

The effects of Palivizumab Prophylaxis on Reducing Complications Associated with Respiratory Syncytial Virus infections in children

A systematic review

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Responsibility

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TABLE OF CONTENTS

ABSTRACT	I
ABBREVIATIONS AND ACRONYMS	VII
INTRODUCTION	1
1 METHODOLOGY	3
1.1 Key research question	3
1.2 Information research strategy	3
1.3 Study selection criteria	4
1.4 Study selection	4
1.5 Data extraction	4
1.6 Evaluation of the methodological quality of the studies	5
1.7 Data analysis and synthesis	5
1.8 Peer validation	6
2 RESULTS	7
2.1 Description of the identified studies	7
2.2 Effectiveness of palivizumab prophylaxis compared to administration of a placebo or to no prophylaxis	9
3 DISCUSSION	30
3.1 Main findings resulting from the critical review of the literature	30
3.2 Strengths and limitations of the systematic review	34
CONCLUSION	37
APPENDIX A INFORMATION RESEARCH STRATEGY	38
APPENDIX B STUDY SELECTION	41
APPENDIX C LIST AND CHARACTERISTICS OF INCLUDED STUDIES	46
APPENDIX D RESULTS OF THE EVALUATION OF THE METHODOLOGICAL QUALITY OF STUDIES	52
REFERENCES	57

LIST OF TABLES

Table 1	Criteria for inclusion and exclusion of scientific studies	4
Table 2	Effectiveness of palivizumab prophylaxis in premature infants with infantile chronic lung disease or heart disease, compared to the administration of a placebo or no prophylaxis	12
Table 3	Effectiveness of palivizumab prophylaxis in premature infants without chronic lung disease, compared to administration of a placebo or to no prophylaxis	17
Table 4	Effectiveness of palivizumab in premature infants with infantile chronic lung disease or bronchopulmonary dysplasia, compared to no prophylaxis	19
Table 5	Effectiveness of palivizumab prophylaxis in children with cystic fibrosis, compared to administration of a placebo or to no prophylaxis	21
Table 6	Effectiveness of palivizumab prophylaxis in children with congenital heart disease with significant hemodynamic consequences, compared to administration of a placebo or to no prophylaxis	24
Table 7	Effectiveness of palivizumab in premature infants residing in remote communities, compared to no prophylaxis	26
Table 8	Effectiveness of palivizumab in children with Down syndrome, COMPARED TO NO PROPHYLAXIS	28

ABSTRACT

Introduction

The ministère de la Santé et des Services sociaux mandated the Institut national d'excellence en santé et en services sociaux to reassess the eligibility criteria for the use of palivizumab in children. This reassessment will allow Héma-Québec to update its circular and related forms for the next respiratory syncytial virus (RSV) infection season (2016-2017).

Methods

A systematic literature review was conducted in order to describe the effectiveness of palivizumab prophylaxis in reducing the risk of RSV complications in children, compared to the administration of a placebo, to no prophylaxis or to another type of prophylaxis. The literature search was conducted using several databases, namely MEDLINE (PubMed), Embase (Ovid), Cochrane Database of Systematic Reviews and Health Technology Assessment (HTA), without restriction on the year of publication. Bibliographies of selected publications were also consulted. A search of the grey literature was performed using the Google Scholar search engine. The intent was to measure the effectiveness of palivizumab in relation to hospitalizations, length of hospital stay, stays in intensive care, use of oxygen therapy (mechanical ventilation), long-term sequelae (wheezing, asthma) or mortality. The first selection of articles identified during the data search was undertaken independently by two examiners, while the second selection was conducted by four examiners. Data were extracted by an examiner and validated by a second examiner. Tools used to assess the methodological quality of the studies were as follows: R-AMSTAR (Revised - a measurement tool to assess the methodological quality of systematic reviews) to assess systematic reviews and CASP (Critical Appraisal Skills Programme) to assess randomized clinical trials (RCTs) and observational studies. Results were summarized in the form of an analytical narrative synthesis.

Results

No RCT, cohort study or case-control study on the effectiveness of palivizumab prophylaxis compared to the administration of a placebo or to no prophylaxis was identified among children who are immunosuppressed, who are affected by a metabolic disorder, who present a serious neuromuscular disorder affecting respiratory function, who present an anomaly of the upper airway affecting respiratory function, from a healthy multiple birth whose twin is eligible to receive palivizumab.

Mixed Population

In studies involving various populations (premature infants or children with bronchopulmonary dysplasia, chronic lung disease [CLD] or congenital heart disease), data from the meta-analyses of RCTs, a meta-analysis based on RCTs and observational studies, an RCT and two observational studies indicate that palivizumab has statistically significant effects in reducing RSV-associated hospitalizations, compared to the administration of a placebo or to no prophylaxis. There is less scientific data available on the other assessed result parameters. On the whole, a number of studies reported a statistically significant reduction of the duration of hospitalization, of the risk of being admitted to an intensive care unit (ICU) and of the duration of hospitalization in an ICU for children who received palivizumab prophylaxis, compared to those who received a placebo. From a methodological point of view, the quality of these studies ranges from 'very poor' to 'good'.

Premature infants without infantile chronic lung disease

In premature infants without CLD, the data from a meta-analysis of RCTs and observational studies as well as the RCT data report a statistically significant reduction in RSV-associated hospitalizations in children born at 32 weeks of gestation or less and in children born at a gestational age ranging from 32 to 35 weeks, who received palivizumab prophylaxis, compared to those who received a placebo or no prophylaxis. Results of the identified observational studies show a reduction in RSV-associated hospitalizations, but this reduction was only statistically significant in some studies. The methodological quality of these studies ranges from 'poor' to 'good'.

All-cause mortality and wheezing in the first year of life were also assessed in the studies identified. A systematic review including RCTs and observational studies reports a reduction in all-cause mortality in children born at 32 weeks of gestation or less and those born at a gestational age ranging from 32 to 35 weeks who received palivizumab prophylaxis, compared to those who received a placebo or no prophylaxis. However, the difference was statistically significant only in children born at 32 weeks of gestation or less. The methodological quality of this literature review is 'average'. Also, in an RCT and two observational studies, a statistically significant reduction of the risk of wheezing in the first year of life was observed in children born at a gestational age of 33 to 35 weeks and in those born at 35 weeks of gestation or less who received palivizumab prophylaxis, compared to those who received a placebo or no prophylaxis. The methodological quality of these three studies ranges from 'good' to 'poor'.

Premature infants with infantile chronic lung disease or bronchopulmonary dysplasia

Data from an RCT with good methodological quality published in 1998 show a statistically significant reduction in the risk of RSV-associated hospitalizations in children aged 24 months or less with bronchopulmonary dysplasia who received palivizumab, compared to those who received a placebo. Data from two observational studies published in 2003 and 2004 indicate that palivizumab causes a statistically significant reduction in the risk of RSV-associated hospitalizations compared with no prophylaxis in children born at 32 or less weeks of gestation, suffering from CLD and aged six months or less at the start of the RSV season. From a methodological point of view, these studies are of 'poor' and 'very poor' quality.

Children with cystic fibrosis

Results of an RCT and two observational studies indicate no statistically significant difference in the number of RSV-associated hospitalizations in children with cystic fibrosis who received palivizumab, compared to those who received a placebo or who did not receive palivizumab. The methodological quality of these studies ranges from 'poor' to 'average'.

Children with hemodynamically significant congenital heart disease

In children with hemodynamically significant congenital heart disease, results of an RCT and observational study indicate a reduction of RSV-associated hospitalizations in children with congenital heart diseases who received palivizumab, compared to those who received a placebo. A statistically significant difference was only reported in the RCT. The methodological quality of the RCT is good, but that of the cohort study is poor.

Children residing in remote communities

In two observational studies of poor methodological quality, a reduced risk of RSV-associated hospitalizations was observed in children who received a palivizumab prophylaxis, compared to those who received no treatment.

Children with Down syndrome

Results of a single observational study of poor methodological quality show a statistically significant reduction in the risk of RSV-associated hospitalizations in children with Down syndrome who received palivizumab, compared to those who did not receive a prophylaxis. It should be noted that for children with no risk factors, no significant difference was reported.

Conclusions

Currently available data indicate that palivizumab is effective in reducing the risk of RSV-associated hospitalizations in premature infants with or without CLD, in non-premature infants with CLD, in children with acyanotic congenital heart disease, in children residing in remote communities and in children with Down syndrome who have risk factors. Little scientific data is available on the other result parameters assessed and results of the various studies are sometimes discordant. None of the identified data supports the effectiveness of palivizumab in children with cystic fibrosis. The effectiveness of palivizumab in certain populations, including premature infants with CLD, children residing in remote communities, children with Down syndrome and children with cystic fibrosis is poorly documented and studies have methodological limitations and uncertainties. Moreover, no studies were identified on the effectiveness of palivizumab prophylaxis compared to the administration of a placebo or to no prophylaxis among children who are immunosuppressed, who are affected by a metabolic disorder, who present a serious neuromuscular disorder affecting respiratory function, who present an anomaly of the upper airway affecting respiratory function, from a healthy multiple birth whose twin is eligible to receive palivizumab.

SUMMARY

Introduction

The Ministère de la Santé et des Services sociaux tasked the Institut national d'excellence en santé et en services sociaux with re-examining the criteria for using palivizumab in infants and young children. This re-examination will enable Héma-Québec to update its circular and the related forms for the next respiratory syncytial virus (RSV) infection season (2016-2017).

Methods

A systematic literature review was carried out to obtain a portrait of the efficacy of palivizumab prophylaxis in reducing the risk of RSV complications in infants and young children compared to the administration of placebo, to no prophylaxis or to another type of prophylaxis. The literature search was conducted in several databases, namely, MEDLINE (PubMed), Embase (Ovid), the Cochrane Database of Systematic Reviews and the Cochrane Health Technology Assessment Database, with no restrictions on the year of publication. The lists of references in the publications selected were consulted as well. A search of the grey literature was performed using the Google Scholar search engine. The efficacy of palivizumab had to have been measured with regard to hospitalizations, the duration of hospital stay, intensive care unit stays, the use of oxygen therapy (mechanical ventilation), long-term-sequelae (wheezing or asthma) or mortality. The first selection of articles identified during the scientific data search was done independently by two examiners, while the second selection was performed by four examiners. Data extraction was carried out by one examiner, and the data were validated by a second examiner. The tools used to assess the methodological quality of the studies were R-AMSTAR (Revised – a measurement tool to assess the methodological quality of systematic reviews) and CASP (Critical Appraisal Skills Programme), for evaluating randomized clinical trials (RCTs) and observational studies. The results were summarized in the form of an analytical narrative synthesis.

Results

No RCTs, cohort studies or case-control studies of the efficacy of palivizumab prophylaxis compared to the administration of placebo or to no prophylaxis were found for immunocompromised infants or young children, those with a metabolic disease, a severe neuromuscular disorder affecting respiratory function or an anomaly of the upper respiratory tract affecting respiratory function, or those of a multiple birth who are healthy but whose twin qualifies for palivizumab.

Mixed population

In the studies involving different populations (premature infants and infants with bronchopulmonary dysplasia, chronic lung disease (CLD) or congenital heart disease), the data from the meta-analyses of RCTs, a meta-analysis based on RCTs and observational studies, an RCT and two observational studies indicate that palivizumab has statistically significant effects in reducing RSV hospitalizations compared to the administration of placebo or to no prophylaxis. The available scientific data on the other outcome measures evaluated are less plentiful. Overall, a statistically significant decrease in the mean number of days of hospital stay, in the risk of ICU admission and in the number of days of hospitalization in an intensive care unit among infants who received palivizumab prophylaxis compared to those who received a placebo was reported in certain studies. The methodological quality of these studies ranges from very poor to good.

The preterm infants who do not have chronic lung disease of the newborn or bronchopulmonary dysplasia

The data from a meta-analysis of RCTs and from observational studies, and data from RCTs indicate, in premature infants who did not have CLD, a statistically significant decrease in RSV hospitalizations in those born at ≤ 32 weeks' gestation and those born at a gestational age of 32 to 35 weeks who received palivizumab prophylaxis relative to those who received placebo or no prophylaxis. The results of the identified observational studies indicate a decrease in RSV hospitalizations, but this decrease was statistically significant in certain studies only. The methodological quality of these studies is poor to good.

All-cause mortality and wheezing in the first year of life were also evaluated in the identified studies. A systematic review including RCTs and observational studies reports a decrease in all-cause mortality in infants born at ≤ 32 weeks' gestation and those born at a gestational age of 32 to 35 weeks who received palivizumab prophylaxis compared to those who received placebo or no prophylaxis. However, the difference was statistically significant only in the infants born at ≤ 32 weeks' gestation. The methodological quality of this literature review is average. As well, in an RCT and two observational studies, there was a statistically significant decrease in the risk of having wheezing in the first year of life in the infants born at a gestational age of 33 to 35 weeks and in those born at ≤ 35 weeks' gestation who received palivizumab prophylaxis compared to those who received placebo or no prophylaxis. The methodological quality of these three studies ranges from good to poor.

Premature infants with chronic lung disease of the newborn or bronchopulmonary dysplasia

The data from one single RCT of good methodological quality published in 1998 indicate a statistically significant decrease in the risk of RSV hospitalization in children ≤ 24 months with bronchopulmonary dysplasia who received palivizumab relative to those who received placebo. The data from two observational studies, one published in 2003, the other in 2004, indicate that palivizumab reduces, in a statistically significant manner, the risk of RSV hospitalization compared to no prophylaxis in infants born at ≤ 32 weeks' gestation who have CLD and are ≤ 6 months of age at the start of the RSV season. The methodological quality of these studies was poor and very poor.

Cystic fibrosis

The results of one RCT and of two observational studies do not indicate a statistically significant difference in the number of RSV hospitalizations in children with cystic fibrosis who received palivizumab compared to those who received placebo or who did not receive palivizumab. The methodological quality of these studies varies from poor to average.

Hemodynamically significant congenital heart disease

For infants with hemodynamically significant congenital heart disease, the results of one RCT and observational study indicate a decrease in the risk of RSV hospitalization in children with congenital heart disease who received palivizumab relative to those who received placebo. A statistically significant difference was reported only in the RCT. The methodological quality of the RCT is good, but that of the cohort study is poor.

Remote communities

In two observational studies of poor methodological quality, there was a decrease in the risk of RSV hospitalization in the infants who received palivizumab prophylaxis compared to those who did not receive any treatment.

Down syndrome

The results of a single observational study of poor methodological quality indicate a statistically significant decrease in the risk of hospitalization for RSV infection in children with Down syndrome who received palivizumab relative to those who did not receive any prophylaxis. It will be noted that no significant difference was reported for children who do not have any risk factors.

Conclusions

The currently available data indicate that palivizumab is effective in reducing the risk of RSV hospitalization in preterm infants with or without CLD, non-preterm infants with CLD, infants with acyanotic congenital heart disease, infants in remote communities, and children with Down syndrome with risk factors. Few scientific data are available for the other outcome measures evaluated, and the results of the different studies are sometimes discordant. None of the data identified support the efficacy of palivizumab in children with cystic fibrosis. The efficacy of palivizumab in certain populations, such as preterm infants with CLD, infants in remote communities, children with Down syndrome and children with cystic fibrosis, is very sparsely documented, and the studies contain methodological limitations and various uncertainties. Furthermore, no studies were found concerning the efficacy of palivizumab prophylaxis compared to the administration of placebo or to no prophylaxis in immunocompromised infants or young children, those with a metabolic disease, a severe neuromuscular disorder affecting respiratory function or an anomaly of the upper respiratory tract affecting respiratory function, or those of a multiple birth who are healthy but whose twin qualifies for palivizumab.

ABBREVIATIONS AND ACRONYMS

CASP	Critical Appraisal Skills Programme
CI	Confidence interval
CLD	Chronic lung disease
HR	Hazard ratio
HTA	Health Technology Assessment
ICU	Intensive care unit
INESSS	Institut national d'excellence en santé et en services sociaux
IRR	Incidence rate ratio
IVIG	Intravenous immunoglobulin
MSSS	Ministère de la Santé et des Services sociaux
n/a	Not applicable
OR	Odds ratio
R-AMSTAR	Revised—a measurement tool to assess the methodological quality of systematic reviews
RCT	Randomized clinical trial
RR	Relative risk
RSV	Respiratory syncytial virus
RT-PCR	Reverse transcription polymerase chain reaction
SR-MA	Systematic review with meta-analysis

INTRODUCTION

Respiratory syncytial virus (RSV) infection is the leading cause of lower respiratory tract illness, mainly bronchiolitis and pneumonia, in young children. Palivizumab (Synagis®) is a human monoclonal antibody that is administered via intramuscular injection. It is indicated for the prevention of serious lower respiratory tract disorders caused by RSV in children who are highly susceptible to infection with RSV.

In June 2005, the Conseil du médicament established the first usage criteria for palivizumab. However, there was reluctance to add the product to the lists of approved drugs, as this would require that health services be reorganized to address the monitoring and optimal use of palivizumab. As such, the ministre de la Santé et des Services sociaux decided that Héma-Québec would retain responsibility for establishing the product's usage criteria. These criteria were amended in June, 2006 following a reassessment carried out under the Conseil du médicament's commitment to review the usage criteria after one year. Additional amendments to the criteria were made in 2009 and 2015.

The usage criteria for palivizumab in the prevention of RSV infections for the 2015-2016 season are as follows:

- Babies born at less than 33 weeks of pregnancy and younger than six months at the start of the RSV season;
- Children younger than 24 months at the start of the RSV season, with an infantile chronic lung disease (CLD) (defined by the need for oxygen at 36 weeks of gestational age) or bronchopulmonary dysplasia (defined by the need for oxygen at 28 days of life and up to at least 36 weeks of gestational age) and
 - who required oxygen in the six months before the RSV season;or
 - who required it during the RSV season;
- Children younger than 24 months at the start of the RSV season, with cystic fibrosis and presenting respiratory symptoms or a significant failure to thrive;
- Children younger than 24 months at the start of the RSV season, for whom the evacuation of airway secretions is significantly hindered due to a neuromuscular disorder;
- Children younger than 24 months at the start of the RSV season, for whom the evacuation of airway secretions is significantly hindered due to a congenital upper airway defect;
- Children younger than 12 months at the start of the RSV season, with congenital heart disease, cardiomyopathy or myocarditis causing clinically significant hemodynamic consequences or with moderate or severe hypertension (the request must be submitted by a pediatric cardiologist to guarantee diagnosis accuracy);
- Children younger than 24 months at the start of the RSV season, having undergone a transplant of bone marrow, stem cells or a solid organ (heart, liver or lung) in the six months before the RSV season or during the RSV season.

To allow the ministère de la Santé et des Services sociaux (MSSS) to optimize the use of palivizumab for the prevention of RSV infection in children, a reassessment of the criteria for use of this type of prophylaxis is necessary. Begun in 2015 (preliminary) and finalized this year, this reassessment will allow the MSSS to transmit the revised criteria for use to Héma-Québec for the next RSV infection season (2016-2017). Héma-Québec may then update its circular and related forms. It is in this context that INESSS was mandated to make recommendations on the criteria for use of palivizumab in children.

The objective of this report is to provide scientific data on the effectiveness of palivizumab in reducing complications associated with RSV in children. These data will support recommendations developed by INESSS on the criteria for use of this type of prophylaxis.

1 METHODOLOGY

A systematic literature review was conducted to assess the effect of palivizumab prophylaxis on reducing complications associated with RSV infection in children. The methodology used to carry out the systematic review from which this report was created respects INESSS's production standards for such reviews.

1.1 Key research question

The key research question was formulated by taking into account elements of the PICO model: study population, intervention, comparison and outcome.

Question

What is the effectiveness of palivizumab prophylaxis in reducing the risk of RSV-associated complications in children compared to the administration of a placebo or to no prophylaxis?

1.2 Search strategy

Search strategy for identifications of studies was developed in collaboration with a scientific information specialist (librarian). To reduce disclosure bias, the research was conducted using multiple databases – MEDLINE (PubMed), Embase (Ovid), Cochrane Database of Systematic Reviews and Health Technology Assessment – without restriction on the year of publication. A search of the grey literature was conducted by consulting websites of agencies, organizations, associations and institutions, including the Canadian Paediatric Society, Guidelines International Network, National Guideline Clearinghouse (United States), International Network of Agencies for Health Technology Assessment, National Institute for Health and Care Excellence (United Kingdom), National Authority for Health (France), American College of Physicians (United States) and the Scottish Intercollegiate Guidelines Network (United Kingdom). Bibliographies of the selected publications were also consulted to identify other relevant documents. The Google search engine was also used. The various strategies are described in Appendix A of this report.

1.3 Study selection criteria

Table 1 Criteria for inclusion and exclusion of scientific studies

Inclusion criteria – Scientific studies	
POPULATION	• Children under 18 years
INTERVENTION	• Palivizumab prophylaxis
COMPARISONS	• Placebo • No prophylaxis
OUTCOMES	• Hospitalization due to RSV infection • Length of hospital stay due to RSV infection • Stay in intensive care due to RSV infection • Length of stay in intensive care due to RSV • Use of oxygen therapy due to RSV infection • Length of oxygen therapy due to RSV infection • Use of mechanical ventilation due to RSV infection • Length of mechanical ventilation due to RSV infection • Long-term sequelae (wheezing, asthma) due to RSV infection • Mortality
TYPES OF PUBLICATIONS	• Systematic review with or without a meta-analysis • Randomized clinical trial (RCT) • Observational study (cohort study and case-control study)
LANGUAGE	• English and French

Exclusion criteria – Scientific studies	
TYPES OF PUBLICATIONS	• Doctoral dissertation or master's thesis, case series, case study, conference summary, economic study, clinical practice guidelines, consensus conference, health technology assessment (HTA) report
SCIENTIFIC QUALITY	• Less than 30 subjects in each group to carry out short-term monitoring • Less than 1,000 subjects to carry out long-term analysis

1.4 Study selection

The first selection of articles identified during the data search was undertaken independently by two reviewers (AF, MCB), according to the above study selection criteria. The second selection of articles was conducted independently by four reviewers (MT, MR, CJ, AF). Disagreements were resolved by considering the opinion of another reviewer (MCB).

1.5 Data extraction

Data extraction was performed by a reviewer (MCB) using extraction forms that were pre-established and pre-tested on a few studies to ensure their validity. Data were validated by a second reviewer (AF).

1.6 Evaluation of the methodological quality of the studies

Methodological quality evaluation of the included studies was performed independently by four reviewers (AF, MT, MR, CJ). Two tools were used to assess the quality of studies, namely:

- R-AMSTAR (Revised - a measurement tool for assessment to the methodological quality of systematic reviews) [Kung *et al.*, 2010] to assess the systematic reviews;
- CASP (Critical Appraisal Skills Programme)¹ to assess RCTs, cohort studies and case-control studies.

Taking into account the two assessors' results:

- an average score of 75 or more on the R-AMSTAR assessment tool was required for a systematic review to be considered of good methodological quality; a score of 50 to 74 corresponded to an average methodological quality; a score of 25 to 49 to a poor methodological quality; while a score below 25 indicated a very poor methodological quality;
- the assessment of an RCT required a positive response to all 6 of the CASP tool questions for RCTs to be considered of good methodological quality; 4 or 5 of the 6 questions to be considered of average methodological quality; 3 or 4 of the 6 questions was considered to be of poor methodological quality; and a positive answer to only 2 or less of these questions indicated a very poor methodological quality;
- the assessment of a cohort study required a positive response to questions 1 to 5a/b of the CASP tool for cohort studies to be considered of good methodological quality; to 4 of these questions to be considered of average methodological quality; to 2 or 3 of these questions was considered to be of poor methodological quality; and a positive answer to only 1 or less questions indicated a very poor methodological quality;
- the assessment of a case-control study required a positive response to questions 1 to 6b of the CASP tool for case-control studies to be considered of good methodological quality; to 5 or 6 of these questions to be considered of average methodological quality; to 3 or 4 of these questions was considered to be of poor methodological quality; and a positive answer to 2 or less of these questions indicated a very poor methodological quality.

Disagreements were resolved by consensus.

1.7 Data analysis and synthesis

Data extracted from selected documents were summarized in the form of an analytical narrative synthesis; the main results were presented in the form of tables. Data regarding the effectiveness of palivizumab were analyzed and presented according to result parameters. In addition, variations in the effects were examined for differences in averages or proportions, relative decrease (RD), relative risk (RR), odds ratio (OR) and hazard ratio (HR). When no measures of association were indicated, RR and 95% confidence interval (CI) were calculated.

¹ Critical Appraisal Skills Programme. CASP checklists [Website], available at: <http://www.casp-uk.net/#!/casp-tools-checklists/c18f8>

1.8 Peer validation

A preliminary report of the results was submitted to two external readers. Comments from these readers were analyzed by the project team and integrated into the final report.

2 RESULTS

2.1 Description of identified studies

The data search identified 726 studies, of which 26 were retained ('included'), namely:

- Seven systematic literature reviews [Homaira *et al.*, 2014; Robinson *et al.*, 2015; Wegzyn *et al.*, 2014; Andabaka *et al.*, 2013; Checchia *et al.*, 2011; Pons *et al.*, 2011; Morris *et al.*, 2009], of which four reviews included a meta-analysis [Andabaka *et al.*, 2013; Checchia *et al.*, 2011; Pons *et al.*, 2011; Morris *et al.*, 2009];
- Five RCTs [Tavsu *et al.*, 2014; Blanken *et al.*, 2013; Cohen *et al.*, 2005; Feltes *et al.*, 2003; IMpact-RSV, 1998];
- Forteen observational studies: 13 cohort studies [Banerji *et al.*, 2014; Yi *et al.*, 2014; Winterstein *et al.*, 2013b; Winterstein *et al.*, 2013a; Harris *et al.*, 2011; Giebels *et al.*, 2008; Grimaldi *et al.*, 2007; Simoes *et al.*, 2007; Mitchell *et al.*, 2006; Grimaldi *et al.*, 2004; Wegner *et al.*, 2004; Pedraz *et al.*, 2003; Singleton *et al.*, 2003] and one case-control study [Yoshihara *et al.*, 2013].

The data search did not identify any RCTs, cohort studies or case-control studies on the effectiveness of palivizumab prophylaxis compared to the administration of a placebo or to no prophylaxis in children who are immunosuppressed, affected by a metabolic disease, presenting a serious neuromuscular disorder affecting respiratory function, presenting an upper airway anomaly affecting respiratory function, from a healthy multiple birth whose twin is eligible to receive palivizumab. Appendix B of this document describes the study selection process in the form of a flow chart and presents the list of excluded studies and reasons for their exclusion.

2.1.1 Systematic literature reviews with meta-analysis

Among the four systematic literature reviews with meta-analysis that were identified, one review is of good methodological quality [Andabaka *et al.*, 2013], while the other three reviews are of average methodological quality [Checchia *et al.*, 2011; Pons *et al.*, 2011; Morris *et al.*, 2009]. Characteristics of these systematic reviews are presented in Appendix C of this document.

In the systematic literature review conducted by the Cochrane group [Andabaka *et al.*, 2013], the effectiveness of palivizumab prophylaxis in preventing RSV infection in children at high risk of contracting this type of infection was assessed. A total of three RCTs aimed to compare palivizumab with a placebo. Data on the approved doses of 15 mg/kg were included in the analyses. Extracted data pertained to a treatment of five injections per RSV season. All of the children were monitored for 150 days after the random allocation (30 days after administration of the last dose). All of the studies included in this systematic review were funded by pharmaceutical companies.

Authors of two systematic reviews with meta-analysis (SR-MA) [Pons *et al.*, 2011; Morris *et al.*, 2009] identified the same three RCTs as those identified by Andabaka and colleagues [2013]. Since the findings of the meta-analysis by Morris and colleagues [2009] and Andabaka and colleagues [2013] were identical, only the results of the latter, i.e. the most recent and of good methodological quality, have been considered in this report. The meta-analysis by Pons and colleagues [2011] included studies on different immunoprophylaxes. Consequently, it was not

retained because it did not meet inclusion criteria established for the purposes of this report.

Checchia and colleagues [2011] performed an SR-MA to assess the effect of palivizumab prophylaxis, compared to a placebo or to no prophylaxis, in children born at 35 weeks of gestation or less and children with CLD or congenital heart disease. A total of 11 studies were included: 3 RCTs and 7 inception or historical cohort studies. The three RCTs comparing the effectiveness of palivizumab to that of a placebo were the same as those identified in the previous systematic reviews [Andabaka *et al.*, 2013; Pons *et al.*, 2011; Morris *et al.*, 2009]. Of the seven observational studies selected, one study dealt with premature infants without CLD [Wegner *et al.*, 2004], five studies dealt with premature infants with or without CLD [Kusuda *et al.*, 2006; Mitchell *et al.*, 2006; Grimaldi *et al.*, 2004; Henckel *et al.*, 2004; Pedraz *et al.*, 2003] and one study dealt with children with bronchopulmonary dysplasia [Perez Perez *et al.*, 2004]. Although this systematic review was of average methodological quality, note that some of the observational studies included in the meta-analyses were of poor methodological quality.

2.1.2 Systematic literature reviews without meta-analysis

Of the three systematic literature reviews without meta-analysis that were identified, one is of good methodological quality [Robinson *et al.*, 2014] while the other two are of average methodological quality [Homaira *et al.*, 2014; Wegzyn *et al.*, 2014]. Characteristics of these systematic reviews are presented in Appendix C of this document.

In the systematic review by Wegzyn and colleagues [2014], the effectiveness of palivizumab prophylaxis on an RSV infection in children born at 35 weeks of gestation or less and children with bronchopulmonary dysplasia or a hemodynamically significant congenital heart disease was assessed. In this review, seven RCTs and eight prospective observational studies were selected. In the systematic review by Homaira and colleagues [2014], a total of 20 observational studies on the effectiveness of palivizumab in children at a high risk of RSV infection were included; targeted children were premature infants and those with any chronic congenital disease likely to increase the risk of aggravating such an infection. In the systematic review by Robinson and colleagues [2014], the effectiveness of palivizumab prophylaxis in children with cystic fibrosis was assessed. In this systematic review, only one RCT was retained. As no meta-analysis was performed in these two systematic reviews, the studies meeting the inclusion criteria established for the purposes of this report have been described individually, depending on the population studied, in Section 2.2 of this document.

2.1.3 Randomized clinical trials

Of the five identified RCTs, three are of good methodological quality [Cohen *et al.*, 2005; Feltes *et al.*, 2003; IMpact-RSV, 1998] and two are of average methodological quality [Tavsu *et al.*, 2014; Blanken *et al.*, 2013]; five RCTs aimed to compare the effectiveness of palivizumab with that of a placebo or no treatment in children:

- Born at 35 weeks of gestation or less or younger than 24 months, with bronchopulmonary dysplasia [IMpact-RSV, 1998];
- Born at less than 32 weeks of gestation and with no other significant medical risk factor than maturity [Tavsu *et al.*, 2014];
- Born at a gestational age from 33 to 35 weeks [Blanken *et al.*, 2013];
- Aged 24 months and less with hemodynamically severe congenital heart disease [Feltes *et al.*, 2003];

- With cystic fibrosis [Cohen *et al.*, 2005].

Characteristics of the five RCTs are presented in Appendix C of this document.

2.1.4 Observational Studies

Among the 14 identified observational studies, methodological quality varies from ‘good’ to ‘very poor’ and the assessment of three of these studies indicated the appearance of a conflict of interest with the pharmaceutical industry [Yoshihara *et al.*, 2013; Simoes *et al.*, 2007; Pedraz *et al.*, 2003]; characteristics of these studies are presented in Appendix C of this document.

In total, four inception cohort studies [Banerji *et al.*, 2014; Yi *et al.*, 2014; Yoshihara *et al.*, 2013; Simoes *et al.*, 2007], seven historical cohort studies [Winterstein *et al.*, 2013b; Winterstein *et al.*, 2013a; Giebels *et al.*, 2008; Mitchell *et al.*, 2006; Wegner *et al.*, 2004; Pedraz *et al.*, 2003; Singleton *et al.*, 2003] and three studies with inception cohorts compared to historical cohorts [Harris *et al.*, 2011; Grimaldi *et al.*, 2007; Grimaldi *et al.*, 2004] were identified. Most of the observational studies identified dealt with premature infants with or without CLD or bronchopulmonary dysplasia [Winterstein *et al.*, 2013a; Yoshihara *et al.*, 2013; Grimaldi *et al.*, 2007; Simoes *et al.*, 2007; Mitchell *et al.*, 2006; Grimaldi *et al.*, 2004; Wegner *et al.*, 2004; Pedraz *et al.*, 2003].

2.2 Effectiveness of palivizumab prophylaxis compared to administration of a placebo or to no prophylaxis

2.2.1 Mixed population

The search for information identified two SR-MA [Andabaka *et al.*, 2013; Checchia *et al.*, 2011], an RCT [IMPact-RSV, 1998] and two observational studies [Mitchell *et al.*, 2006. Pedraz *et al.*, 2003] combining various populations, including premature infants, children with bronchopulmonary dysplasia, CLD or congenital heart disease. Note that the combinations of populations can vary from one study to another.

2.2.1.1 Hospitalization due to RSV

The results of the meta-analysis conducted by Andabaka and colleagues [2013] indicate that among premature infants or those with CLD, bronchopulmonary dysplasia or heart disease, those who received palivizumab showed a statistically significant reduction in the risk of RSV-associated hospitalizations (three RCTs; RR = 0.49; 95% CI: 0.37 to 0.64) compared with those who received a placebo. In the meta-analysis conducted by Checchia and colleagues [2011] on RCTs and observational studies, a statistically significant reduction in the risk of RSV-associated hospitalizations was also observed in premature infants or those with CLD who received palivizumab prophylaxis, compared to those who received a placebo or no prophylaxis (eight studies; OR = 0.35; 95% CI: 0.25 to 0.47, $p < 0.001$) (see Table 2).

In the RCT conducted by the IMpact-RSV Study Group [1998], a statistically significant reduction (RR = 0.45; 95% CI: 31 to 66) in the risk of RSV-associated hospitalizations was observed in premature infants or those aged 24 months or less with bronchopulmonary dysplasia who received palivizumab, compared to those who received a placebo (see Table 2).

Results of the two identified historical cohort studies [Mitchell *et al.*, 2006; Pedraz *et al.*, 2003] generally agree with those of the meta-analyses [Andabaka *et al.*, 2013; Checchia *et al.*, 2011] and of the RCT [IMpact-RSV, 1998]. In Alberta, Mitchell and colleagues [2006] assessed the risk of RSV-associated hospitalizations in children at high risk², before (1995-1998) and after (1999-2002) the entry into force of the palivizumab immunoprophylaxis program. A statistically significant reduction of 60% in RSV-associated hospitalizations was observed in children who received palivizumab prophylaxis, compared to those who did not receive the prophylaxis (OR = 0.40; 95% CI: 0.21 to 0.75). In a historical cohort study in Spain [Pedraz *et al.*, 2003] among children born at 32 weeks of gestation or less and with or without CLD, the risk of RSV-associated hospitalizations among those who had received palivizumab during 2000-2002 seasons was statistically lower than that of children who did not receive treatment (1998-2000), for children born at 28 weeks of gestation or less (RR = 0.26; IC 95%: 0.19 to 0.35) and for those born at a gestational age of 29 to 32 weeks (RR = 0.54; 95% CI: 0.39 to 0.77) (see Table 2).

2.2.1.2 Length of hospital stay due to RSV

In the RCT conducted by the IMpact-RSV Study Group [1998], in premature infants or those aged 24 months or less with bronchopulmonary dysplasia who received palivizumab, the total number of days of RSV-associated hospitalizations per 100 children was significantly lower than that of children who received a placebo: 36.4 and 62.6 days of hospitalization, respectively ($p < 0.001$). In the historical cohort study conducted by Pedraz and colleagues [2003], the median duration of hospitalization was statistically lower in children who received palivizumab prophylaxis (six days) than in children who received no treatment (eight days) ($p < 0.01$).

2.2.1.3 Stay in an intensive care unit due to RSV

Results of the meta-analysis conducted by Andabaka and colleagues [2013] indicate a statistically significant 50% reduction in the risk of a stay in an ICU in premature infants, with or without CLD, who received palivizumab compared to those who received a placebo (two RCTs; RR = 0.50; 95% CI: 0.30 to 0.81) (see Table 2). RCT results from the IMpact-RSV Study Group [1998] also showed a statistically significant reduction in the risk of a stay in an ICU in premature infants or those aged 24 months or less with bronchopulmonary dysplasia who received palivizumab, compared to those who received a placebo (two RCTs; RR = 0.43; 95% CI: 0.21 to 0.90, $p = 0.026$). However, in the historical cohort study conducted by Pedraz and colleagues [2003], no statistically significant difference was reported between the risk of a stay in an ICU in children who received palivizumab prophylaxis compared with children who received no prophylaxis (RR = 0.62; 95% CI: 0.31 to 1.22) (see Table 2).

2.2.1.4 Length of stay in intensive care due to RSV

In the RCT conducted by the IMpact-RSV Study Group [1998], in premature infants or those aged 24 months or less with bronchopulmonary dysplasia who received palivizumab, the total number

² High-risk children are children born at less than 33 weeks of gestation or born at a gestational age of 33-35 weeks who received a diagnosis of infantile chronic lung disease, or children born at a gestational age of 33-35 weeks who received oxygen therapy at home and who were born six months before the start of the RSV season.

of days in an ICU due to RSV was significantly higher than that of children who received a placebo, 13.3 and 12.7 days respectively, for 100 children ($p = 0.023$) (see Table 2).

2.2.1.5 Mortality

The results of the meta-analysis conducted by Andabaka and colleagues [2013] indicate a reduced risk of all-cause mortality in premature infants or those aged 24 months or less with CLD or heart disease who received palivizumab, compared to those who received a placebo (three RCTs; RR = 0.69; 95% CI: 0.42 to 1.15). The results of the meta-analysis conducted by Checchia and colleagues [2011], involving RCTs and observational studies, also reported a statistically significant reduction in all-cause mortality among all premature infants, with an OR of 0.30 (four studies; 95% CI: 0.17 to 0.55, $p < 0.001$). According to the RCT results from the IMpact-RSV Study Group [1998], a non-statistically significant reduction in all-cause mortality was observed in premature infants or those aged 24 months or less with bronchopulmonary dysplasia who received palivizumab, compared to children who received a placebo (RR = 0.40; 95% CI: 0.11 to 1.48). In the study conducted by Pedraz and colleagues [2003], rates of mortality due to RSV infection in children who received palivizumab prophylaxis and in children who received no treatment were 0% and 0.06%, respectively (see Table 2).

2.2.1.6 Use of mechanical ventilation due to RSV

According to meta-analysis results from Andabaka and colleagues [2013], a non-statistically significant increase in the use of mechanical ventilation due to RSV was observed in children with or without CLD who received palivizumab prophylaxis, compared to those who received a placebo (two studies; RR = 1.1; 95% CI: 0.20 to 6.09). The RCT conducted by the IMpact-RSV Study Group [1998] also reported a non-statistically significant increase in the use of mechanical ventilation in cases of RSV infection in premature infants or those aged 24 months or less with bronchopulmonary dysplasia who received palivizumab, compared to children who received a placebo (RR = 3.49; 95% CI: 0.43 to 28.31, $p = 0.280$). Pedraz and colleagues [2003] also reported a non-statistically significant increase in the use of mechanical ventilation in premature infants with or without CLD who received palivizumab prophylaxis, compared to those who received no prophylaxis (RR = 1.40; 95% CI: 0.61 to 3.22) (see Table 2).

2.2.1.7 Length of mechanical ventilation due to RSV infection

According to RCT results from the IMpact-RSV Study Group [1998], the total number of days of mechanical ventilation due to RSV infection in premature infants or those aged 24 months or less with bronchopulmonary dysplasia was higher for children who received palivizumab prophylaxis than for those who received a placebo: 8.4 and 1.7 days respectively, for 100 children. However, this difference was not statistically significant ($p = 0.210$) (see Table 2).

2.2.1.8 Length of oxygen therapy due to RSV infection

In the RCT conducted by the IMpact-RSV Study Group [1998], the total number of days of oxygen therapy due to RSV infection in premature infants or those aged 24 months or less with bronchopulmonary dysplasia was significantly lower for children who received palivizumab prophylaxis than for those who received a placebo: 30.3 and 50.6 days respectively, for 100 children ($p < 0.001$) (see Table 2).

Table 2 Effectiveness of palivizumab prophylaxis in premature infants with infantile chronic lung disease or heart disease, compared to the administration of a placebo or no prophylaxis

AUTHORS, YEAR	STUDY DESIGN (GESTATIONAL AGE)	PALIVIZUMAB	COMPARISONS		RELATIVE RISK (RR) ODDS RATIO (OR) (95% CI) VALUE OF P	STUDY QUALITY
			PLACEBO	NO PROPHYLAXIS		
Hospitalizations due to RSV (number of persons) on the total number of participants						
Andabaka <i>et al.</i> , 2013	SR-MA	82/1,663 (4.9%)	118/1,168 (10.1%)	n/a	RR = 0.49 (0.37 to 0.64) (three studies)*	Good
Checchia <i>et al.</i> , 2011	SR-MA	160/3,904 (4.1%)	349/3,351 (10.4%)		OR = 0.35 (0.25 to 0.47) p < 0.001 (eight studies) [‡]	Average
IMpact-RSV, 1998	RCT	48/1,002 (4.8%)	53/500 (10.6%)	n/a	RR = 0.45 (0.31 to 0.66)	Good
Mitchell <i>et al.</i> , 2006	Historical cohort	15/496 (3.0%)	n/a	30/411 (7.3%)	OR = 0.40 (0.21 to 0.75) p = 0.003	Poor
Pedraz <i>et al.</i> , 2003	Historical cohort (≤ 28 weeks)	76/1,919 (4.0%)	n/a	210/1,583 (13.3%)	OR = 0.26 (0.19 to 0.35) p = 0.0001	Very poor
	(29 to 32 weeks)	40/739 (5.4%)	n/a	129/1,297 (9.9%)	RR = 0.54 (0.39 to 0.77) p = 0.0001	
Length of hospital stay due to RSV (total number of days/100 children)						
IMpact-RSV, 1998	RCT	36.4	62.6	n/a	p < 0.001	Good
Pedraz <i>et al.</i> , 2003 ^u	Historical cohort	6 (median) (interquartile range: 4 to 9)	N/A	8 (median) (interquartile range 5 to 11)	p < 0.01	Very poor

Stay in an intensive care unit due to RSV (number of persons) on the total number of participants						
Andabaka <i>et al.</i> , 2013	SR-MA	26/1,641 (1.6%)	39/1,148 (3.4%)	n/a	RR = 0.50 (0.30 to 0.81) (two studies) [†]	Good
IMpact-RSV, 1998	RCT	13/1,002 (1.3%)	15/500 (3.0%)	n/a	RR = 0.43 (0.21 to 0.90) p = 0.026	Good
Pedraz <i>et al.</i> , 2003 ^u	Historical cohort	9/71 (13%)	n/a	33/161 (20%)	RR = 0.62 (0.31 to 1.22)	Very poor
Length of stay in intensive care due to RSV (total number of days/100 children)						
IMpact-RSV, 1998	RCT	13.3	12.7	n/a	p = 0.023	Good
All-cause mortality (number) on the total number of participants						
Andabaka <i>et al.</i> , 2013	SR-MA	25/1,663 (1.5%)	33/1,168 (2.8%)	n/a	RR = 0.69 (0.42 to 1.15) (three studies)*	Good
Checchia <i>et al.</i> , 2011	SR-MA	12/6,380 (0.19%)	33/6,182 (0.53%)		OR = 0.30 (0.17 to 0.55) p < 0.001 (four studies)	Average
IMpact-RSV, 1998	RCT	4/1,002 (0.40%)	5/500 (1.0%)	n/a	RR = 0.40 (0.11 to 1.48)	Good
Pedraz <i>et al.</i> , 2003 ^ε	Historical cohort	0/1,919 (0%)	n/a	1/1,583 (0.06%)	Not estimable	Very poor
Use of mechanical ventilation due to RSV (number of persons) on the total number of participants						
Andabaka <i>et al.</i> , 2013	SR-MA	15/1,641 (0.9%)	15/1,148 (1.3%)	n/a	RR = 1.1 (0.2 to 6.09) (two studies) [†]	Good
IMpact-RSV, 1998	RCT	7/1,002 (0.7%)	1/500 (0.2%)	n/a	RR = 3.49 (0.43 to 28.31) p = 0.280	Good
Pedraz <i>et al.</i> , 2003 ^u	Historical cohort	8/71 (11%)	n/a	13/161 (8%)	RR = 1.40 (0.61 to 3.22)	Very poor

Length of mechanical ventilation due to infection with RSV (total number of days/100 children)						
IMpact-RSV, 1998	RCT	8.4	1.7	n/a	p = 0.210	Good
Length of oxygen therapy due to RSV (total number of days/100 children)						
IMpact-RSV, 1998	RCT	30.3	50.6	n/a	p < 0.001	Good

RCT: randomized clinical trial; CI: confidence interval; OR: odds ratio; SR-MA: systematic review with meta-analysis; RR: relative risk; RSV: respiratory syncytial virus; n/a: not applicable

* The three studies included in the meta-analysis by Andabaka and colleagues [2013] were those by Feltes *et al.*, 2003; IMpact-RSV, 1998; Subramanian *et al.*, 1998.

‡ The eight studies included in the meta-analysis by Checchia and colleagues [2011] were those by Mitchell *et al.*, 2006; Grimaldi *et al.*, 2004; Henckel *et al.*, 2004; Perez Perez *et al.*, 2004; Wegner *et al.*, 2004; Pedraz *et al.*, 2003; IMpact-RSV, 1998; Subramanian *et al.*, 1998.

† The two studies included in the meta-analysis by Andabaka and colleagues [2013] were those by Feltes *et al.*, 2003 and IMpact-RSV, 1998.

‡ The median number of days of hospitalization, rates of stays in an intensive care unit and rates of patients who received respiratory assistance (mechanical ventilation) were calculated.

£ Mortality due to RSV

2.2.2 Premature infants without infantile chronic lung disease

Regarding the assessment of the effectiveness of palivizumab in premature infants without CLD, one systematic literature review on RCTs and observational studies with meta-analysis [Checchia *et al.*, 2011], three RCTs [Tavsu *et al.*, 2014; Blanken *et al.*, 2013; IMpact-RSV, 1998] and six observational studies [Winterstein *et al.*, 2013a; Yoshihara *et al.*, 2013; Grimaldi *et al.*, 2007; Simoes *et al.*, 2007; Mitchell *et al.*, 2006; Wegner *et al.*, 2004] were identified. Characteristics of these studies are described in Appendix C of this document.

2.2.2.1 Hospitalization due to RSV

Results of the meta-analysis [Checchia *et al.*, 2011] and three RCTs [Tavsu *et al.*, 2014; Blanken *et al.*, 2013; IMpact-RSV, 1998] show a statistically significant reduction in the risk of RSV-associated hospitalizations in premature infants without CLD who received palivizumab prophylaxis, compared to those who received a placebo or no prophylaxis (see Table 3).

Specifically, results of the meta-analysis conducted by Checchia and colleagues [2011] indicate a statistically significant reduction in the risk of RSV-associated hospitalizations, for children without CLD and who received palivizumab, born at 32 weeks of gestation or less (three studies; OR = 0.28; 95% CI: 0.21 to 0.36, $p < 0.001$) as well as children born at a gestational age of 32 to 35 weeks (two studies; OR = 0.26; 95% CI: 0.11 to 0.62, $p < 0.001$), compared to children who received a placebo or no prophylaxis (see Table 3).

RCT results from Tavsu and colleagues [2014] show a statistically significant reduction in the risk of RSV-associated hospitalizations in children born at 32 weeks of gestation or less with no medical risk factor other than prematurity who were aged six months or less at the start of the RSV season and had no CLD, heart disease or other health problems who received palivizumab prophylaxis, compared to those who did not receive prophylaxis (OR = 0.26; 95% CI: 0.10 to 0.68, $p = 0.001$). The results of another RCT [Blanken *et al.*, 2013] indicate a statistically significant 82% reduction ($p < 0.01$) in the number of RSV-associated hospitalizations among healthy children born at a gestational age of 33 to 35 weeks and six months of age or less at the start of the RSV season who received palivizumab, compared to those who received a placebo. Similar results were reported in the RCT conducted by the IMpact-RSV Study Group [1998]: a statistically significant reduction in the RR of RSV-associated hospitalizations by 78% ($p \leq 0.001$), 47% ($p = 0.003$) and 80% ($p = 0.002$), respectively, in children born at 35 weeks of gestation or less, children born at 32 weeks of gestation or less and children born at a gestational age of 32-35 weeks who were aged six months or less at the start of the RSV season who have no CLD and who received palivizumab prophylaxis, compared to those who received a placebo (see Table 3).

In a cohort study assessing the effectiveness of an immunoprophylaxis program in France [Grimaldi *et al.*, 2007], a statistically significant reduction in the risk of RSV-associated re-hospitalizations was observed when palivizumab was administered to hospitalized children, born at 30 weeks of gestation or less and aged six months or less at the start of the RSV season and with no bronchopulmonary dysplasia (2002 to 2004), compared with no treatment (1999 to 2002) (1.5% against 13.6%, $p < 0.0001$). In a historical cohort study in the United States [Winterstein *et al.*, 2013a], a statistically significant reduction in the risk of RSV-associated hospitalizations in children born at a gestational age of 32-34 weeks, without CLD, who received palivizumab prophylaxis compared to those who received no treatment, was observed in Texas (OR = 0.45; 95% CI: 0.26 to 0.78, $p < 0.005$), but not in Florida (OR = 0.81; 95% CI: 0.42 to 1.58, p

< 0.54). In a historical cohort study in Alberta, no statistically significant difference was observed between children who received palivizumab and those who received no treatment (OR = 0.79; 95% CI: 0.47 to 1.33, $p = 0.389$). Wegner and colleagues [2004] reported a non-statistically significant reduction in RSV-associated hospitalizations in children who received palivizumab, compared to those who received no treatment (OR = 0.27, $p = 0.058$).

2.2.2.2 Mortality

In the study by Checchia and colleagues [2011], results of the meta-analysis show a statistically significant 75% reduction in all-cause mortality risk among children born at 32 weeks of gestation or less who received palivizumab prophylaxis, compared to those who received a placebo or no prophylaxis (three studies; OR = 0.25; 95% CI: 0.13 to 0.49, $p < 0.001$). However, in premature infants born at a gestational age of 32-35 weeks, no statistically significant reduction was reported between the two groups (three studies; OR = 0.22; 95% CI: 0.03 to 1.89, $p = 0.085$) (see Table 3).

2.2.2.3 Wheezing in the first year of life

In an RCT conducted by Blanken and colleagues [2013], involving healthy children born at a gestational age of 33-35 weeks, a statistically significant reduction in the risk of wheezing in the first year of life was observed following administration of palivizumab, compared to the administration of a placebo (RR = 0.66; 95% CI: 0.51 to 0.84). In an inception cohort study in Japan [Yoshihara *et al.*, 2013], the risk of wheezing in the first year of life was significantly reduced in children who received palivizumab, compared to those who received no treatment (RR = 0.34; 95% CI: 0.19 to 0.60). In another international multicentre inception cohort study, a statistically significant reduction in the risk of wheezing in the first year was also reported (RR = 0.51; 95% CI: 0.33 to 0.38) (see Table 3).

Table 3 Effectiveness of palivizumab prophylaxis in premature infants without chronic lung disease, compared to the administration of a placebo or to no prophylaxis

AUTHORS, YEAR	STUDY DESIGN(GESTATION AL AGE)	PALIVIZUMAB	COMPARISONS		ODDS RATIO (OR) RELATIVE RISK (RR) RELATIVE DECREASE (RD) (95% CI) VALUE OF P	STUDY QUALITY
			PLACEBO	NO PROPHYLAXIS		
Hospitalizations due to RSV (number of persons) on the total number of participants						
Checchia <i>et al.</i> , 2011	SR-MA (≤ 32 weeks)	83/2,275 (3.7%)	240/2,274 (10.6%)		OR = 0.28 (0.21 to 0.36) p < 0.001 (three studies)*	Average
	(32 to 35 weeks)	9/410 (2.2%)	23/292 (7.9%)		OR = 0.26 (0.11 to 0.62) p = 0.002 (2 studies)**	
Tavsu <i>et al.</i> , 2014	RCT (≤ 32 weeks)	0/39 (0%)	n/a	10/41 (24.4%)	OR = 0.26 (0.10 to 0.68) p = 0.001	Average
Blanken <i>et al.</i> , 2013	RCT (33 to 35 weeks)	2/214 (0.9%)	11/215 (5.1%)	n/a	RR = 0.18 (0.04 to 0.81)	Average
IMpact-RSV, 1998	RCT (≤ 35 weeks)	9/506 (1.8%)	19/234 (8.1%)	n/a	RR = 0.22 (0.10 to 0.48)	Good
	(≤ 32 weeks)	n/a	n/a	n/a	RD = 47%, p = 0.003	
	(32 to 35 weeks)	5/281 (1.8%)	8/124 (6.5%)	n/a	RR = 0.28 (0.09 to 0.83)	
Winterstein <i>et al.</i> , 2013a	Historical cohort (32 to 34 weeks)	n/a / 461 (Florida)	n/a	n/a / 1,853 (Florida)	OR = 0.81 (0.42 to 1.58) p = 0.54	Average
		n/a / 671 (Texas)		n/a / 3,015 (Texas)	OR= 0.45 (0.26 to 0.78) p = 0.005	

Grimaldi <i>et al.</i>, 2007	Inception cohort (compared to a historical cohort) (≤ 30 weeks)	1/70 (1.5%)	n/a	16/118 (13.6%)	RR = 0.11 (0.01 to 0.78) p < 0.0001	Poor
Mitchell <i>et al.</i>, 2006	Historical cohort (33 to 35 weeks)	28/842 (3.3%) (Calgary)	n/a	24/907 (2.7%) (Calgary)	OR = 0.79 (0.47 to 1.33) p = 0.389	Poor
Wegner <i>et al.</i>, 2004	Historical cohort (32 to 35 weeks)	5/185 (2.7%)	n/a	12/182 (6.6%)	RC = 0.27 (n/r) p = 0.058 [€]	Good
All-cause mortality (number) on the total number of participants						
Checchia <i>et al.</i>, 2011	SR-MA (≤ 32 weeks)	8/3,435 (0.2%)	28/2,827 (0.99%)		OR = 0.25 (0.13 to 0.49) p < 0.001 (3 studies) [¥]	Average
	(32 to 35 weeks)	1/1,087 (0.09%)	3/2,359 (0.13%)		OR = 0.22 (0.03 to 1.89) p = 0.085 (three studies) ⁺	
Wheezing in the first year of life (number of persons) on the total number of participants						
Blanken <i>et al.</i>, 2013	RCT (33 to 35 weeks)	66/214 (30.8%)	101/215 (47.0%)	n/a	RR = 0.66 (0.51 to 0.84)	Good
Yoshihara <i>et al.</i>, 2013	Inception cohort (33 to 35 weeks)	22/345 (6.4%)	n/a	18/95 (18.9%)	RR = 0.34 (0.19 to 0.60) p < 0.001	Poor
Simoes <i>et al.</i>, 2007	Inception cohort (≤ 35 weeks)	25/191 (13%)	59/230 (26%)	n/a	RR = 0.51 (0.33 to 0.78) p = 0.001	Average

RCT: randomized clinical trial; CI: confidence interval; n/r: not reported; n/a: not applicable; OR: odds ratio; RR: relative risk; RSV: respiratory syncytial virus

*The three studies included in the meta-analysis by Checchia and colleagues [2011] are those by Henckel *et al.*, 2004; Pedraz *et al.*, 2003; IMpact-RSV, 1998.

** The two studies included in the meta-analysis by Checchia and colleagues [2011] are those by Wegner *et al.*, 2004 and IMpact-RSV, 1998.

[€] Statistical model adjusted for potentially confounding variables

[¥] The three studies included in the meta-analysis by Checchia and colleagues [2011] were those by Wegner *et al.*, 2004; Pedraz *et al.*, 2003; IMpact-RSV, 1998.

⁺ The three studies included in the meta-analysis by Checchia and colleagues [2011] were those by Kusuda *et al.*, 2006; Wegner *et al.*, 2004; IMpact-RSV, 1998.

2.2.3 Premature infants with infantile chronic lung disease or bronchopulmonary dysplasia

An RCT assessing the effectiveness of palivizumab in children aged 24 months or less with bronchopulmonary dysplasia was identified [IMpact-RSV, 1998], as well as two observational studies [Grimaldi *et al.*, 2004; Pedraz *et al.*, 2003] assessing the effectiveness of palivizumab in premature infants with CLD or bronchopulmonary dysplasia. Characteristics of these studies are presented in Appendix C of this document.

2.2.3.1 Hospitalization due to RSV

In the RCT conducted by the IMpact-RSV Study Group [1998], a statistically significant reduction in the risk of RSV-associated hospitalizations was observed in children aged 24 months or less with bronchopulmonary dysplasia who received palivizumab prophylaxis, compared to those who received a placebo (RR = 0.61; 95% CI: 0.40 to 0.95).

In a historical cohort study in Spain [Pedraz *et al.*, 2003], a statistically significant reduction in the risk of RSV-associated hospitalizations was observed in children born at 32 weeks of gestation or less who were aged six months or less at the start of the RSV season who had CLD and who received palivizumab during RSV seasons, from 2000 to 2002, compared to those who did not receive palivizumab, from 1998 to 2000 (RR = 0.28; 95% CI: 0.14 to 0.58). Similar results were reported in another study in France [Grimaldi *et al.*, 2004]: a statistically significant reduction in the risk of RSV-associated hospitalizations in children with bronchopulmonary dysplasia who received palivizumab during the RSV seasons from 2000 to 2002, who were born at 32 weeks of gestation or less and who were aged six months or less at the start of the RSV season, compared to those who did not receive palivizumab, from 1999-2000 (RR = 0.15; 95% CI: 0.05 to 0.49) (see Table 4).

Table 4 Effectiveness of palivizumab in premature infants with infantile chronic lung disease or bronchopulmonary dysplasia, compared to no prophylaxis

AUTHORS, YEAR	STUDY DESIGN (GESTATIONAL AGE)	PALIVIZUMAB	NO PROPHYLAXIS	RELATIVE RISK 95% CI VALUE OF P	STUDY QUALITY
RSV-associated hospitalizations (number of persons) on the total number of participants					
IMpact-RSV, 1998	RCT	39/496 (7.9%)	34/266 (12.8%)	0.61 (0.40 to 0.95)	Good
Grimaldi <i>et al.</i>, 2004	Inception cohort (compared to a historical cohort) (≤ 32 weeks)	3/43 (6.98%)	12/26 (46.2%)	0.15 (0.05 to 0.49) p < 0.01	Poor
Pedraz <i>et al.</i>, 2003	Historical cohort (≤ 32 weeks)	12/217 (5.5%)	14/71 (19.7%)	0.28 (0.14 to 0.58) p < 0.007	Very poor

RCT: randomized clinical trial; CI: confidence interval; RSV: respiratory syncytial virus

2.2.4 Children with cystic fibrosis

A systematic literature review [Robinson *et al.*, 2014.], an RCT [Cohen *et al.*, 2005] and two observational studies [Winterstein *et al.*, 2013b; Giebels *et al.*, 2008] assessing the effectiveness of palivizumab compared with that of a placebo or no prophylaxis in children with cystic fibrosis were identified. In the systematic review, one RCT was selected, that by Cohen and colleagues [2005]. Consequently, only results of the primary study were reported. Characteristics of these studies are presented in Appendix C of this document.

2.2.4.1 Hospitalization due to RSV

In the RCT conducted by Cohen and colleagues [2005], in children with cystic fibrosis aged 24 months or less, no statistically significant difference concerning RSV-associated hospitalizations was observed in children who received palivizumab prophylaxis compared to those who received a placebo (RR = 1.02; 95% CI: 0.06 to 16.09). A historical cohort study [Winterstein *et al.*, 2013b] conducted on children under 24 months of age with cystic fibrosis reported a statistically non-significant beneficial effect of palivizumab on reducing the number of RSV-associated hospitalizations, compared with no prophylaxis (RR = 0.57; 95% CI: 0.20 to 1.60). Another historical cohort study, conducted in Canada [Giebels *et al.*, 2008], also reported a statistically non-significant reduction in the risk of RSV-associated hospitalizations in children with cystic fibrosis who received palivizumab prophylaxis, compared to children who received no treatment (RR = 0.49; 95% CI: 0.14 to 1.75) (see Table 5).

2.2.4.2 Mortality

In the study conducted by Cohen and colleagues [2005], no cases of all-cause mortality were reported, regardless of the group (see Table 5).

2.2.4.3 Use of oxygen therapy due to RSV

In the study conducted by Cohen and colleagues [2005], no statistically significant difference in the use of oxygen therapy was observed in children with cystic fibrosis under 24 months of age who received palivizumab prophylaxis, compared to those who received placebo (RR = 1.02; 95% CI: 0.06 to 16.09) (see Table 5).

Table 5 Effectiveness of palivizumab prophylaxis in children with cystic fibrosis, compared to the administration of a placebo or to no prophylaxis

AUTHORS, YEAR	STUDY DESIGN	PALIVIZUMAB	COMPARISONS		RELATIVE RISK (RR) ODDS RATIO (OR) HAZARD RATIO (HR) (95% CI)	STUDY QUALITY
			PLACEBO	NO PROPHYLAXIS		
Hospitalizations due to RSV (number of persons) on the total number of participants						
Cohen <i>et al.</i> , 2005	RCT	1/92 (1.09%)	1/94 (1.06%)	n/a	RR = 1.02 (0.06 to 16.09)	Not assessed*
Winterstein <i>et al.</i> , 2013b	Historical cohort	n/a / 575	n/a	n/a / 2,300	HR = 0.57 (0.20 to 1.60)**	Average
Giebels <i>et al.</i> , 2008	Historical cohort	3/35 (8.6%)	n/a	7/40 (17.5%)	RR = 0.49 (0.14 to 1.75)	Poor
Length of hospital stay due to RSV (median number of days)						
Giebels <i>et al.</i> , 2008	11 (interquartile range: 3 to 14)	n/a	13 (interquartile range: 2 to 14)	n/a	OR = 0.46 (0.16 to 1.31)	Poor
All-cause mortality (number) on the total number of participants						
Cohen <i>et al.</i> , 2005	RCT	0/92 (0%)	0/94 (0%)	n/a	Not estimable	Not assessed*
Use of oxygen therapy due to RSV (number of persons) on the total number of participants						
Cohen <i>et al.</i> , 2005	RCT	1/92 (0.01%)	0/94 (0%)	n/a	RR = 3.06 (0.13 to 74.27)	Not assessed*

RCT: randomized clinical trial; CI: confidence interval; n/a: not applicable; RSV: respiratory syncytial virus

* The study by Cohen and colleagues [2005] was not published in the form of a complete article.

** Statistical model adjusted for potentially confounding variables

2.2.5 Children with hemodynamically significant congenital heart disease

An SR-MA [Checchia *et al.*, 2011], an RCT [Feldes *et al.*, 2003] and a historical cohort study [Harris *et al.*, 2011] on the effectiveness of palivizumab compared to that of a placebo or no prophylaxis in children with hemodynamically significant congenital heart disease were identified. The meta-analysis focused on a single study, that of Feldes and colleagues [2003]. Consequently, only results of the primary study were reported. Characteristics of these studies are provided in Appendix C of this document.

2.2.5.1 Hospitalization due to RSV

Results of the RCT conducted by Feldes and colleagues [2003] indicate a statistically significant 45% reduction in hospitalizations ($p = 0.003$) in children aged less than 24 months with hemodynamically significant congenital heart disease that was not operated upon or only partially corrected and who had received palivizumab, compared to those who received a placebo. In addition, a statistically significant 58% reduction of the risk of hospitalization was observed in children with acyanotic heart disease who received palivizumab prophylaxis, compared to those who received a placebo ($p = 0.003$). Finally, a statistically non-significant 29% reduction in the number of hospitalizations was observed in children with cyanotic heart disease who received palivizumab prophylaxis, compared to those who received a placebo ($p = 0.285$).

A statistically non-significant reduction in the risk of RSV-associated hospitalizations was observed in children who received palivizumab during the immunoprophylaxis program from 2003 to 2007, compared with those who met the eligibility criteria to receive palivizumab before the start of the prophylaxis program, from 1998 to 2003 [Harris *et al.*, 2011] (see Table 6).

2.2.5.2 Length of hospital stay due to RSV

In the study conducted by Feldes and colleagues [2003], a statistically significant 56% reduction ($p = 0.003$) in the number of total days of RSV-associated hospitalizations per 100 children was observed in children with hemodynamically significant congenital heart disease who received palivizumab, compared to those who received a placebo (see Table 6).

2.2.5.3 Stays in intensive care due to RSV

In the study conducted by Feldes and colleagues [2003], a statistically non-significant 46% reduction ($p = 0.094$) in RSV-associated hospitalizations in an ICU was observed in children with hemodynamically significant congenital heart disease who received palivizumab prophylaxis, compared to those who received a placebo. In the study conducted by Harris and colleagues [2011], an 86% reduction in the number of RSV-associated hospitalizations in an ICU was observed in children who received palivizumab, from 2003 to 2007, compared to children who met the eligibility criteria for the palivizumab program but who did not receive prophylaxis, from 1998 to 2003. No statistical analysis was performed on these results (see Table 6).

2.2.5.4 Length of stay in intensive care due to RSV

In the study conducted by Feldes and colleagues [2003], a statistically non-significant 78% reduction in the total number of days of RSV-associated hospitalizations in an ICU was observed in children with hemodynamically significant congenital heart disease who received palivizumab

prophylaxis, compared to those who received a placebo ($p = 0.80$). In the study conducted by Harris and colleagues [2011], an 83% reduction in the average number of days of RSV-associated hospitalizations in an ICU was observed in children who received palivizumab, from 2003 to 2007, compared to children who meet the eligibility criteria for the palivizumab program but who did not receive prophylaxis, from 1998 to 2003. No statistical analysis was performed on these results (see Table 6).

2.2.5.5 Mortality

A statistically non-significant reduction in all-cause mortality was observed in children with hemodynamically significant congenital heart disease who received palivizumab prophylaxis, compared to those who received a placebo in the study conducted by Feltes and colleagues [2003]. In the study conducted by Harris and colleagues [2011], no case of all-cause mortality was reported in children who received palivizumab prophylaxis, while one death occurred in the group of children who did not receive it (see Table 6).

2.2.5.6 Use of mechanical ventilation due to RSV

A non-statistically significant 41% reduction in the use of mechanical ventilation due to RSV was observed in children with congenital heart disease with hemodynamically significant consequences who received palivizumab prophylaxis, compared to those who received a placebo [Feltes *et al.*, 2003] (see Table 6).

2.2.5.7 Length of oxygen therapy due to RSV

In the study conducted by Feltes and colleagues [2003], a statistically significant 73% reduction ($p = 0.014$) in the average number of days of oxygen therapy due to RSV was observed in children with hemodynamically significant congenital heart disease who received palivizumab, compared to those who received a placebo (see Table 6).

Table 6 Effectiveness of palivizumab prophylaxis in children with hemodynamically significant congenital heart disease, compared to the administration of a placebo or to no prophylaxis

AUTHORS, YEAR	STUDY DESIGN	PALIVIZUMAB	COMPARISONS		RELATIVE RISK (RR) RELATIVE DECREASE (RD) (95% CI) VALUE OF P	STUDY QUALITY
			PLACEBO	NO PROPHYLAXIS		
Hospitalizations due to RSV (number of persons) on the total number of participants						
Feltes <i>et al.</i> , 2003	RCT	34/639 (5.3%)	63/648 (9.7%)	n/a	RD = 45%, p = 0.003	Good
	Acyanotic heart disease	n/a / 300 (5.0%)	n/a / 305 (11.8%)	n/a	RD = 58%, p = 0.003	
	Cyanotic heart disease	n/a / 339 (5.6%)	n/a / 343 (7.9%)	n/a	RD = 29%, p = 0.285	
Harris <i>et al.</i> , 2011	Inception cohort	5/292 (1.7%)	n/a	12/412 (2.9%)	RR = 0.58 (0.21 to 1.65)	Poor
Length of hospital stay due to RSV (total number of days/100 children)						
Feltes <i>et al.</i> , 2003	RCT	57.4	129	n/a	RD = 56%, p = 0.003	Good
Stays in an intensive care unit due to RSV (number of persons) on the total number of participants						
Feltes <i>et al.</i> , 2003	RCT	13/639 (2.0%)	24/648 (3.7%)	n/a	RD = 46% P = 0.094	Good
Harris <i>et al.</i> , 2011	Inception cohort (compared to a historical cohort)	1/292 (0.3%)	n/a	7/412 (1.7%)	RD = 86% p = (n/r)	Poor
Length of stay in intensive care due to RSV (total number of days/100 children)						
Feltes <i>et al.</i> , 2003	RCT	15.9	71.2	n/a	RD = 78%, p = 0.80	Good
Harris <i>et al.</i> , 2011	Inception cohort (compared to a historical cohort)	11.6 (n/a)	n/a	69.7 (n/a)	RD = 83%, p = (n/r)	Poor

All-cause mortality (number) on the number of participants						
Feltes <i>et al.</i>, 2003	RCT	21/639 (3.3%)	27/648 (4.2%)	n/a	RR = 0.79 (0.45 to 1.38)	Good
Harris <i>et al.</i>, 2011	Inception cohort (compared to a historical cohort)	0/292	n/a	1/412 (0.24%)	Not estimable	
Use of mechanical ventilation due to RSV (number of persons) on the total number of participants						
Feltes <i>et al.</i>, 2003	RCT	8/639 (1.3%)	14/648 (2.2%)	n/a	RD = 41%, p = 0.282	Good
Length of oxygen therapy due to RSV (total number of days/100 children)						
Feltes <i>et al.</i>, 2003	RCT	27.9	101.5	n/a	RD = 73%, p = 0.014	Good

RCT: randomized clinical trial; CI: confidence interval; n/r: not reported; n/a: not applicable; RSV: respiratory syncytial virus

2.2.6 Children residing in remote communities

Regarding the assessment of the effectiveness of palivizumab in children residing in remote communities, two observational studies [Banerji *et al.*, 2014; Singleton *et al.*, 2003] were identified. Characteristics of these studies are provided in Appendix C of this document.

2.2.6.1 Hospitalization due to RSV

Banerji and colleagues [2014] conducted a study in Nunavut, with children who were eligible to receive palivizumab, children under 6 months of age at the start of the 2009 and 2010 RSV season, born at 36 weeks of gestation or less, and children with significant heart disease. A statistically significant reduction in the number of RSV-associated hospitalizations was observed in children who received palivizumab, compared to those who did not receive treatment (OR = 0.04; 95% CI: 0.0008 to 0.26; $p = 0.0005$) (see Table 7).

Singleton and colleagues [2003] reported a 62% reduction in the risk of RSV-associated hospitalizations among Aboriginal peoples in Alaska born at 36 weeks of gestation or less who received palivizumab during the immunoprophylaxis program, from 1998 to 2001, compared with those who met the eligibility criteria for receiving palivizumab prophylaxis before the start of the program, from 1993 to 1996 (RR = 0.34; 95% CI: 0.17 to 0.68; $p < 0.01$). However, a statistically non-significant 4% reduction in the risk of RSV-associated hospitalizations was observed in non-premature infants who received palivizumab prophylaxis, compared to those who received no prophylaxis (RR = 0.96; 95% CI: 0.82 to 1.13) (see Table 7).

Table 7 Effectiveness of palivizumab in premature infants residing in remote communities, compared to no prophylaxis

AUTHORS, YEAR	STUDY DESIGN (GESTATIONAL AGE)	PALIVIZUMAB	NO PROPHYLAXIS	ODDS RATIO (OR) RELATIVE RISK (RR) (95% CI) VALUE OF P	STUDY QUALITY
Hospitalizations due to RSV (number of persons) on the total number of participants					
Banerji <i>et al.</i>, 2014	Inception cohort	2/91 (2.2%)	5/10 (50%)	OR = 0.04 (0.008 to 0.26) $p = 0.0005$	Poor
Singleton <i>et al.</i>, 2003	Inception cohort (≤ 36 weeks)	150/1,000 (15%)	439/1,000 (43.9%)	RR = 0.34 (0.17 to 0.68) $p < 0.001$	Poor
	(> 36 weeks)	142/1,000 (14.2%)	148/1,000 (14.8%)	RR = 0.96 (0.82 to 1.13)	

CI: confidence interval; RSV: respiratory syncytial virus

2.2.7 Children with Down syndrome

One observational study assessing the effectiveness of palivizumab in children with Down syndrome was identified [Yi *et al.*, 2014]. In the study conducted by Yi and colleagues [Yi *et al.*, 2014], children with Down syndrome who received palivizumab prophylaxis were enrolled in the Canadian registry of palivizumab (CARESS) and children who did not receive it were entered in the Netherlands register of births.

2.2.7.1 Hospitalization due to RSV

In the inception cohort study conducted by Yi and colleagues [2014], a statistically significant reduction in the number of RSV-associated hospitalizations was observed in children with Down syndrome who received palivizumab, compared to those who did not receive palivizumab (incidence rate ratio (IRR) = 0.28; 95% CI: 0.12 to 0.66). Subpopulation analyses were also performed in children who had no risk factors and those who had at least one risk factor. These risk factors are as follows: hemodynamically-severe congenital heart disease, benign heart disease and gestational age of 35 weeks or less. A statistically non-significant reduction in the number of hospitalizations was observed in children with Down syndrome with no risk factors who received palivizumab, compared to those who did not receive palivizumab (IRR = 0.15; 95% CI: 0.02 to 1.43). However, among those with at least one risk factor, the reduction in the number of RSV-associated hospitalizations was statistically significant (IRR = 0.29; 95% CI: 0.09 to 0.98) (see Table 8).

2.2.7.2 Length of hospital stay due to RSV

In the study conducted by Yi and colleagues [2014], the average number of days of RSV-associated hospitalizations was significantly lower among children with Down syndrome who received palivizumab (6.4 days) compared to those who received no prophylaxis (12.4 days) ($p = 0.48$) (see Table 8).

2.2.7.3 Stay in an intensive care unit due to RSV

In the study conducted by Yi and colleagues [2014], no stay in an ICU was reported in the group of children who received palivizumab prophylaxis, while four children (0.02%) from the control group were admitted (see Table 8).

2.2.7.4 Length of stay in intensive care due to RSV

In the study conducted by Yi and colleagues [2014], no stay in an ICU was reported in the group of children who received palivizumab prophylaxis, while 10.3 days were reported for this type of stay in the group of children who did not receive prophylaxis (see Table 8).

2.2.7.5 Use of mechanical ventilation due to RSV

The study conducted by Yi and colleagues [2014] reported no cases of mechanical ventilation due to RSV in children who received palivizumab prophylaxis, compared with four cases (0.02%) among children who received no prophylaxis (see Table 8).

2.2.7.6 Length of mechanical ventilation due to RSV

The study conducted by Yi and colleagues [2014] reported no cases of mechanical ventilation

due to RSV in children who received palivizumab prophylaxis, compared to 10.3 days when mechanical ventilation was necessary in children who did not receive prophylaxis (see Table 8).

2.2.7.7 Use of oxygen therapy due to RSV

In the study conducted by Yi and colleagues [2014], the use of oxygen therapy was significantly lower in children with Down syndrome who received palivizumab (0.004% of these children) compared to those who received no prophylaxis (0.08%) ($p < 0.001$) (see Table 8).

2.2.7.8 Length of oxygen therapy due to RSV

In the study conducted by Yi and colleagues [2014], the number of days of oxygen therapy was significantly lower in children with Down syndrome who received palivizumab (four days) compared to those who received no prophylaxis (13.7 days) ($p = 0.046$) (see Table 8).

Table 8 Effectiveness of palivizumab in children with Down syndrome, compared to no prophylaxis

AUTHORS, YEAR	STUDY DESIGN	PALIVIZUMAB	NO PROPHYLAXIS	INCIDENCE RATE RATIO (95% CI) VALUE OF P	STUDY QUALITY
Hospitalizations due to RSV (number of persons) on the total number of participants					
Yi <i>et al.</i> , 2014	Inception cohort	8/532 (1.5%) (all participants)	23/233 (9.9%) (all participants)	0.28 (0.12 to 0.66)* p = 0.45	Poor
		n/a / 196 (no risk factor)**	n/a / 67 (no risk factor)**	0.15 (0.02 to 1.43)	
		n/a / 228 (common risk factor)**	n/a / 94 (common risk factor)**	0.29 (0.09 to 0.98)	
Length of hospital stay due to RSV (average number of days)					
Yi <i>et al.</i> , 2014	Inception cohort	6.4 (standard deviation ± 4.5)	12.4 (standard deviation ± 16.2)	p = 0.48	Poor
Stay in an intensive care unit due to RSV (number of persons) on the total number of participants					
Yi <i>et al.</i> , 2014	Inception cohort	0 (0%)	4/233 (0.02%)	n/a	Poor
Length of stay in intensive care due to RSV (average number of days)					
Yi <i>et al.</i> , 2014	Inception cohort	0	10.3 (standard deviation ± 8.9)	n/a	Poor
Use of mechanical ventilation due to infection with RSV (number of persons) on the total number of participants					
Yi <i>et al.</i> , 2014	Inception cohort	0 (0%)	4/233 (0.02%)	n/a	Poor
Length of mechanical ventilation due to infection with RSV (total number of days)					
Yi <i>et al.</i> , 2014	Inception cohort	0	10.3 (standard deviation ± 8.9)	0	Poor
Use of oxygen therapy due to infection with RSV (number of persons) on the total number of participants					

Yi et al., 2014	Inception cohort	2/532 (0.004%)	19/233 (0.08%)	p < 0.001	Poor
Length of oxygen therapy due to infection with RSV (average number of days)					
Yi et al., 2014	Inception cohort	4 (standard deviation ± 0)	13.7 (standard deviation ± 0)	p = 0.046	Poor

RCT: randomized clinical trial; CI: confidence interval; n/a: not applicable; RSV: respiratory syncytial virus

* Model adjusted for the following risk factors: hemodynamically severe congenital heart disease, benign heart disease, gestational age and birth weight

** No hemodynamically severe congenital heart disease, benign heart disease, gestational age of 35 weeks or less

3 DISCUSSION

In this systematic literature review, the effectiveness of palivizumab prophylaxis in reducing the risk of complications in children, compared to the use of a placebo or to no prophylaxis, was assessed according to 10 result parameters. In total, seven systematic literature reviews, five RCTs and 14 observational studies were identified. The main findings emerging from all of the data from these studies are presented below, according to the populations studied.

3.1 Main findings resulting from the critical review of the literature

Mixed population

In total, three SR-MA [Andabaka *et al.*, 2013; Checchia *et al.*, 2011; Morris *et al.*, 2009] on the effectiveness of palivizumab compared to the administration of a placebo or to no prophylaxis, combined in their analyses studies pertaining to various populations (premature infants, children with bronchopulmonary dysplasia, CLD or congenital heart disease). In the meta-analyses conducted by Andabaka and colleagues [2013] and Morris and colleagues [2009], the same three RCTs were included, which resulted in identical conclusions. Specifically, a statistically significant 50% reduction in the relative risk (RR) of RSV-associated hospitalizations in children who received palivizumab prophylaxis, compared to those who received a placebo, was reported. Andabaka and colleagues [2013], whose study was of good methodological quality, assessed the quality of the scientific evidence as high, which means that further research is very unlikely to change the conclusions on the effect of this type of prophylaxis.

The meta-analysis conducted by Checchia and colleagues [2011] featured observational studies, in addition to the three RCTs identified in the previous meta-analyses. Results of this meta-analysis are also consistent with those of the other two meta-analyses [Andabaka *et al.*, 2013; Morris *et al.*, 2009], but they indicate a higher reduction in the RR of RSV-associated hospitalizations, i.e. around 65%. From a methodological point of view, the quality of the study conducted by Checchia and colleagues [2011] was average.

Results of one RCT [IMpact-RSV, 1998] and of two identified observational studies, which also combined several populations, indicated a reduction in the RR of RSV-associated hospitalizations from 60% to 76%. The quality of these studies varied from 'very poor' to 'good'.

There is less scientific data available on the other assessed result parameters. Overall, in studies combining diverse populations, a statistically significant reduction in the duration of hospitalization, the risk of being admitted to an ICU and the duration of hospitalization in this type of unit was observed in children who received palivizumab prophylaxis, compared to those who received a placebo.

Premature infants without infantile chronic lung disease

Results of the meta-analysis conducted by Checchia and colleagues [2011], for which the methodological quality is average, show a statistically significant reduction of 72% to 74% in the number of RSV-associated hospitalizations in children born at 32 weeks of gestation or less and infants born at a gestational age of 32-35 weeks who received palivizumab prophylaxis, compared to those who received a placebo or received no prophylaxis. The rates of hospitalization for children born at 32 weeks of gestation or less who received palivizumab compared to those who received a placebo or no prophylaxis were 3.7% and 10.6% respectively. Among children born at a gestational age of 32-35 weeks, the rates were 2.2% and 7.6% respectively. However this meta-analysis, published in 2011, did not include two recent RCTs [Tavsu *et al.*, 2014; Blanken *et al.*, 2013] or a recent historical cohort study [Winterstein *et al.*, 2013a].

The two recent RCTs [Tavsu *et al.*, 2014; Blanken *et al.*, 2013], for which the methodological quality is average, report statistically significant reductions in the risk of RSV-associated hospitalizations in children born at 32 weeks of gestation or less and those born at a gestational age of 33-35 weeks: 74% and 82%, respectively.

- Among children born at 32 weeks of gestation or less, the hospitalization rate was 0% in those who received palivizumab prophylaxis and 24% in those who received no prophylaxis [Tavsu *et al.*, 2014].
- Among children born at a gestational age of 32-35 weeks, the hospitalization rate was 0.9% in those who received palivizumab and 5.1% in those who received no prophylaxis [Blanken *et al.*, 2013].

In the RCT conducted by the IMPact-RSV Study Group [1998], statistically significant reductions in the risk of RSV-associated hospitalizations of 53%, 72% and 78% were reported in children born at 32 weeks of gestation or less, in children born at a gestational age of 33-35 weeks and in those born at 35 weeks or less of gestation, respectively.

Results of the four identified observational studies [Winterstein *et al.*, 2013a; Grimaldi *et al.*, 2007; Mitchell *et al.*, 2006; Wegner *et al.*, 2004] show a decrease in RSV-associated hospitalizations in children who received palivizumab prophylaxis compared to those who did not receive it, but this decrease was only statistically significant in some studies. In two studies, a statistically significant reduction in the RR of RSV-associated hospitalizations of about 50% was observed in children who received palivizumab, compared to those who received no prophylaxis [Winterstein *et al.* 2013a; Mitchell *et al.*, 2006]. In contrast, in these same two studies, statistically non-significant reductions in RR of RSV-associated hospitalizations of 20% to 75% were reported in different regions. The differences between the same studies regarding the extent of the observed effect of palivizumab could be explained by significant variations in the RSV epidemic among regions from the same country [Winterstein *et al.*, 2013a]. In the other two observational studies [Grimaldi *et al.*, 2007; Wegner *et al.*, 2004], a reduction in RSV-associated hospitalizations was observed in children who received palivizumab prophylaxis, compared to those who did not receive treatment. However, the decrease in the number of hospitalizations was statistically significant in only one study. Results of the four identified observational studies [Winterstein *et al.*, 2013a; Grimaldi *et al.*, 2007; Mitchell *et al.*, 2006; Wegner *et al.*, 2004] are difficult to compare, partly because of the definitions of prematurity and the statistical analyses, which differ from one study to another. The methodological quality of these four observational studies ranges from 'good' to 'poor'.

Although results of the observational studies are not consistent, the fact of having a meta-analysis including RCTs and observational studies can partially lift the doubt concerning the discordant results of the various primary studies. In addition, results of the two recent RCTs match those of the meta-analysis.

Scientific data were also available on two other result parameters assessed in this systematic review: all-cause mortality and wheezing in the first year of life. Regarding all-cause mortality, a systematic review including RCTs and observational studies reported a reduction in all-cause mortality in children born at 32 weeks of gestation or less and those born at a gestational age of 32-35 weeks who received palivizumab prophylaxis compared to those who received a placebo or received no prophylaxis. However, the difference was statistically significant only in children born at 32 weeks of gestation or less. The methodological quality of this literature review is average.

A statistically significant reduction in the risk of wheezing in the first year of life was also observed in children born at a gestational age of 33-35 weeks and babies born at 35 weeks of gestation or less who received palivizumab, compared to those who received a placebo or received no prophylaxis, according to reports of an RCT and two observational studies. The real medium or long-term effect is unknown. The methodological quality of these three studies ranges from 'good' to 'poor'.

Premature infants with infantile chronic lung disease or bronchopulmonary dysplasia

Among premature infants with CLD or bronchopulmonary dysplasia, the effectiveness of palivizumab compared to the use of a placebo in preventing RSV-associated hospitalizations was assessed in an RCT [IMpact-RSV, 1998] and in two observational studies [Grimaldi *et al.*, 2004; Pedraz *et al.*, 2003].

The RCT [IMpact-RSV, 1998], which reports convincing data on the effectiveness of palivizumab prophylaxis, was of good methodological quality. A statistically significant reduction of approximately 40% in the number of RSV-associated hospitalizations was observed in children aged 24 months or younger with bronchopulmonary dysplasia who received palivizumab, compared to those who received a placebo. Note that in this study, most of the children were premature, although their exact number was not specified. Furthermore, no specific definition of bronchopulmonary dysplasia was provided; the one that was used in the late 1990s probably differs from the one currently used.

In both observational studies, a statistically significant reduction in the risk of RSV-associated hospitalization was observed in children born at 32 weeks of gestation or less, with CLD, who were aged six months or less at the beginning of the RSV season and who received palivizumab, compared to those who did not receive it. From a methodological point of view, these studies are of poor and very poor quality.

Children with cystic fibrosis

One systematic literature review [Robinson *et al.*, 2014], an RCT [Cohen *et al.*, 2005] and two observational studies [Winterstein *et al.*, 2013b; Giebels *et al.*, 2008] assessing the effectiveness of palivizumab prophylaxis compared to the use of a placebo or to no prophylaxis in children with cystic fibrosis were identified.

In the systematic review [Robinson *et al.*, 2014], one RCT was selected, that of Cohen and colleagues [Cohen *et al.*, 2005]. Note that this trial has not been published in the form of a full article in a peer-reviewed journal. None of the identified studies reported a statistically significant reduction in the number of RSV-associated hospitalizations in children with cystic fibrosis who received palivizumab prophylaxis compared to those who received a placebo or who did not receive palivizumab. Since two primary studies involved small numbers [Giebels *et al.*, 2008; Cohen *et al.*, 2005], it is possible that the small sample size did not allow a statistically significant difference between the two groups to be established. New research could therefore have implications on the assessment of the preventive effect of palivizumab in children with cystic fibrosis and change it. The methodological quality of these studies ranges from 'poor' to 'average'. Evaluation of the methodological quality of the RCT conducted by Cohen and colleagues [2005] was not assessed because the full article was not available. Current data are insufficient to conclude this.

Children with hemodynamically significant congenital heart disease

In total, an RS-MA [Checchia *et al.*, 2011], an RCT [Feldes *et al.*, 2003] and a historical cohort study [Harris *et al.*, 2011] have looked at the effectiveness of palivizumab, compared to the use of a placebo or to no prophylaxis, in children with hemodynamically significant congenital heart disease. The meta-analysis included only one RCT, that of Feldes and colleagues [2003]. Results of this RCT and inception cohort study indicate a reduction of RSV-associated hospitalizations of 42-45% in children with congenital heart disease who received palivizumab prophylaxis, compared to those who received a placebo. A statistically significant difference was only reported in the RCT.

In addition, subgroup analyses revealed a rate of RSV-associated hospitalizations that was 58% lower in children with acyanotic heart disease who received palivizumab (5.0%), compared to those who received a placebo (11.8%) ($p = 0.03$). In children with cyanotic heart disease, a rate of RSV-associated hospitalizations that was 29% lower was observed in the group of patients who received palivizumab (5.6%), compared to the group of patients who received a placebo (7.9%) ($p = 0.285$) [Feldes *et al.*, 2003].

Overall, regarding other result parameters, a statistically significant reduction in the length of hospital stays [Feldes *et al.*, 2003] and in the duration of oxygen therapy [Feldes *et al.*, 2003] was observed in children who received palivizumab prophylaxis compared to those who received a placebo. Regarding the methodological quality of the studies listed, that of the RCT was good, but that of the cohort study was poor.

Children residing in remote communities

Two observational studies [Banerji *et al.* studies, 2014; Singleton *et al.*, 2003], of poor methodological quality, assessing the effectiveness of palivizumab in children residing in remote communities were identified. In these two studies, a reduction in the risk of RSV-associated hospitalizations was observed in children who received palivizumab, compared to those who did not receive treatment.

Children with Down syndrome

One observational study assessing the effectiveness of palivizumab in children with Down syndrome was identified [Yi *et al.*, 2014]. A statistically significant reduction in the number of RSV-associated hospitalizations was observed in children with Down syndrome who received palivizumab, compared to those who did not receive treatment. When the study population was stratified according to the presence or absence of risk factors for contracting RSV, a statistically significant reduction in the number of hospitalizations was observed, but only in children who had at least one risk factor. However, this study was of poor methodological quality and has major weaknesses. Children with Down syndrome who received palivizumab prophylaxis were registered in the Canadian CARESS registry while children who received treatment were entered in a Netherlands register. In addition, study periods, population characteristics and risk factors likely to affect the severity of RSV infection and the number of hospitalizations differed between the two groups. In addition, hospitalization criteria and criteria for establishing the diagnosis of viral infection could differ between the two cohorts. Uncertainty about the comparison method, the clinical context and the study population limits the generalization of these results. It is therefore difficult to draw conclusions on the effectiveness of palivizumab from this single study of poor methodological quality.

3.2 Strengths and limitations of the systematic review

This systematic review was based on a rigorous methodology, which included a systematic literature search, an evaluation of the methodological quality of the selected publications and a presentation and summary of the conclusions. Given the comprehensive search strategy and inclusion of five systematic literature reviews, it is unlikely that relevant studies have been omitted from this process. However, the results of this review do have limitations, which originate primarily within the included studies.

First, note that no study was identified on the effectiveness of palivizumab prophylaxis, compared to the use of a placebo or no prophylaxis, in children who are immunosuppressed, affected by a metabolic disorder, presenting a serious neuromuscular disorder affecting respiratory function, presenting an upper airway anomaly affecting respiratory function, from a healthy multiple birth whose twin is eligible to receive palivizumab. It is therefore impossible to draw conclusions about the possible advantages of palivizumab prophylaxis for these populations.

Moreover, results from the three identified meta-analyses [Andabaka *et al.*, 2013; Checchia *et al.*, 2011; Morris *et al.*, 2009] included various populations at high risk of contracting an RSV infection. Consequently, assessing the effect of palivizumab could be potentially confounding, since certain populations might benefit disproportionately to others. As such, in order to obtain an assessment of the effect of palivizumab in premature infants and children with bronchopulmonary dysplasia, CLD or congenital heart disease, the results of each primary study identified that met the inclusion criteria were analyzed.

Findings of this systematic literature review are limited by the fact that palivizumab prophylaxis, compared to the administration of a placebo, was only assessed in five RCTs. As such, findings are based mainly on results from observational studies. All identified RCTs were of good or average methodological quality and they were all funded by pharmaceutical companies [Blanken *et al.*, 2013; Feltes *et al.*, 2003; IMPact-RSV, 1998], except for one [Tavsu *et al.*, 2014].

A total of 14 observational studies likely to present a higher risk of bias were included in this review. These studies allow for an estimate of the effectiveness of palivizumab in actual usage situations, where doctors and parents have decided together whether or not to use palivizumab prophylaxis to treat a child. Because observational studies do not consider factors that influence whether or not palivizumab is used, they are likely to present a selection bias. Moreover, in these studies, compliance with treatment could be lower than in the RCTs. Knowing that a suboptimal use of palivizumab reduces its effectiveness [Froegel *et al.*, 2008], the effects of actual treatment in clinical situations may be lower than those observed in the RCTs.

Moreover, it is difficult to compare observational studies, for several reasons. The annual distribution of the RSV epidemic varies considerably across regions, years and subtypes (A or B) in circulation. Differences regarding the RSV epidemic could affect hospitalization rates between various study regions and within a single study conducted at different times, which favours the introduction of a bias whose effect on the results is impossible to measure. In addition, differences in the rates of RSV-associated hospitalizations in one region can result from a change in the treatment of RSV over the years. Different hospitalization criteria (e.g. the lower saturation percentage justifying oxygen therapy in a patient) and an increased emphasis on the prevention of viral infections and methods to reduce exposure could have an effect on decreasing hospitalization rates. For example, studies assessing the effectiveness of an immunoprophylaxis program in which palivizumab is administered, comparing inception cohorts of children who received palivizumab to historical cohorts of children who met the eligibility criteria to receive palivizumab before the start of the immunoprophylaxis program, are likely to present this type of bias.

In addition, characteristics of the populations studied in the observational studies are heterogeneous in many aspects. Study populations vary in terms of age, presence or absence of underlying diseases, severity of the CLD and, in some studies, hospitalized patients are included while in others, patients are ambulatory. Additionally, the definitions of prematurity and CLD differ between studies. A more precise definition of the underlying health problems and of the CLD would also be required in order to better analyze the results. Finally, the fact that the studies were conducted in different geographical regions could result in considerable variability regarding provision of care and hospitalization criteria. The bottom line is that results from observational studies can be difficult to generalize to other populations and to other contexts, other than for those assessed in these studies.

On one hand, it is important to specify that children included in the RCTs had undergone a test to detect RSV when they were hospitalized for respiratory problems, while in observational studies, which represent the current practice, tests used to diagnose RSV were performed at the discretion of the treating physician. When a small number of tests are performed, the burden associated with an RSV infection may be underestimated. That being said, documentation of RSV infections has improved in recent years, thanks to the use of molecular techniques. This means that RSV infection diagnoses are now better than they were previously.

On the other hand, depending on the test used, the number of confirmed RSV diagnoses may vary. For example, the test that searches for antigens to detect a protein of RSV in secretions, which is a quick and low-cost technique, offers a specificity of 90-95%. However, the sensitivity of this test ranges from 60% to 70%, which can produce false negative results. A more specific and sensitive technique, such as reverse transcription polymerase chain reaction (RT-PCR), would detect a greater number of patients with RSV [Abels *et al.*, 2001]. Diagnosis of RSV infections was less reliable for the earliest RCTs on palivizumab than it is now, but as this applied to the two

compared groups (palivizumab and placebo), this should not modify the effectiveness percentage. However, RSV infection rates in studies from the '90s and early 2000s are probably slightly underestimated due to the viral infection diagnostic techniques of the time.

Moreover, in some observational studies, authors did not consider many potential confounding factors, due to the lack of data needed to perform multivariate analyses. For example, differences in the prevalence of certain risk factors, including smoking, could lead to biased estimates of the effectiveness of palivizumab on the studied result parameters. Also note that several studies were conducted using small samples. Therefore, measurement of the effect may be imprecise or it may be impossible to establish a statistically significant difference between groups.

CONCLUSION

Data currently available indicate that palivizumab is effective in reducing the risk of RSV-associated hospitalizations in premature infants with or without CLD, in non-premature infants with CLD, in children with acyanotic congenital heart disease, in children residing in remote communities, and in children with Down syndrome who present risk factors. Little scientific data is available on the other assessed result parameters, and these results are sometimes discordant. None of the identified data supports the effectiveness of palivizumab in children with cystic fibrosis. The effectiveness of palivizumab in certain populations, including premature infants with CLD, children residing in remote communities, children with Down syndrome and those with cystic fibrosis is poorly documented and the available data come from studies with methodological limitations and uncertainties. Moreover, no studies were identified on the effectiveness of palivizumab prophylaxis compared to the use of a placebo or no prophylaxis among children who are immunosuppressed, affected by a metabolic disorder, presenting a serious neuromuscular disorder affecting respiratory function, presenting an upper airway anomaly affecting respiratory function, from a healthy multiple birth whose twin is eligible to receive palivizumab.

APPENDIX A

Information research strategy

MEDLINE (PubMed)

Search date: December 22, 2015

Limits: none

N° 1	antibodies, monoclonal, humanized[mh] OR antiviral agents[mh] OR immunoglobulins[mh] OR palivizumab[nm] OR antibody protein[tiab] OR anti viral agent*[tiab] OR anti viral drug*[tiab] OR antiviral agent*[tiab] OR antiviral drug*[tiab] OR antiviral substance[tiab] OR antivirals[tiab] OR antiviral agent*[tiab] OR antiviral drug*[tiab] OR anti-RSV[tiab] OR clonal antibody[tiab] OR endobulin[tiab] OR flebogamma[tiab] OR flebogammadif[tiab] OR gamastan[tiab] OR gamimmune n[tiab] OR gamimmune[tiab] OR gamma globulin*[tiab] OR gamma-globulin*[tiab] OR gammaglobulin*[tiab] OR gammar[tiab] OR gamulin[tiab] OR globuman[tiab] OR humanized antibody[tiab] OR humanized monoclonal antibody[tiab] OR hybridoma antibody[tiab] OR ig[tiab] OR igam[tiab] OR igc[tiab] OR immune gamma globulin[tiab] OR immune globin[tiab] OR immune globulin*[tiab] OR immune serum globulin*[tiab] OR immuno gamma globulin*[tiab] OR immuno globulin*[tiab] OR immunogammaglobulin*[tiab] OR immunoglobulin*[tiab] OR immunoglobulin*[tiab] OR immunoprotein*[tiab] OR intragam[tiab] OR intraglobin f[tiab] OR isiven[tiab] OR iveegam[tiab] OR ivega[tiab] OR mAbs[tiab] OR MEDI 493[tiab] OR monoclonal antibodies[tiab] OR monoclonal antibody[tiab] OR palivizumab[tiab] OR panglobulin*[tiab] OR passive immunization[tiab] OR sandoglobin*[tiab] OR sandoglobulin*[tiab] OR synagis[tiab] OR tegelin*[tiab] OR veinoglobulin*[tiab] OR venoglobulin*[tiab] OR viral inhibitor[tiab] OR virostatic agent*[tiab] OR virucidal agent*[tiab] OR virucide agent*[tiab] OR virustatic agent* [tiab] OR vivaglobin[tiab]	1003024
N° 2	respiratory syncytial virus infections/pc OR ((respiratory syncytial virus infection*[tiab] OR RSV[tiab]) AND (control[tiab] OR health protection[tiab] OR immunoprophylaxis[tiab] OR prevention[tiab] OR preventive measures[tiab] OR preventive medication[tiab] OR preventive therapy[tiab] OR preventive treatment[tiab] OR prophylactic institution[tiab] OR prophylactic management[tiab] OR prophylactic medication[tiab] OR prophylactic therapy[tiab] OR prophylactic treatment[tiab] OR prophylaxis[tiab]))	2844
N° 3	N° 1 ET N° 2	1290
N° 4	N° 1 ET N° 2 Filtres : English	1192
N° 5	N° 1 ET N° 2 Filtres : English; French	1209
N° 6	infant[mh] OR infant* OR infancy OR newborn* OR baby* OR babies OR neonat* OR preterm* OR prematur* OR postmatur* OR child[mh] OR child OR children OR schoolchild* OR school age* OR preschool* OR kid OR kids OR toddler* OR adolescent[mh] OR adoles* OR teen* OR boy OR boys OR girl* OR minors[mh] OR minors* OR puberty[mh] OR pubert* OR pubescen* OR prepubescen* OR pediatrics[mh] OR pediatric* OR paediatric* OR peadiatric* OR schools[mh] OR Nursery school* OR kindergar* OR primary school* OR secondary school* OR elementary school* OR high school* OR highschool*	3874825
N° 7	N° 5 ET N° 6	937
N° 8	(guidelines as topic[mh] OR practice guidelines as topic[mh] OR guideline[pt] OR health planning guidelines[mh] OR practice guideline[pt] OR consensus[mh] OR consensus development conference, NIH[pt] OR consensus development conference[pt] OR consensus development conferences, NIH as topic[mh] OR consensus development conferences as topic[mh] OR critical pathways[mh] OR clinical conference[pt] OR algorithms[mh] OR review literature as topic[mh] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta-analysis[pt] OR technology assessment,biomedical[mh] OR guideline*[tiab] OR guide line*[tiab] OR CPG[tiab] OR CPGs[tiab] OR guidance[tiab] OR practical guide*[tiab] OR practice parameter*[tiab] OR best practice*[tiab] OR evidence base*[tiab] OR consensus[tiab] OR algorithm*[tiab] OR clinical pathway*[tiab] OR critical pathway*[tiab] OR recommendation*[tiab] OR committee opinion*[tiab] OR policy	1695950

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N° 9	N° 7 ET n° 8	205
N° 10	N° 5 ET n° 6 Filtres : Systematic Reviews; Randomized Controlled Trial; Practice Guideline; Observational Study; Meta-Analysis; Guideline; Controlled Clinical Trial; Consensus Development Conference; Comparative Study; Clinical Trial	190
N° 11	N° 9 OU n° 10	325
	After having deleted duplicates	305

Embase (Ovid)

Search date: December 22, 2015

Limits: none

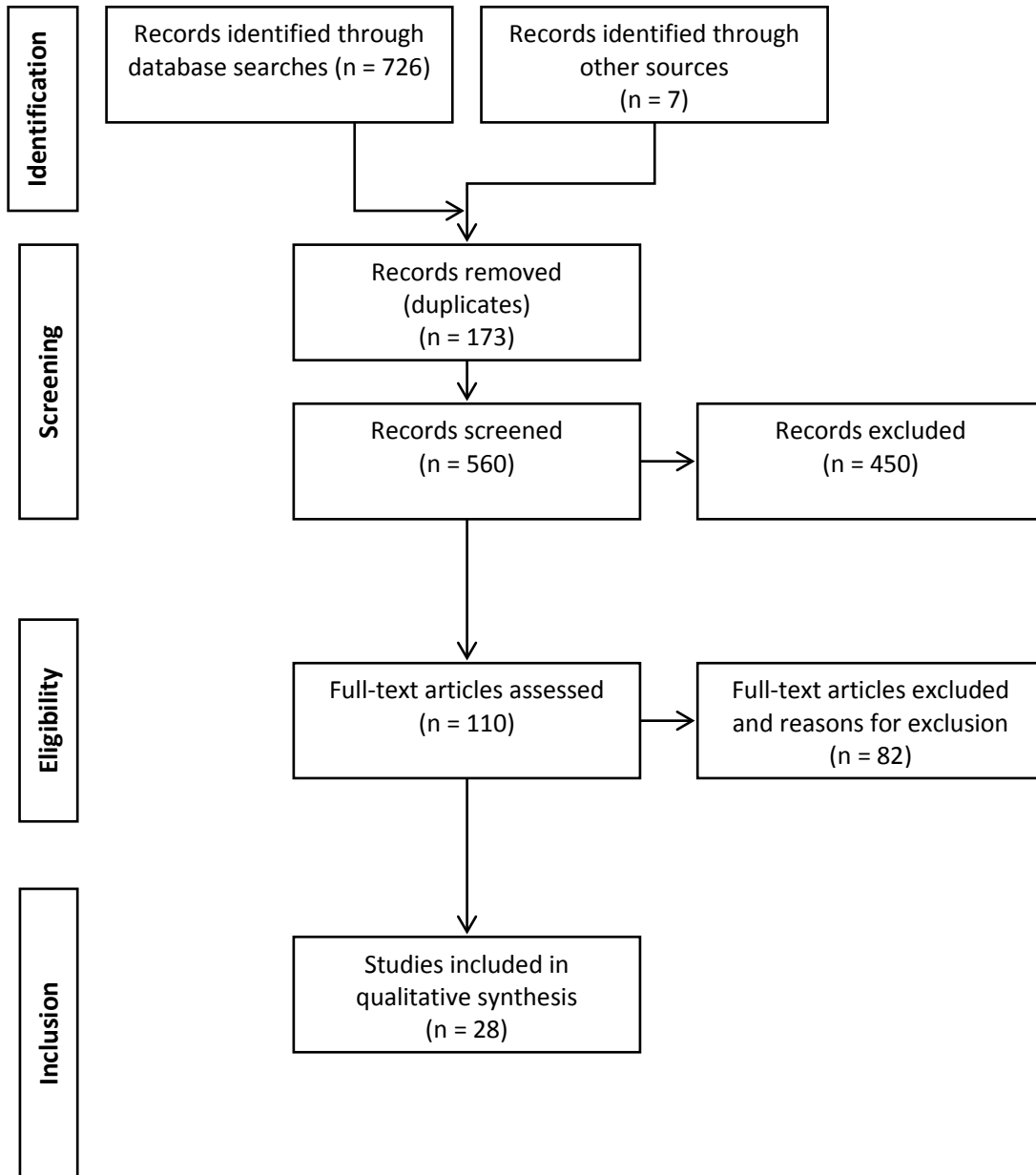
N° 1	antivirus agent/ OR immunoglobulin/ OR monoclonal antibody/ OR palivizumab/ OR (abbosynagis OR antibody protein OR anti viral agent* OR anti viral drug* OR antiviral agent* OR antiviral drug* OR antiviral substance OR antivirals OR antiviral agent* OR antiviral drug* OR anti-RSV OR clonal antibody OR endobulin OR flebogamma OR flebogammadif OR gamastan OR gamimmune n OR gamimmune OR gamma globulin* OR gamma immunoglobulin* OR gamma-globulin* OR gammagee OR gammaglobulin* OR gammar OR gammimmune OR gamulin OR globuman OR glovenin i OR humanized antibody OR humanized monoclonal antibody OR hybridoma antibody OR Ig OR igam OR igc OR immune gamma globulin OR immune globin* OR immune globulin* OR immune serum globulin* OR immuno gamma globulin* OR immuno globulin* OR immunogammaglobulin* OR immunoglobulin* OR immunoglobulin* OR immunoprotein* OR intragam OR intraglobin* f OR isiven OR iveegam OR ivega OR mAbs OR MEDI493 OR MEDI 493 OR monoclonal antibodies OR monoclonal antibody OR palivizumab OR panglobulin* OR passive immunization OR sandoglobin* OR sandoglobulin* OR synagis OR synagys OR tegelin* OR veinoglobulin* OR venoglobulin* OR viral inhibitor OR virostatic agent* OR virucidal agent* OR virucide agent* OR virus repressor OR virustatic agent* OR vivaglobin).ti,ab.	344371
N° 2	respiratory syncytial virus infection/pc	474
N° 3	respiratory syncytial virus infection/ OR (respiratory syncytial virus infection* OR RSV).ti,ab.	10277
N° 4	prophylaxis/ OR (control OR health protection OR immunoprophylaxis OR prevention OR preventive measures OR preventive medication OR preventive therapy OR preventive treatment OR prophylactic institution OR prophylactic management OR prophylactic medication OR prophylactic therapy OR prophylactic treatment OR prophylaxis).ti,ab.	2304536
N° 5	N° 2 OU (n° 3 ET n° 4)	2997
N° 6	N° 1 ET n° 5	1249
N° 7	limit 6 to (embase and (english or french))	1038
N° 8	infant/ OR child/ OR adolescent/ OR minors/ OR puberty/ OR pediatrics/ OR school/ OR (infant* OR infancy OR newborn* OR baby* OR babies OR neonat* OR preterm* OR prematur* OR postmatur* OR child OR children OR schoolchild* OR school age* OR preschool* OR kid OR kids OR toddler* OR adoles* OR teen* OR boy OR boys OR girl* OR minors* OR pubert* OR pubescen* OR prepubescen* OR pediatric* OR paediatric* OR peadiatric* OR nursery school* OR kindergar* OR primary school* OR secondary school* OR elementary school* OR high school* OR highschool*).mp.	2279035
N° 9	N° 7 ET n° 8	818
N° 10	(exp practice guideline/ OR health care planning/ OR consensus/ OR algorithm/ OR systematic review/ OR «systematic review (topic)»/ OR meta-analysis/ OR «meta analysis (topic)»/ OR biomedical technology assessment/ OR (guideline* OR guide line* OR CPG OR CPGs OR guidance OR practical guide* OR practice parameter* OR (best ADJ3 practice*) OR evidence base* OR consensus OR algorithm* OR (clinical ADJ3 pathway*) OR (critical ADJ3 pathway*) OR recommendation* OR committee opinion* OR policy statement* OR position statement* OR standard OR standards OR (systematic* ADJ3 (review* OR overview* OR literature OR search* OR research*)) OR meta-analy* OR metaanaly* OR met analy* OR metanaly* OR HTA	1977353

	OR HTAs OR technology assessment* OR technology overview* OR technology appraisal*).ti,ab.) NOT (case report/ OR editorial/ OR letter/)	
N° 11	N° 9 ET n° 10	268
N° 12	limit 9 to (consensus development or meta analysis or «systematic review»)	42
N° 13	limit 9 to (clinical trial or randomized controlled trial or controlled clinical trial)	147
N° 14	(observational study/ OR comparative study/ OR («comparative study» OR «comparative studies» OR comparison OR «non experimental studies» OR «non experimental study» OR «nonexperimental studies» OR «nonexperimental study» OR «observation studies» OR «observation study» OR «observational studies» OR «observational study»).ti,ab.) NOT (case report/ OR editorial/ OR letter/)	1181730
N° 15	N° 9 ET n° 14	59
N° 16	N° 12 OU n° 13 OU n° 15	211
N° 17	N° 11 OU n° 16	401
	After having deleted duplicates	248

APPENDIX B

Study selection

Figure B-1 Flow chart



List of articles included from EndNote bank (21/103)

AUTHORS (YEAR)	TITLE
IMpact-RSV, 1998	Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. The IMpact-RSV Study Group
Andabaka <i>et al.</i> , 2013	Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children. Cochrane
Banerji <i>et al.</i> , 2014	The real-life effectiveness of palivizumab for reducing hospital admissions for respiratory syncytial virus in infants residing in Nunavut
Checchia <i>et al.</i> , 2011	Mortality and morbidity among infants at high risk for severe respiratory syncytial virus infection receiving prophylaxis with palivizumab: A systematic literature review and meta-analysis
Carbonell-Estrany <i>et al.</i> , 2010	Motavizumab for prophylaxis of respiratory syncytial virus in high-risk children: A noninferiority trial
Feltes <i>et al.</i> , 2003	Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease
Feltes <i>et al.</i> , 2011	Résultats – Innocuité du Motavizumab c. Palivizumab (phase 2), mais les auteurs rapportent des données sur les taux d'hospitalisation
Grimaldi <i>et al.</i> , 2007	Palivizumab efficacy in preterm infants with gestational age < or = 30 weeks without bronchopulmonary dysplasia
Homaira <i>et al.</i> , 2014	Effectiveness of palivizumab in preventing RSV hospitalization in high risk children: A real-world perspective
Mitchell <i>et al.</i> , 2006	Beyond randomized controlled trials: A «real life» experience of respiratory syncytial virus infection prevention in infancy with and without palivizumab
Morris <i>et al.</i> , 2009	A meta-analysis of the effect of antibody therapy for the prevention of severe respiratory syncytial virus infection
Pedraz <i>et al.</i> , 2003	Effect of palivizumab prophylaxis in decreasing respiratory syncytial virus hospitalizations in premature infants
Pons <i>et al.</i> , 2011	Intervention – La méta-analyse combine tous les types de prophylaxie passive (palivizumab, et RSG-IG). Le document est utile par contre pour comparer les RR de chaque essai clinique à répartition aléatoire (ECRA) avec d'autres RS ou méta-analyses.
Robinson <i>et al.</i> , 2014	Palivizumab for prophylaxis against respiratory syncytial virus infection in children with cystic fibrosis
Simoes <i>et al.</i> , 2007	Palivizumab prophylaxis, respiratory syncytial virus, and subsequent recurrent wheezing
Singleton <i>et al.</i> , 2003	Impact of palivizumab prophylaxis on respiratory syncytial virus hospitalizations in high risk Alaska Native infants
Tavsu <i>et al.</i> , 2014	Palivizumab prophylaxis: Does it have any influence on the growth and development of the infants?
Wegzyn <i>et al.</i> , 2014	Safety and effectiveness of palivizumab in children at high risk of serious disease due to respiratory syncytial virus infection: A systematic review
Winterstein <i>et al.</i> , 2013a	Appropriateness of age thresholds for respiratory syncytial virus immunoprophylaxis in moderate-preterm infants: A cohort study
Yi <i>et al.</i> , 2014	Respiratory syncytial virus prophylaxis in Down syndrome: A prospective cohort study
Yoshihara <i>et al.</i> , 2013	Effect of palivizumab prophylaxis on subsequent recurrent wheezing in preterm infants

List of articles included based on manual search (7)

AUTHOR (YEAR)	TITLE
Blanken <i>et al.</i> , 2013	Respiratory Syncytial Virus and Recurrent Wheeze in Healthy Preterm Infants
Winterstein <i>et al.</i> , 2013b	Palivizumab Immunoprophylaxis Effectiveness in Children With Cystic Fibrosis
Harris <i>et al.</i> , 2011	Economic Evaluation of Palivizumab in Children With Congenital Heart Disease: A Canadian Perspective
Cohen <i>et al.</i> , 2005*	Cohen AH, Boron ML, Dingivan C. A phase IV study of the safety of Synagis® (Palivizumab) for prophylaxis of respiratory syncytial virus disease in children with cystic fibrosis
Giebels <i>et al.</i> , 2008	Prophylaxis Against Respiratory Syncytial Virus in Young Children With Cystic Fibrosis
Grimaldi <i>et al.</i> , 2004	Severe Respiratory Syncytial Virus Bronchiolitis Epidemiologic Variations Associated With the Initiation of Palivizumab in Severely Premature Infants With Bronchopulmonary Dysplasia
Wegner <i>et al.</i> , 2004	Direct Cost Analyses of Palivizumab Treatment in a Cohort of At-Risk Children: Evidence from the North Carolina Medicaid Program

* Poster presented at the American Thoracic Society International Conference 2005, from May 20 to 25, 2005 in San Diego, CA (United States)

List of articles excluded and reasons for exclusion (82/103)

AUTHOR (YEAR)	REASONS FOR EXCLUSION
Abadesso <i>et al.</i> , 2004	Specification – case study (case occurred during two outbreaks in a neonatal intensive care unit (NICU))
Abarca <i>et al.</i> , 2009	Results – safety study
Afghani <i>et al.</i> , 2006	Not relevant – study on adherence to PAA recommendations
Alexander <i>et al.</i> , 2012	Comparison – children who received a prophylaxis from 2008 to 2009, compared to children who received an ad hoc prophylaxis from 2005 to 2007
Ambrose <i>et al.</i> , 2014	Specification – projection on the weighted effectiveness of palivizumab according to the prevalence in certain populations of children at risk; lack of observational data
Andabaka and Rojas-Reyes, 2013	Not relevant – summary of the Cochrane systematic review by the same author
Atkins <i>et al.</i> , 2000	Intervention – RSV-IVIG
Bouthillier, 1997	Specification – letter to the editor
Buckley <i>et al.</i> , 2010	Scientific quality – cohort whose indications are different from those of the control group (without palivizumab)
Butt <i>et al.</i> , 2014	Specification – no comparison group (risk factor)
Butt <i>et al.</i> , 2011	Specification – no comparison group (risk factor)
Carbonell-Estrany, 2003	Specification – editorial comment
Centre for Reviews and Dissemination, 2007	Not relevant – comes from the 2007 assessment report by Dunfield and Mierzwinski-Urban (CADTH/ACMTS)
Centre for Reviews and Dissemination, 2003	Specification – summary of the systematic review by Simpson and Burls (2001)
Chadha <i>et al.</i> , 2012	Specification – no comparison group
Chang and Chen, 2010	Specification – study with simulation by mathematical calculation to estimate the effect of palivizumab; lack of observational data
Chen <i>et al.</i> , 2015	Results – study on safety and tolerability
Clark <i>et al.</i> , 2000	Specification – cohort study on two at-risk groups and not on exposure to the drug or lack thereof Moreover, exposure was not assessed afterwards in both groups.

Cody Meissner, 2004	Not relevant – expert opinion on risk factors
Cohen <i>et al.</i> , 2008	Comparison – cohort study conducted using a database of people who received palivizumab; no information on people with CHD, not exposed to the prophylaxis.
Connor <i>et al.</i> , 1997	Intervention – RSV-IVIG
DeVincenzo <i>et al.</i> , 2003	Results – viral load measured in the exposed group and the non-exposed group
Duppenthaler <i>et al.</i> , 2004	Specification – population study in which the compared groups are CHD and non-CHD and results relate to the rate of RSV-associated hospitalizations; does not relate to palivizumab
Elnazir <i>et al.</i> , 2012	Not relevant – not a study strictly speaking.
Emerick <i>et al.</i> , 2006	Specification – narrative review
Estrada <i>et al.</i> , 2011	Specification – conference summary
Faldella <i>et al.</i> , 2010	Scientific quality – cohort whose indications are different from those of the control group (without palivizumab)
Fernandez <i>et al.</i> , 2010	Results – safety of motavizumab compared to palivizumab (phase 2)
Forbes <i>et al.</i> , 2014	Comparison – low palivizumab serum concentration vs high concentration
Frogel <i>et al.</i> , 2008	Specification – no comparison group
Geskey <i>et al.</i> , 2004	Specification – narrative review
Groothuis, 2001	Results – safety and tolerability (palivizumab)
Groothuis, 2003	Results – safety and tolerability ()
Groothuis and Nishida, 2002	Specification – narrative review
Groothuis <i>et al.</i> , 1995a	Intervention – effectiveness of RSV-IG infusion (750 mg/kg or 150 mg/kg or without RSV-IG) (3-5 doses). It is not known if the injection is intravenous, intramuscular or other.
Groothuis <i>et al.</i> , 1995b	Intervention and outcome – safety and bioequivalence of an infusion of various RSVIG preparations (750 mg/kg)
Groothuis <i>et al.</i> , 1993	Intervention – effectiveness and safety of RSV-IG infusion (750 mg/kg or 150 mg/kg or without RSV-IG) (3-5 doses). It is not known if the injection is intravenous, intramuscular or other.
Handforth <i>et al.</i> , 2004	Specification – editorial
Harkensee <i>et al.</i> , 2006	Specification – narrative review on the synthesis of evidence regarding safety, effectiveness and cost-effectiveness of palivizumab
Heikkinen <i>et al.</i> , 2005	Specification – cohort study on hospitalization rates for different gestational ages. Does not specifically deal with palivizumab.
Henckel <i>et al.</i> , 2004	Not a cohort study.
Kusuda <i>et al.</i> , 2006	Scientific quality – cohort whose indications are different from those of the control group (without palivizumab)
Lacaze-Masmonteil <i>et al.</i> , 2002	Results-safety of palivizumab
Lacaze-Masmonteil <i>et al.</i> , 2003	Specification – no comparison group
Lacaze-Masmonteil <i>et al.</i> , 2002	Results-safety of palivizumab
Lagos <i>et al.</i> , 2009	Intervention and results – safety of motavizumab
Malkin <i>et al.</i> , 2013	Intervention – vaccine against attenuated RSV
Meberg and Bruu, 2006	Dimension – economic
Medrano Lopez and Garcia-Guereta, 2010	Comparison – inadequate vs adequate prophylaxis
Mitchell <i>et al.</i> , 2011	Specification – not a cohort study or RCT, but data on rates of hospitalization and characteristics of patients from the CARESS registry of persons who received palivizumab in Canada. No information on persons who were not exposed to the treatment.
Mitchell <i>et al.</i> , 2006	Specification – observational study, but not a cohort or case-control study. Populations are from two cities (Calgary and Alberta), of which one had the palivizumab immunoprophylaxis program implemented and the other did not. Rates of RSV-associated hospitalizations before and after are analyzed.
Mori <i>et al.</i> , 2014	Specification – non-randomized clinical trial in Japan on newborns and immunosuppressed children. N < 30
Naver <i>et al.</i> , 2004	Specification – not a cohort or case-control study. Evaluation of the impact of guidelines
Null <i>et al.</i> , 2005	Specification and results – case report on the effects of prophylaxis received for two consecutive seasons. 55 of the participants from the IMPact-RSV study received palivizumab during a second season. Safety and tolerance.
Oh <i>et al.</i> , 2002	Specification – evaluation of risk factors for RSV-associated hospitalizations No comparison group

Ohler and Pham, 2013	Comparison – the two groups are exposed to palivizumab, but at different times.
Onuzo, 2004	Not relevant – follow-up of responses to a letter
Paes <i>et al.</i> , 2013	Comparison – both groups are exposed to palivizumab (comparison between data from the Canadian CARESS registry and registries in other territories).
Paes <i>et al.</i> , 2012a	Comparison – study based on the CARESS registry for which participants received at least one dose of palivizumab; separation in two groups having different indications (risk factors)
Paes <i>et al.</i> , 2012b	Comparison – study based on the CARESS registry for which participants received at least one dose of palivizumab; separation in two groups having different indications (risk factors)
Paes <i>et al.</i> , 2014	Comparison – study based on the CARESS registry for which participants received at least one dose of palivizumab; separation into three groups with different indications: those with Down syndrome, those meeting current indication criteria for prophylaxis and those who potentially had other health problems in addition to a risk of serious RSV infection
Prais <i>et al.</i> , 2005	Specification and scientific quality – survey comparing a period before and after palivizumab, but the article does not report any palivizumab exposure data.
Parmigiani <i>et al.</i> , 2001	Article cannot be obtained
Resch, 2008a	Specification – narrative review
Resch, 2008b	Specification – narrative review
Resch <i>et al.</i> , 2009	Specification – narrative review
Robinson and Nahata, 2000	Specification – narrative review
Romero, 2003	Specification – observational study, using a registry from the United States on persons who received palivizumab; no data on persons who were not exposed
Saadah <i>et al.</i> , 2014	Specification – retrospective analysis in the United Arab Emirates using an artificial neural network model to determine subgroups of premature infants likely to benefit most from palivizumab prophylaxis during a nosocomial outbreak of RSV
Saez-Llorens <i>et al.</i> , 1998	Specification and results – phase I/II clinical study on safety, immunogenicity and pharmacokinetics of palivizumab (intramuscular) (5, 10 and 15 mg/kg) as well as tolerance to palivizumab in premature infants and newborns with bronchopulmonary dysplasia
Shireman and Braman, 2002	Intervention – retrospective study from a MEDICAID registry where participants received palivizumab OR RSV-IVIG. Impossible to distinguish data regarding palivizumab.
Silva <i>et al.</i> , 2012	Not relevant – analysis of several cases in a Brazil hospital
Simoes <i>et al.</i> , 1998	Intervention – effectiveness of intravenous RSV-IG (750 mg/kg)
Subramanian <i>et al.</i> , 1998	Results – phase-I/II safety trial. Very small N to measure the effectiveness on hospitalization (2/4 vs 0/2) N with confirmed RSV infection
Thomas <i>et al.</i> , 2000a	Dimension – economic projection study
Thomas <i>et al.</i> , 2000b	Article cannot be obtained, but seems to be a projection study
Vogel <i>et al.</i> , 2002	Specification – narrative review and expert recommendations for New Zealand
Wang and Tang, 2000	Specification – notice stating that Cochrane withdrew this systematic review given its update by another group
Wang and Law, 1998	Specification – narrative review
Weinberger <i>et al.</i> , 2015	Dimension – economic analysis (4 vs 5 doses of palivizumab)
Winchester <i>et al.</i> , 2002	Specification – no comparison group (without prophylaxis), but data on safety of palivizumab
Wenzel <i>et al.</i> , 2002	Scientific quality – 7-10 year monitoring of 13 children with CLD who received palivizumab N < 30

APPENDIX C

List of included studies and their characteristics

Table C-1 Characteristics of systematic literature reviews on the effectiveness of palivizumab

AUTHORS, YEAR	SPECIFICATION	STUDY PERIODS	PARTICIPANTS	NUMBER OF PARTICIPANTS
HOMAIRA ET AL., 2014	Systematic review of observational studies	1999 to 2013	Children presenting an elevated risk of contracting an RSV infection	89,469
WEGZYN ET AL., 2014	Systematic review of prospective observational studies and RCTs	1996 to 2013	Children born at 35 weeks of gestation or less or with CLD or congenital heart disease	About 42,000
ROBINSON ET AL., 2014	Systematic RCT review	1995 to 2014	Children with cystic fibrosis	186
ANDABAKA ET AL., 2013	Systematic RCT review	1996 to 2012	Children born at 35 weeks of gestation or less and aged six months or less at the start of the RSV season, or less than 24 months of age, with CLD due to prematurity or with hemodynamically severe congenital heart disease and under 24 months at the start of the RSV season	11,096
CHECCHIA ET AL., 2011	Systematic review of RCTs and observational studies	1990 to 2007	Children born at 35 weeks of gestation or less or with CLD or congenital heart disease	About 15,000
PONS ET AL., 2011	Systematic RCT review	1990 to 2009	Children presenting an elevated risk of contracting an RSV infection	2,831
MORRIS ET AL., 2009	Systematic RCT review	1966 to 2009	Children under 48 months old	2,831

RCT: randomized clinical trial; CLD: chronic lung disease; RSV: respiratory syncytial virus

Table C-2 **Characteristics of randomized clinical trials on the effectiveness of palivizumab, compared to the administration of a placebo or to no prophylaxis**

AUTHORS, YEAR	STUDY DESIGN	STUDY PERIODS (LOCATION)	PARTICIPANTS	METHOD USED TO ESTABLISH RSV DIAGNOSIS	PALIVIZUMAB PROPHYLAXIS: NUMBER OF CHILDREN (DOSAGE)	PLACEBO: NUMBER OF CHILDREN (DOSAGE)
TAVSU ET AL., 2014	Random allocation (1:1), compared to no prophylaxis	Two RSV seasons: 2009 to 2010 2010 to 2011 (Turkey)	Children born at less than 32 weeks of gestation and who were hospitalized (children born at less than 28 weeks of gestation and aged less than 12 months at the start of the RSV season; children born at a gestational age of 29-32 weeks and less than six months of age at the start of the RSV season)	Nasal secretions	39 (15 mg/kg per intramuscular injection every 30 days; total of five doses)	41 (without placebo)
BLANKEN ET AL., 2013	Randomized (1:1), double-blind where the control group received a placebo	Two RSV seasons 2008 to 2010 (Netherlands: 15 sites)	Children born at a gestational age of 33-35 weeks, in good health and who were six months of age or less at the start of the RSV season	RT-PCR	214 (15 mg/kg per intramuscular injection every 30 days; total of five doses)	215 (15 mg/kg per intramuscular injection every 30 days; total of five doses)
COHEN ET AL., 2005	Randomized (1:1), double-blind with the control group receiving a placebo, multicenter	n/a (United States: 40 sites)	Children with cystic fibrosis aged 24 months or less	Unreported	92 (15 mg/kg per intramuscular injection every 30 days; total of five doses)	94 (15 mg/kg per intramuscular injection every 30 days; total of five doses)
FELTES ET AL., 2003	Randomized (1:1), double-blind with the control group receiving a placebo, multicenter	Four RSV seasons 1998 to 2002 (United States: 47 sites Canada: 6 sites Switzerland: 3 sites Germany: 4 sites Poland: 6 sites France: 4 sites United Kingdom: 6 sites)	Children with congenital heart disease, with: - aged 24 months or less at the start of the RSV season (time of the random allocation); - hemodynamically significant congenital heart disease; - un-operated or partially corrected congenital heart disease	Test to detect an antigen in respiratory secretions	639 (15 mg/kg per intramuscular injection every 30 days; total of five doses)	648 (15 mg/kg per intramuscular injection every 30 days; total of five doses)

IMPACT-RSV STUDY GROUP, 1998	Randomized (2:1), double-blind with the control group receiving a placebo, multicenter, phase- III study	One RSV season 1996 to 1997 (United States: 119 sites United Kingdom: 11 sites Canada: 9 sites)	Children born at 35 weeks of gestation or less who were aged six months or less at the start of the RSV season or aged 24 months or less at the start of the RSV season, who were diagnosed with bronchopulmonary dysplasia and who received steroids, bronchodilators, diuretics or a supplementary oxygen supply in the previous six months	Test to detect an antigen in respiratory secretions	1002 (15 mg/kg per intramuscular injection every 30 days; total of five doses)	500 (15 mg/kg per intramuscular injection every 30 days; total of five doses)
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CLD: chronic lung disease; RT-PCR: reverse transcription polymerase chain reaction; RSV: respiratory syncytial virus

Table C-3 Characteristics of observational studies on the effectiveness of palivizumab compared to no prophylaxis

AUTHORS, YEAR	STUDY DESIGN	STUDY DATES (LOCATION)	PARTICIPANTS	METHOD USED TO ESTABLISH DIAGNOSIS OF RSV INFECTION	PALIVIZUMAB PROPHYLAXIS: NUMBER OF PARTICIPANTS	NO PROPHYLAXIS: NUMBER OF PARTICIPANTS
BANERJI ET AL., 2014	Inception cohort study	2009-2010 (Nunavut)	Children less than six months of age at the start of the RSV season, born at less than 36 weeks of gestation or with severe congenital heart disease	EIA or RT-PCR	91	9
YI ET AL., 2014	Inception cohort study (registry)	2005 to 2012 (Canada)	Exposed group: children under 24 months old with Down syndrome (Canadian registry) Unexposed group: children under 24 months old with Down syndrome (Dutch registry)	EIA, RT-PCR or test to detect an antigen in respiratory secretions	552 (2005 to 2012)	233 (2003 to 2005)
YOSHIHARA ET AL., 2013	Inception cohort study (registry)	2007-2008 (Japan)	Children born at a gestational age of 33-35 weeks without CLD	Unreported	345	95
WINTERSTEIN ET AL., 2013A	Historical cohort study	1999 to 2004 (United States)	Children born at a gestational age of 32-34 weeks without CLD, cardiac disease or cystic fibrosis and who are not immunosuppressed	Unreported	461 (Florida) 671 (Texas)	1,853 (Florida) 3,015 (Texas)
WINTERSTEIN ET AL., 2013B	Historical cohort study	1999 to 2006 (United States)	Children under 24 months of age diagnosed with cystic fibrosis	Unreported	2,300	575
HARRIS ET AL., 2011	Inception cohort study (compared to a historical cohort)	1998 to 2007 (Canada)	Children with congenital heart disease, aged less than 24 months at the start of the RSV season, born at 36 weeks of gestation or less	Unreported	292 (after the immunoprophylaxis program of 2003 to 2007)	412 (before the immunoprophylaxis program of 1998 to 2003)
GIEBELS ET AL., 2008	Historical cohort study	1997 to 2005 (Canada)	Children diagnosed with cystic fibrosis at less than 18 months, born in years 1997 to 2005 inclusively and who were monitored at the CHU Sainte-Justine cystic fibrosis clinic	ELISA or virus culture	35	40

GRIMALDI ET AL., 2007	Inception cohort study (compared to a historical cohort)	1999 to 2004 (France)	Children born at 30 weeks of gestation or less without CLD	ELISA or rapid immunofluorescence test	88 (after the 2002-2004 immunoprophylaxis program)	118 (before the 1999-2002 immunoprophylaxis program)
SIMÕES ET AL., 2007	Inception cohort study	Two RSV seasons 1998 to 2002 (Spain, Canada, Germany Netherlands, Poland, Switzerland)	Children born at 35 weeks of gestation or less, without CLD or cardiac disease	Unreported	191	230
MITCHELL ET AL., 2006	Historical cohort study	RSV season 1995 to 2002 (Canada)	- Children at high risk, from Calgary: born at less than 33 weeks of gestation or born at a gestational age of 33-35 weeks and diagnosed with CLD or born at a gestational age of 33-35 weeks and requiring oxygen therapy at home and born six months before the start of the RSV season - Children at moderate risk, from Calgary: born at a gestational age of 33-35 weeks without congenital lung disease or who do not require oxygen therapy at home	RSV infection diagnosis must be confirmed by a laboratory test, but tests used are not specified.	After the 1999-2002 immunoprophylaxis program 411 842	Before the 1995-1998 immunoprophylaxis program 496 907
GRIMALDI ET AL., 2004	Inception cohort study (compared to a historical cohort)	RSV seasons 1999 to 2002 (France)	Children born at 32 weeks of gestation or less with bronchopulmonary dysplasia, aged six months or less at the start of the RSV season	ELISA or rapid immunofluorescence test	43 (after the 2000-2002 immunoprophylaxis program)	332 (before the 1999-2000 immunoprophylaxis program)

WEGNER ET AL., 2004	Historical cohort	2002 to 2003 (United States)	Children born at a gestational age of 32-35, without CLD	Rapid test to detect an antigen in nasal secretions	185	182
PEDRAZ ET AL., 2003	Historical cohort study	RSV seasons 1998 to 2002 (Spain)	Children born at 32 weeks of gestation or less, with or without congenital lung disease and aged six months or less at the start of the RSV season	ELISA or rapid immunofluorescence test	1,919 (after the 2000-2002 immunoprophylaxis program)	1,583 (before the 1998-2000 immunoprophylaxis program)
SINGLETON ET AL., 2003	Historical cohort study	1993 to 2001 (Alaska)	Children born before 36 weeks of gestation	EIA or virus culture	1,087 (after the immunoprophylaxis program of 1998 to 2001)	992 (before the immunoprophylaxis program of 1993 to 1996)

EIA: enzyme immunoassay; ELISA: enzyme-linked immunosorbent assay; CLD: chronic lung disease; RT-PCR: reverse transcription polymerase chain reaction; RSV: respiratory syncytial virus

APPENDIX D

Methodological quality evaluation of the studies: Results

Table D1 Methodological quality evaluation of systematic reviews using R-AMSTAR grid

QUESTIONS		Robinson <i>et al.</i> , 2014		Wegzyn <i>et al.</i> , 2014 [†]		Homaira <i>et al.</i> , 2014 [‡]		Andabaka <i>et al.</i> , 2013		Checchia <i>et al.</i> , 2011		Pons <i>et al.</i> , 2011		Morris <i>et al.</i> , 2009	
		1	2	1	2	1	2	1	2	1	2	1	2	1	2
1	Was an 'a priori' design provided?	3	3	3	3	3	3	3	3	3	3	2	2	2	2
2	Was there duplicate study selection and data extraction?	3	3	2	2	1	2	3	3	3	3	3	3	3	3
3	Was a comprehensive literature search performed?	4	4	4	4	4	4	4	4	4	4	3	2	3	3
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	3	3	2	2	2	3	4	4	2	2	1	1	3	3
5	Was a list of studies (included and excluded) provided?	4	4	2	2	2	2	4	4	2	2	2	2	2	2
6	Were the characteristics of included studies provided?	1	1	3	3	2	3	3	3	3	4	4	4	3	3
7	Was the scientific quality of included studies assessed and documented?	3	3	1	1	3	2	4	4	2	2	1	1	2	2
8	Was the scientific quality of included studies used appropriately in formulating conclusions?	4	4	1	1	2	1	3	3	1	1	1	1	1	1
9	Were the methods used to combine findings of studies appropriate?	4	4	4	3	1	1	4	4	2	3	4	3	3	3
10	Was the likelihood of publication bias assessed?	4	4	1	1	1	1	2	2	1	1	1	2	4	4
11	Were conflicts of interest stated?	4	4	1	2	2	2	4	4	2	2	1	2	3	3
Sum of scores		37	37	24	24	21	24	38	38	25	27	23	23	29	29
% (on 44)		84	84	54	54	64*	67*	86	86	57	61	52	52	66	66
Methodological quality evaluation **		Good		Average		Average		Good		Average		Average		Average	

*The percentage is calculated on 36 because items 9 and 10 are not applicable.

[†]initiative of MedImmune, AbbVie or AstraZeneca

[‡]exclusively observational studies

** For the study to be considered of good methodological quality, the average score must have been greater than 75; to be considered of average quality, the average score must have been between 50 and 74; to be considered of poor quality, the average score would have to be between 25 and 49 and to be considered of very poor quality, the average score was below 25.

Table D2 Methodological quality evaluation of randomized clinical trials using CASP-RCT grid

QUESTIONS		Tavsu <i>et al.</i> , 2014		Blanken <i>et al.</i> , 2013		Feldes <i>et al.</i> , 2003		IMpact-RSV, 1998	
		1	2	1	2	1	2	1	2
1	Was the trial based on a well-defined question?	yes	yes	yes	yes	yes	yes	yes	yes
2	Were the patients assigned to treatments in a random manner?	Yes	Yes	Yes	Yes	Yes	Yes	No	No
3	Were the patients admitted to the trial all accounted for at the end of the trial?	yes	yes	yes	yes	yes	yes	yes	yes
4	Was the trial blind with respect to the patients, health care workers and staff who were assigned to it?	no	no	no	no	yes	yes	yes	yes
5	Were the groups similar at the start of the trial?	yes	yes	no	no	yes	yes	yes	yes
6	Besides the intervention in the study, were the groups treated the same way?	no	no	yes	yes	yes	yes	yes	yes
9	Can the results be applied in your environment (or to the local population)?	no	no	yes	yes	yes	no	yes	yes
10	Did the authors consider all of the important clinical parameters?	no	no	no	no	yes	yes	no	no
11	Are the disadvantages and costs justified given the advantages?	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Ethical consideration and conflicts of interest		No conflict of interest declared with pharmaceutical industry		Appearance of a conflict of interest with pharmaceutical industry		Appearance of a conflict of interest with pharmaceutical industry		Appearance of a conflict of interest with pharmaceutical industry	
Total of «Yes» (questions 1 to 6)*		3	3	4	4	6	6	6	6
Methodological quality evaluation		Average		Average		Good		Good	

n/a: not applicable

* Methodological quality is established based on answers to questions 1 to 6. For the trial to be considered of:

- good methodological quality, the answer to questions 1 to 6 must be «yes»;
- average methodological quality, the answer to 4 or 5 of these 6 questions must be «yes»;
- poor methodological quality, the answer to 2 or 3 of these 6 questions must be «yes»;
- very poor methodological quality, the answer to less than 5 of these 6 questions is «yes»;

Table D3 Methodological quality evaluation of systematic reviews using CASP-Cohorts grid

QUESTIONS		Banerji <i>et al.</i> , 2014		Yi <i>et al.</i> , 2014		Winterstein <i>et al.</i> , 2013a		Winterstein <i>et al.</i> , 2013b		Harris <i>et al.</i> , 2011		Giebels <i>et al.</i> , 2008	
		1	2	1	2	1	2	1	2	1	2	1	2
1	Is the study based on a well-defined question?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
2	Was the cohort recruited in an acceptable manner?	yes	yes	no	no	yes	yes	yes	yes	no	no	no	no
3	Was the exposure precisely measured in order to reduce bias?	no	no	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
4	Were results precisely measured in order to reduce bias?	yes	yes	yes	yes	yes	yes	no	no	no	yes	yes	yes
5a/b	Did authors consider all of the important confounding factors? Did authors consider all of the potential confounding factors in the study methodology and/or in their analysis?	no	no	no	no	no	no	no	no	no	no	no	no
6a	Was monitoring of subjects exhaustive?	yes	yes	no	no	yes	yes	yes	yes	yes	yes	yes	yes
6b	Was monitoring of subjects long enough?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
9	Do the results seem credible to you?	no	no	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
10	Can the results be applied to the local population?	no	no	yes	yes	no	no	no	no	yes	yes	no	no
11	Do the results of this study match those of previous studies?	yes	yes	no	no	yes	yes	no	no	yes	yes	no	no
Ethical consideration and conflicts of interest		No conflict of interest declared with pharmaceutical industry		No conflict of interest declared with pharmaceutical industry		No conflict of interest declared with pharmaceutical industry		No conflict of interest declared with pharmaceutical industry		No conflict of interest declared with pharmaceutical industry besides a remuneration to author of less than \$1000 by Abbott.		No conflict of interest declared with pharmaceutical industry	
Total of «Yes» (questions 1 to 5)*		3	3	3	3	4	4	3	3	2	2	3	3
Methodological quality evaluation*		Poor		Poor		Average		Poor		Poor		Poor	

Table D3 Methodological quality evaluation of systematic reviews using CASP-Cohorts grid (*continued*)

QUESTIONS		Grimaldi <i>et al.</i> , 2007		Simoes <i>et al.</i> , 2007		Mitchell <i>et al.</i> , 2006		Grimaldi <i>et al.</i> , 2004		Wegner <i>et al.</i> , 2004		Pedraz <i>et al.</i> , 2003		Singleton <i>et al.</i> , 2003	
		1	2	1	2	1	2	1	2	1	2	1	2	1	2
1	Is the study based on a well-defined question?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	yes
2	Was the cohort recruited in an acceptable manner?	yes	no	no	no	yes	yes	yes	yes	yes	yes	no	no	no	no
3	Was the exposure precisely measured in order to reduce bias?	no	yes	yes	yes	no	no	yes	yes	yes	yes	no	no	yes	yes
4	Were results precisely measured in order to reduce bias?	no	no	yes	yes	no	no	no	no	yes	yes	no	no	yes	yes
5a/b	Did authors consider all of the important confounding factors? Did authors consider all of the potential confounding factors in the study methodology and/or in their analysis?	no	no	yes	yes	no	no	no	no	yes	yes	no	no	no	no
6a	Was monitoring of subjects exhaustive?	no	no	yes	yes	yes	yes	no	no	yes	yes	no	no	yes	yes
6b	Was monitoring of subjects long enough?	n/a	n/a	yes	yes	yes	yes	yes	yes	yes	yes	no	no	yes	yes
9	Do the results seem credible to you?	no	no	no	no	yes	yes	no	no	yes	yes	no	no	yes	yes
10	Can results be applied to the local population?	no	no	no	no	yes	yes	no	no	no	no	no	no	no	no
11	Do the results of this study match those of previous studies?	no	no	no	no	no	no	no	no	yes	yes	no	no	no	no
Ethical consideration and conflicts of interest		No conflict of interest declared with pharmaceutical industry		Appearance of a conflict of interest with pharmaceutical industry: same group as Carbonell-Estrany studies		Appearance of conflict of interest declared with pharmaceutical industry		No conflict of interest declared with pharmaceutical industry		No conflict of interest declared with pharmaceutical industry		Appearance of a conflict of interest with pharmaceutical industry		No conflict of interest declared with pharmaceutical industry	
Total of «Yes» (questions 1 to 5)*		2	2	4	4	2	2	3	3	5	5	1	0	3	3
Methodological quality evaluation*		Poor		Average		Poor	Poor	Poor		Good		Very poor		Poor	

n/a: not applicable

* Methodological quality is established based on answers to questions 1 to 5a/b. For reviews to be considered of:

- good methodological quality, the answer to questions 1 to 5a/b must be «yes»;
- average methodological quality, the answer to 4 of questions 1 to 5a/b must be «yes»;
- poor methodological quality, the answer to 2 or 3 of questions 1 to 5a/b must be «yes»;
- very poor methodological quality, the answer to 1 of questions 1 to 5a/b, or to none of these questions, must be «yes»;

Table D4 Methodological quality evaluation of systematic reviews using CASP-Case-Control grid

ITEMS	QUESTIONS	Yoshihara <i>et al.</i> , 2013	
		1	2
1	Is the study based on a well-defined question?	yes	yes
2	Did authors use an appropriate method to answer their question?	no	no
3	Were cases recruited in an acceptable manner?	yes	yes
4	Were witnesses recruited in an acceptable manner?	no	no
5	Was the exposure precisely measured in order to reduce bias?	no	no
6a	Which confounding factors did authors take into account?	no	no
6b	Did authors consider all of the potential confounding factors in the study methodology and/or in their analysis?	yes	yes
9	Do the results seem credible to you?	no	no
10	Can results be applied to the local population?	no	no
11	Do the results of this study match those of previous studies?	yes	yes
Ethical consideration and conflicts of interest		Appearance of conflict of interest with pharmaceutical industry	
Total of «Yes» (questions 1 to 6)*		3	3
Methodological quality evaluation*		Poor	

* Methodological quality is established based on answers to questions 1 to 6b. For a case-control study to be considered of:

- good methodological quality, the answer to all of questions 1 to 6b must be «yes»;
- average methodological quality, the answer to 5 or 6 of questions 1 to 6b must be «yes»;
- poor methodological quality, the answer to 3 or 4 of questions 1 to 6b must be «yes»;
- poor low methodological quality, the answer to 2 or less of questions 1 to 6b must be «yes»;

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