cochrane Collaboration 2008. Available at: www.cochrane-handbook.org [Accessed November 2015]

[18] Oxford Centre for Evidence-based Medicine – Levels of Evidence 2009. Available at: http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/ [Accessed November 2015]

[19] Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17:1-12.