

Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children (Protocol)

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[Intervention Protocol]

Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

1. To assess the effects of prophylaxis with RSV monoclonal antibody compared with placebo, no prophylaxis or another type of prophylaxis for reducing the risk of hospitalization due to RSV infection in high-risk infants and children.
2. To assess the effects of prophylaxis with RSV monoclonal antibody as assessed by the use of resources, compared with placebo, no prophylaxis or another type of prophylaxis.
3. To assess the incremental costs associated with changes in resource use in patients receiving RSV monoclonal antibody prophylactically, compared with placebo, no prophylaxis or another type of prophylaxis.

BACKGROUND

Description of the condition

Respiratory syncytial virus (RSV) is one of the most important viral pathogens to cause acute respiratory infections (ARIs) in children (Nair 2010), with virtually all children having been infected with RSV at least once by their second birthday (Peters 2009). In the USA, RSV infection is associated with substantial childhood morbidity, necessitating inpatient and outpatient care (Hall 2009a).

RSV Infection carries a considerable disease burden, with an estimated 2.1 million children under five years of age requiring medical care in the USA each year. Among children with RSV-related illnesses, approximately 3% are hospitalised, 25% are treated in emergency departments and 73% are treated by paediatricians. In the USA each year, it is estimated that in children under five, RSV infection accounts for one out of every 334 hospitalisations, one out of 38 visits to an emergency department and one out of 13 visits to a primary care physician (Hall 2009a). Globally, it is estimated that RSV causes about 34 million episodes of acute lower respiratory tract infections in children under five, resulting in about 3.4 million hospitalisations each year (Nair 2010). RSV has also been shown to be the most important viral cause of death in children under five, especially in those younger than one year (Fleming 2005; Shay 2001; Thompson 2003). In data compiled by the Center for Disease Control and Prevention (CDC), RSV pneumonia causes about 2700 adult and paediatric deaths each year (Thompson 2003). Globally, it is estimated to result in up to 199,000 deaths per year (Nair 2010).

The exact timing of RSV season varies by location and year (Mullins 2003). In temperate climates of the USA, RSV outbreaks usually begin in November or December, peaking in January or February and end by March or April; whereas in countries with tropical or subtropical climates, RSV activity correlates with rainy seasons or may be present throughout the year (AAP 2009; Hall 2009b; Simoes 2003). In recent years, the median duration of the RSV season in the USA has been 16 weeks (CDC 2010). Knowledge of RSV seasonality can be used by clinicians and public health officials to determine when to consider RSV as a cause of ARIs and when to provide RSV immunoprophylaxis to children at high risk of serious disease (Peters 2009).

The incubation period of infection frequently lasts four to six days. Inoculation of the virus happens through the upper respiratory tract (URT), followed by infection of the respiratory epithelium. The virus spreads along the respiratory tract, mainly by cell-to-cell transfer along intracytoplasmic bridges and may involve the conducting airways at all levels (Hall 2009b).

RSV initially manifests in infants as an upper respiratory tract infection (URTI), but progresses to a lower respiratory tract infection (LRTI) in approximately 50% of infants with varying degrees of severity, ranging from mild to life-threatening respiratory failure (Peters 2009). Bronchiolitis usually develops one to three days

following common cold symptoms such as nasal congestion and discharge, mild cough, fever and reduced appetite. As the infection progresses and the small airways are affected, other symptoms develop, such as rapid breathing, wheezing, persistent cough and difficulty in feeding, which can result in dehydration. Apnoea (a pause in breathing for more than 15 or 20 seconds) is the presenting symptom in up to 20% of infants admitted to hospital with RSV and may be the first symptom of bronchiolitis (Arms 2008; Hall 1979; Ralstone 2009). In severe cases, oxygenation may worsen and a child may develop acute respiratory or ventilatory failure, necessitating mechanical ventilation and admission to an intensive care unit (ICU).

Characteristics that are most frequently associated with RSV illness requiring hospitalization include male sex, chronic co-existing medical conditions, lower socio-economic status, smoke exposure, contact with other children and lack of breast-feeding (Hall 2009a). Characteristics that increase the risk of severe RSV illness are preterm birth, cyanotic or complicated congenital heart disease (CHD), especially conditions that cause pulmonary hypertension, chronic lung disease (CLD) of prematurity (formerly called bronchopulmonary dysplasia) and immunodeficiency (Purcell 2004).

Description of the intervention

The observation that passively transferred maternal RSV-neutralising antibodies provided some protection from severe lower respiratory tract (LRT) disease has led to the development of passive immunity products to prevent and modify the severity of RSV infection. The first product available for this use was RSV-IVIG (RespiGam), a polyclonal human RSV-neutralising antibody (a combination of different immunoglobulin molecules), administered intravenously during RSV-risk months. RSV-IVIG is no longer available.

In 1996, palivizumab (Synagis) entered into clinical trials. Palivizumab is an anti-RSV monoclonal antibody (set of identical immunoglobulin molecules), administered intramuscularly at a dose of 15 mg/kg once every 30 days. The efficacy and safety of palivizumab have been evaluated in multicentre randomized controlled trials (RCTs), which in two trials demonstrated 45% and 55% decreases in RSV-related hospitalisations (Feldes 2003; Impact-RSV 1998). In both trials, palivizumab prophylaxis was generally safe and well tolerated. In June 1998, palivizumab was licensed by the USA Food and Drug Administration (FDA) for prevention of serious LRT disease caused by RSV in paediatric patients who are at an increased risk of severe disease (infants and children with CLD, with a history of preterm birth (35 weeks gestation or less), or with haemodynamically significant CHD) (AAP 2009).

In 2008, MedImmune filed for FDA approval of motavizumab (Numax), another RSV-neutralising monoclonal antibody intended for the same indication. The efficacy and safety of motavizumab and palivizumab were compared in a multinational

non-inferiority RCT (Carbonell-Estrany 2010). In December 2010, the company announced it had discontinued further development of motavizumab for the prophylaxis of serious RSV disease. Therefore, palivizumab is currently the only monoclonal antibody approved for this purpose.

The cost of immunoprophylaxis with palivizumab is high and economic analyses have failed to demonstrate overall savings in health care dollars if all infants who are at risk receive prophylaxis (ElHassan 2006; Joffe 1999; Kamal-Bahl 2002; Stevens 2000; Wang 2008; Wegner 2004; Yount 2004). In the USA, a total of five monthly doses for infants and young children with CLD, CHD, or preterm birth born before 32 weeks gestation, will provide an optimal balance of benefit and cost, even with variation in the season's onset and end (AAP 2009).

How the intervention might work

Respiratory syncytial virus is a ribonucleic acid (RNA) virus of the *Paramyxoviridae* family. The virus uses attachment (G) and fusion (F) surface glycoproteins to infect cells. Palivizumab is a humanised mouse monoclonal immunoglobulin G1, produced by recombinant DNA technology and directed to an epitope of the F glycoprotein of RSV. Palivizumab binds to this glycoprotein and prevents viral invasion of the host cells in the airway. This reduces viral activity and cell-to-cell transmission and blocks the fusion of infected cells (Johnson 1997). As a result, preventive use of palivizumab may be associated with reduced risk for developing LRT disease (Hall 2010).

Why it is important to do this review

In a previous Cochrane systematic review, the effects of both RSV-IVIG and palivizumab were assessed, with the last search performed in March 1999 (Wang 1999). Since then, RSV-IVIG has been withdrawn, methodologies have changed and additional RCTs with palivizumab have been conducted. The review was withdrawn from *The Cochrane Library* in 2003, as the authors could not commit time to further update it. A new team of authors took over this review in 2007 and published a protocol which focused on effectiveness and safety of prophylaxis with palivizumab (Lozano 2007). The protocol was withdrawn from *The Cochrane Library* in 2010, as authors could not commit time to writing a review.

Our review, unlike the ones published previously, will focus on palivizumab prophylaxis, in terms of efficacy and safety, as well as its cost-effectiveness. Moreover, the effects will be assessed not only in infants and children born preterm, with CLD or CHD but also in children with immunodeficiency, congenital anomalies or neuromuscular disease. We expect that the findings will provide more sound evidence on which healthcare decisions should be made.

OBJECTIVES

1. To assess the effects of prophylaxis with RSV monoclonal antibody compared with placebo, no prophylaxis or another type of prophylaxis for reducing the risk of hospitalization due to RSV infection in high-risk infants and children.
2. To assess the effects of prophylaxis with RSV monoclonal antibody as assessed by the use of resources, compared with placebo, no prophylaxis or another type of prophylaxis.
3. To assess the incremental costs associated with changes in resource use in patients receiving RSV monoclonal antibody prophylactically, compared with placebo, no prophylaxis or another type of prophylaxis.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs) comparing monoclonal antibody (palivizumab) prophylaxis with a placebo, no prophylaxis or another type of prophylaxis in preventing serious LRT disease caused by RSV, in paediatric patients at high risk of RSV disease. We will consider the following types of studies for inclusion in the critical review of health economics studies.

1. Full economic evaluation studies such as cost-effectiveness analyses and cost-utility analyses comparing monoclonal antibody prophylaxis with a placebo, no prophylaxis or another type of prophylaxis.
2. Partial economic evaluation studies that report cost analyses, or cost-outcome descriptions comparing monoclonal antibody prophylaxis with placebo, no prophylaxis or another type of prophylaxis.

We will consider for inclusion only health economics studies conducted alongside high quality randomized trials or economic modelling studies based on a meta-analysis of data from high quality randomized trials.

Types of participants

We will include infants and children at high risk of developing LRT disease caused by RSV, i.e. those with chronic lung disease, congenital heart disease, immunodeficiency, chronic neuromuscular disease, congenital anomalies or those born preterm. We will exclude children with cystic fibrosis as a related Cochrane review has already been published on that topic (Robinson 2010).

Types of interventions

We will compare passive immunisation of monoclonal antibody palivizumab (any setting, regimen or dose) with either placebo, no prophylaxis or another type of prophylaxis.

Types of outcome measures

We will include the following outcomes in the 'Summary of findings' table.

1. RSV hospitalization.
2. Number of days in hospital.
3. ICU admission.
4. Mechanical ventilation.
5. Oxygen therapy.
6. Number of children with secondary complications.
7. Adverse events.

Primary outcomes Hospitalisation for RSV infection.Mortality.

Primary outcomes

1. Hospitalisation for RSV infection.
2. Mortality.

Secondary outcomes

1. Number of days in hospital attributable to RSV infection.
2. Admission to ICU.
3. Number of days in the ICU.
4. Mechanical ventilation for RSV infection.
5. Number of days of mechanical ventilation.
6. Oxygen therapy for RSV infection.
7. Number of days of oxygen therapy.
8. Bronchodilator therapy for RSV infection.
9. Number of days of bronchodilator therapy.
10. Number of children who develop secondary complications following RSV infection and/or immunisation with palivizumab (e.g. asthma, allergies, acute right heart failure, nosocomial infections, etc.).
11. Adverse events.

Economic evaluation outcomes

1. Effectiveness outcome measures: hospitalization for RSV infection avoided (number of RSV hospitalisations avoided, due to the use of prophylaxis), or any other effect measure reported by trial authors such as quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs).
2. The final costs associated with:
 - o administration of palivizumab (palivizumab injections, administration by physicians, nurses or both);
 - o length of hospital stay;

- o days of mechanical ventilation;
 - o days in ICU;
 - o need for supplemental oxygen after discharge;
 - o incidence of complications such as air leak syndrome and aggregated bacterial infections;
 - o treatment of adverse events;
 - o number of outpatient visits;
 - o number of outpatient emergency department visits;
 - o number of days-off work (parents or caregivers); and
 - o patient out-of-pocket expenses.
3. Incremental cost-effectiveness ratios (ICERs).
 4. Incremental cost per QALY.

Search methods for identification of studies

Electronic searches

To identify studies on effectiveness and safety we will search the Cochrane Central Register of Controlled Studies (CENTRAL) (*The Cochrane Library*, latest issue), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (1996 to present), EMBASE (1996 to present), CINAHL (1996 to present) and LILACS (1996 to present).

We will search MEDLINE and CENTRAL using the keywords and MeSH terms in [Appendix 1](#). We will use the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE ([Lefebvre 2011](#)). We will adapt this strategy to search EMBASE, CINAHL and LILACS. In addition we will combine the search terms with the search strategy developed by Golder to identify studies on adverse effects in MEDLINE and EMBASE ([Golder 2006](#)). We will impose no language or publication restrictions.

To identify economic studies we will adapt the search terms in [Appendix 1](#) to search the NHS Economic Evaluations Database (NHS EED, latest issue), Health Economics Evaluations Database (HEED, latest issue) and Paediatric Economic Database Evaluations (PEDE, latest issue). We will also search MEDLINE and EMBASE using a filter based on the work of [Glanville 2009](#).

Searching other resources

We will search the reference lists of relevant trials and review articles to identify additional eligible studies and trial reports. We will contact the drug manufacturer (MedImmune LLC), trial authors and content experts to obtain information on ongoing or unpublished studies. We will search appropriate clinical trials databases utilising the World Health Organization's (WHO) International Clinical Trials Registry Platform (ICTRP - www.who.int/ictip/).

Data collection and analysis

Selection of studies

We will merge the search results using reference management software and we will remove duplicate records of the same report. Two review authors (TA, JN) will independently examine titles and abstracts to remove obviously irrelevant reports. We will retrieve the full texts of the potentially relevant reports and we will link multiple reports of the same study. Two review authors (TA, JN) will independently examine full-text reports to determine which studies meet the eligibility criteria. We will resolve disagreements by discussion or consultation with a third review author (BB).

Two review authors (TA, MXR) will independently examine titles and abstracts for the selection of economic studies to be included in the critical economic review. We will remove obviously irrelevant reports. We will retrieve the full texts of potentially relevant reports (i.e. health economics studies conducted alongside randomized trials or economic modelling studies based on a meta-analysis of data from randomized trials). Two review authors (TA, MXR) will independently examine full-text reports to determine which studies meet the eligibility criteria. We will include only full economic evaluations with high methodological quality (see [Assessment of risk of bias in included studies](#)).

Data extraction and management

Two review authors (TA, JN) will independently extract data from eligible studies using a customised data collection form. We will collect details on source, eligibility and reasons for exclusion, methods, potential source of bias, participants, settings, interventions, outcomes and results. We will contact trial authors for any missing data. We will resolve disagreements by discussion or by consultation with a third review author (BB). We will enter all collected data into Review Manager Software for analysis ([RevMan 2011](#)). For the economic evaluation studies, in addition to the aspects described above, we will collect other useful information such as:

- type of economic analysis;
- time horizon considered in the study;
- analytical point of view;
- cost (resources) considered in the obtained total cost per patient;
 - year prices used for cost;
 - cost-effectiveness ratio of each alternative; and
 - ICER and incremental cost per QALY.

Assessment of risk of bias in included studies

Two review authors (TA, JN) will independently assess risk of bias using the Cochrane Collaboration's tool for assessing risk of bias, which addresses the following domains: random sequence generation, allocation concealment, blinding of participants and

personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases.

We will record each piece of information extracted for the risk of bias tool together with the precise source of this information. We will test data collection forms and assessments of the risk of bias on a pilot sample of articles. The assessors will not be blinded to the names of the authors, institutions, journal or results of a study. We will resolve disagreements by discussion or consultation with a third review author (BB). We will attempt to contact the study authors and obtain important missing information for the assessment of risk of bias in the included reports by using open-ended questions. We will tabulate risk of bias for each included study, along with a judgement of 'low', 'high' or 'unclear' risk of bias, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011a](#)). Risk of bias will also be summarised for each outcome across studies in a 'Summary of findings' table. We will consider two main aspects for quality assessment of economic evaluation studies.

1. Assessment of risk of bias in results of the single effectiveness study on which the full economic evaluation study is based.
2. Assessment of the methodological quality of the full economic evaluation study using the Drummond checklist ([Drummond 1996](#)).

Measures of treatment effect

We will calculate risk ratios (RRs) and their associated 95% confidence intervals (CIs) for dichotomous outcomes. We will report the mean post-intervention value, as well as the mean difference (MD) between treatment groups and their associated 95% CIs for continuous outcomes. We will calculate odds ratios (ORs) and their associated 95% CIs for adverse events. We will analyse count data in the following way.

1. Total days of RSV hospitalization as continuous data.
2. Total days in the ICU as continuous data and as rate number of ICU days per 100 children.
3. Total days of mechanical ventilation as continuous data and as rate number of days per 100 children.
4. Total days of oxygen therapy as continuous data.
5. Total days of bronchodilator therapy as continuous data and as rate number of days per 100 children.
6. Number of children with secondary complications as dichotomous data.

We will summarise the results of included health economics studies (e.g. incremental cost-effectiveness or the incremental cost per QALY) in a 'Summary of findings' table and we will provide a commentary on tabulated results. We will include the information of resource use and cost reported in the included studies in the results tables if it is available, so that readers can easily identify the variation in the distribution of cost and resources in different studies and settings.

Dealing with missing data

There are several types of missing data in a systematic review or meta-analysis as described in Table 16.1.a in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). The problem of missing studies and outcomes is addressed in the [Assessment of reporting biases](#) section of this protocol. A common problem is missing summary data, such as standard deviations for continuous outcomes. We will not exclude a study from the review because it has missing summary data; we will use the methods outlined in section 16.1.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b) for imputing missing standard deviations. In some studies, data on individuals may be missing from the reported results. When necessary, we will attempt to contact trial authors and ask them for more information.

We will make explicit our assumptions about why data are missing. Analysis will include only available data and we will ignore missing data if the data is judged to be 'missing at random', i.e. their absence is unrelated to their actual values. We will perform a sensitivity analysis to assess how the changes in assumptions may affect the results if data are judged to be 'not missing at random'. We will address the potential impact of missing data on the findings of the review in the 'Discussion' section.

Assessment of heterogeneity

We will assess heterogeneity between included studies using the χ^2 test and I^2 statistic (Higgins 2003). We will consider a χ^2 P value of less than 0.10 indicative of statistical heterogeneity. We will calculate the I^2 statistic to quantify inconsistency across studies. We will interpret the I^2 statistic in the following way: heterogeneity might not be important (I^2 statistic value of 0% to 40%); heterogeneity may be moderate (I^2 statistic of 30% to 60%); heterogeneity may be substantial (I^2 statistic of 50% to 90%); and considerable heterogeneity (I^2 statistic of 75% to 100%).

Assessment of reporting biases

We will assess possible reporting biases on two levels: within-study and between-studies.

We will examine within-study selective outcome reporting as a part of the overall risk of bias assessment (see [Assessment of risk of bias in included studies](#)). We will attempt to find protocols of included studies and compare the outcomes stated in the protocols with those reported in the publications. We will compare the outcomes listed in the methods section of a publication with those whose results are reported if protocols are not found. We will contact trial authors for clarification if we identify indications of reporting bias.

We will create a funnel plot of effect estimates against their standard errors (SEs) to assess possible between-studies reporting bias if there are at least 10 studies included in the review. We will consider possible explanations if we find asymmetry of the funnel

plot, either by inspection or statistical tests, and we will take into account the interpretation of the overall estimate of treatment effects.

Data synthesis

We will perform a fixed-effect meta-analysis for the estimation of pooled effects (in safety and effectiveness outcomes). We will perform a random-effects meta-analysis if we identify important statistical heterogeneity between included studies (I^2 statistic > 40%). As previously stated, we will present results of included economic studies (including measures of incremental resource use, incremental cost-effectiveness or the incremental cost per QALY) in a 'Summary of findings' table. We are not planning to calculate pooled combined estimates of cost-effectiveness or resource use and cost, extracted from multiple economic evaluations.

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analyses based on the presence of risk factors (preterm birth, CLD, CHD, immunodeficiency, chronic neuromuscular disease and congenital anomalies), in case there are at least three studies per subgroup. Should the information be available, we will report the evidence of economic impact and the incremental cost (ICER or incremental cost per QALY) independently for infants (neonates) and for other age subgroups.

Sensitivity analysis

We will include all studies in a primary meta-analysis, irrespective of their assessed risk of bias. We will then perform a sensitivity analysis to assess how the results of the meta-analysis will be affected by excluding studies determined to be at high risk of bias. We will compare the results of both meta-analyses to assess the effect of the high risk of bias trials.

The sensitivity analysis will take into account those biases that could significantly impact on the outcomes of the included studies. As previously noted in the [Assessment of risk of bias in included studies](#) section, we will use the Cochrane Collaboration's tool for assessing risk of bias (categorised as 'low', 'high' and 'unclear'), focusing on domains such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases, such as the source of funding of the included studies.

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* Indicates the major publication for the study

APPENDICES**Appendix I. MEDLINE and CENTRAL search strategy**

- 1 Respiratory Syncytial Virus Infections/
- 2 respiratory syncytial viruses/ or respiratory syncytial virus, human/
- 3 (respiratory syncytial vir* or rsv).tw.
- 4 Respiratory Tract Infections/
- 5 (acute respiratory infection* or acute respiratory tract infection*).tw.
- 6 (lower respiratory tract infection* or lrti).tw.
- 7 exp Bronchiolitis/
- 8 bronchiolit*.tw.
- 9 pneumonia/ or pneumonia, viral/
- 10 pneumon*.tw.
- 11 or/1-10
- 12 palivizumab.tw,nm.
- 13 synagis.tw,nm.
- 14 exp Antibodies, Monoclonal/
- 15 (monoclonal antibod* or mab or mabs).tw.
- 16 Antiviral Agents/
- 17 Antibodies, Viral/
- 18 or/12-17
- 19 11 and 18

WHAT'S NEW

Date	Event	Description
11 August 2010	New citation required and major changes	A new review team took over this previously withdrawn protocol.

HISTORY

Protocol first published: Issue 3, 2007

Date	Event	Description
7 September 2009	Amended	Withdrawn from <i>The Cochrane Library</i> , 2010, issue 1
13 May 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Tea Andabaka (TA) searched for articles for the background section. Maria Ximena Rojas-Reyes (MXR) defined the methods and planning of the economics components of this review. Jason Nickerson (JN) contributed to the writing and critical editing of the protocol. Bruno Barsic (BB) contributed to the conception of the idea for the review. All review authors approved the final protocol.

DECLARATIONS OF INTEREST

This review is in no way funded by commercial entities that could possibly benefit financially from its results. The review authors have no financial interest in the subject matter of the review (e.g. private clinical practice, stocks, legal advice, consultancies, employment).

Bruno Barsic (BB) is a co-founder and co-owner of the company Synovia, involved in consulting activities for an international epidemiological study on the incidence and characteristics of RSV infections (H09-116: RSV Survey in CEE). That study is sponsored by the pharmaceutical company Abbott.

Maria Ximena Rojas-Reyes (MXR) has participated in a number of research studies supported by Abbott Laboratories and Fisher & Paykel Healthcare.

Tea Andabaka (TA) and Jason Nickerson (JN) have no conflicts of interest to declare.

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