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

A systematic review

**Sent to the minister: July 29, 2016**
**Official publication: August 9, 2016**

Produced by the Institut national d'excellence en santé et en services sociaux

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This report was submitted to the Comité scientifique d'évaluation des médicaments aux fins d'inscription of the Institut national d'excellence en santé et en services sociaux (INESSS) during the meetings of June 9 and July 5, 2016.

The content of this publication was written and edited by INESSS.

This paper is available online in the *Publications* section of INESSS website.

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Bibliothèque et Archives nationales du Québec, 2017
Library and Archives Canada, 2017
ISSN 1915-3104 INESSS (PDF) ISBN 978-2-550-78553-8 (PDF)



To cite this document: Institut national d'excellence en santé et en services sociaux (INESSS). Effect of Palivizumab Prophylaxis on the Reduction of Complications Associated with Respiratory Syncytial Virus in Infants: Systematic Review. Report prepared by Marie-Claude Breton, Michel Rossignol, Mélanie Tardif, Alvine K. Fansi and Cédric Jehanno Québec, QC: INESSS; 2017. 65p.

English translation by [Caroline Quach-Thanh] with the permission of the Institut national d'excellence en santé et en services sociaux (INESSS). Original text available at www.inesss.qc.ca

INESSS wishes to thankmembers of its staff who contributed to the preparation of this document.

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## Declaration of Interests

Authors of the report declare having no conflicts of interest. No external funding was received for the preparation of this document.


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# 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 significantly 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 stategy 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<br>• No prophylaxis |
| **OUTCOMES** | • Hospitalization due to RSV infection<br>• Length of hospital stay due to RSV infection<br>• Stay in intensive care due to RSV infection<br>• Length of stay in intensive care due to RSV<br>• Use of oxygen therapy due to RSV infection<br>• Length of oxygen therapy due to RSV infection<br>• Use of mechanical ventilation due to RSV infection<br>• Length of mechanical ventilation due to RSV infection<br>• Long-term sequelae (wheezing, asthma) due to RSV infection<br>• Mortality |
| **TYPES OF PUBLICATIONS** | • Systematic review with or without a meta-analysis<br>• Randomized clinical trial (RCT)<br>• 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<br>• 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 RVS-associated hospitalizations in children at high risk[2], 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 2003[µ]** | 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 *et al.*, 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 *et al.*, 2003[μ]** | 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 *et al.*, 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 *et al.*, 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 *et al.*, 2003[£]** | 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 *et al.*, 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 *et al.*, 2003[μ]** | 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.

[µ] 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(GESTATIONAL 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 *et al.*, 2011** | SR-MA<br>(≤ 32 weeks) | 83/2,275<br>(3.7%) | 240/2,274<br>(10.6%) | | OR = 0.28 (0.21 to 0.36)<br>p < 0.001<br>(three studies)* | Average |
| | (32 to 35 weeks) | 9/410<br>(2.2%) | 23/292<br>(7.9%) | | OR = 0.26 (0.11 to 0.62)<br>p = 0.002<br>(2 studies)** | |
| **Tavsu *et al.*, 2014** | RCT<br>(≤ 32 weeks) | 0/39<br>(0%) | n/a | 10/41<br>(24.4%) | OR = 0.26 (0.10 to 0.68)<br>p = 0.001 | Average |
| **Blanken *et al.*, 2013** | RCT<br>(33 to 35 weeks) | 2/214<br>(0.9%) | 11/215<br>(5.1%) | n/a | RR = 0.18 (0.04 to 0.81) | Average |
| **IMpact-RSV, 1998** | RCT<br>(≤ 35 weeks) | 9/506<br>(1.8%) | 19/234<br>(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<br>(1.8%) | 8/124<br>(6.5%) | n/a | RR = 0.28 (0.09 to 0.83) | |
| **Winterstein *et al.*, 2013a** | Historical cohort<br>(32 to 34 weeks) | n/a / 461<br>(Florida) | n/a | n/a / 1,853<br>(Florida) | OR = 0.81 (0.42 to 1.58)<br>p = 0.54 | Average |
| | | n/a / 671<br>(Texas) | | n/a / 3,015<br>(Texas) | OR= 0.45 (0.26 to 0.78)<br>p = 0.005 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Grimaldi *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 2005** | RCT | 1/92 (1.09%) | 1/94 (1.06%) | n/a | RR = 1.02 (0.06 to 16.09) | Not assessed* |
| **Winterstein *et al.*, 2013b** | Historical cohort | n/a / 575 | n/a | n/a / 2,300 | HR = 0.57 (0.20 to 1.60)** | Average |
| **Giebels *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 [Feltes *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 Feltes 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 Feltes 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 Feltes 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 Feltes 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 Feltes 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 2003** | RCT | 13/639 (2.0%) | 24/648 (3.7%) | n/a | RD = 46% P = 0.094 | Good |
| **Harris *et al.*, 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 *et al.*, 2003** | RCT | 15.9 | 71.2 | n/a | RD = 78%, p = 0.80 | Good |
| **Harris *et al.*, 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 *et al.*, 2003** | RCT | 21/639 (3.3%) | 27/648 (4.2%) | n/a | RR = 0.79 (0.45 to 1.38) | Good |
| **Harris *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 2014** | Inception cohort | 2/91 (2.2%) | 5/10 (50%) | OR = 0.04 (0.008 to 0.26) p = 0.0005 | Poor |
| **Singleton *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 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 [Feltes *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 Feltes 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%) ($p = 0.285$) [Feltes *et al.*, 2003].

Overall, regarding other result parameters, a statistically significant reduction in the length of hospital stays [Feltes *et al.*, 2003] and in the duration of oxygen therapy [Feltes *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 [Frogel *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

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| N° 3 | N° 1 ET n° 2 | 1290 |
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| N° 5 | N° 1 ET n° 2 Filtres : English; French | 1209 |
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| 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

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| 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 |
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| | 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 |
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| N° 13 | limit 9 to (clinical trial or randomized controlled trial or controlled clinical trial) | 147 |
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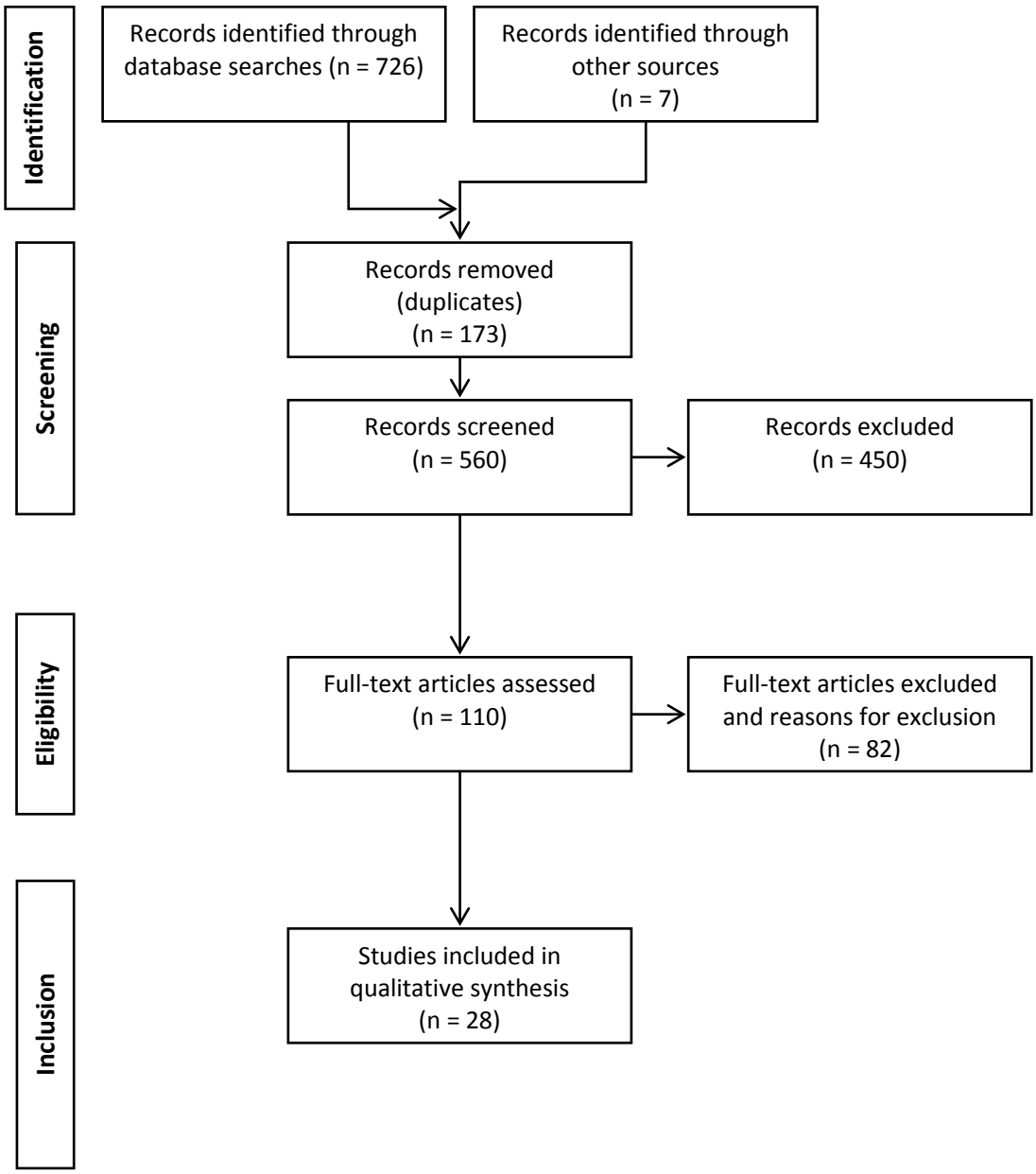
# APPENDIX B
## Study selection

**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 *et al.*, 2013 | Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children. Cochrane |
| Banerji *et al.*, 2014 | The real-life effectiveness of palivizumab for reducing hospital admissions for respiratory syncytial virus in infants residing in Nunavut |
| Checchia *et al.*, 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 *et al.*, 2010 | Motavizumab for prophylaxis of respiratory syncytial virus in high-risk children: A noninferiority trial |
| Feltes *et al.*, 2003 | Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease |
| Feltes *et al.*, 2011 | Résultats – Innocuité du Motavizumab c. Palivizumab (phase 2), mais les auteurs rapportent des données sur les taux d'hospitalisation |
| Grimaldi *et al.*, 2007 | Palivizumab efficacy in preterm infants with gestational age < or = 30 weeks without bronchopulmonary dysplasia |
| Homaira *et al.*, 2014 | Effectiveness of palivizumab in preventing RSV hospitalization in high risk children: A real-world perspective |
| Mitchell *et al.*, 2006 | Beyond randomized controlled trials: A «real life» experience of respiratory syncytial virus infection prevention in infancy with and without palivizumab |
| Morris *et al.*, 2009 | A meta-analysis of the effect of antibody therapy for the prevention of severe respiratory syncytial virus infection |
| Pedraz *et al.*, 2003 | Effect of palivizumab prophylaxis in decreasing respiratory syncytial virus hospitalizations in premature infants |
| Pons *et al.*, 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 *et al.*, 2014 | Palivizumab for prophylaxis against respiratory syncytial virus infection in children with cystic fibrosis |
| Simoes *et al.*, 2007 | Palivizumab prophylaxis, respiratory syncytial virus, and subsequent recurrent wheezing |
| Singleton *et al.*, 2003 | Impact of palivizumab prophylaxis on respiratory syncytial virus hospitalizations in high risk Alaska Native infants |
| Tavsu *et al.*, 2014 | Palivizumab prophylaxis: Does it have any influence on the growth and development of the infants? |
| Wegzyn *et al.*, 2014 | Safety and effectiveness of palivizumab in children at high risk of serious disease due to respiratory syncytial virus infection: A systematic review |
| Winterstein *et al.*, 2013a | Appropriateness of age thresholds for respiratory syncytial virus immunoprophylaxis in moderate-preterm infants: A cohort study |
| Yi *et al.*, 2014 | Respiratory syncytial virus prophylaxis in Down syndrome: A prospective cohort study |
| Yoshihara *et al.*, 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 *et al.*, 2013 | Respiratory Syncytial Virus and Recurrent Wheeze in Healthy Preterm Infants |
| Winterstein *et al.*, 2013b | Palivizumab Immunoprophylaxis Effectiveness in Children With Cystic Fibrosis |
| Harris *et al.*, 2011 | Economic Evaluation of Palivizumab in Children With Congenital Heart Disease: A Canadian Perspective |
| Cohen *et al.*, 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 *et al.*, 2008 | Prophylaxis Against Respiratory Syncytial Virus in Young Children With Cystic Fibrosis |
| Grimaldi *et al.*, 2004 | Severe Respiratory Syncytial Virus Bronchiolitis Epidemiologic Variations Associated With the Initiation of Palivizumab in Severely Premature Infants With Bronchopulmonary Dysplasia |
| Wegner *et al.*, 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 *et al.*, 2004 | Specification – case study (case occurred during two outbreaks in a neonatal intensive care unit (NICU)) |
| Abarca *et al.*, 2009 | Results – safety study |
| Afghani *et al.*, 2006 | Not relevant – study on adherence to PAA recommendations |
| Alexander *et al.*, 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 *et al.*, 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 *et al.*, 2000 | Intervention – RSV-IVIG |
| Bouthillier, 1997 | Specification – letter to the editor |
| Buckley *et al.*, 2010 | Scientific quality – cohort whose indications are different from those of the control group (without palivizumab) |
| Butt *et al.*, 2014 | Specification – no comparison group (risk factor) |
| Butt *et al.*, 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 *et al.*, 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 *et al.*, 2015 | Results – study on safety and tolerability |
| Clark *et al.*, 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 *et al.*, 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 *et al.*, 1997 | Intervention – RSV-IVIG |
| DeVincenzo *et al.*, 2003 | Results – viral load measured in the exposed group and the non-exposed group |
| Duppenthaler *et al.*, 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 *et al.*, 2012 | Not relevant – not a study strictly speaking. |
| Emerick *et al.*, 2006 | Specification – narrative review |
| Estrada *et al.*, 2011 | Specification – conference summary |
| Faldella *et al.*, 2010 | Scientific quality – cohort whose indications are different from those of the control group (without palivizumab) |
| Fernandez *et al.*, 2010 | Results – safety of motavizumab compared to palivizumab (phase 2) |
| Forbes *et al.*, 2014 | Comparison – low palivizumab serum concentration vs high concentration |
| Frogel *et al.*, 2008 | Specification – no comparison group |
| Geskey *et al.*, 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 *et al.*, 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 *et al.*, 1995b | Intervention and outcome – safety and bioequivalence of an infusion of various RSVIG preparations (750 mg/kg) |
| Groothuis *et al.*, 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 *et al.*, 2004 | Specification – editorial |
| Harkensee *et al.*, 2006 | Specification – narrative review on the synthesis of evidence regarding safety, effectiveness and cost-effectiveness of palivizumab |
| Heikkinen *et al.*, 2005 | Specification – cohort study on hospitalization rates for different gestational ages. Does not specifically deal with palivizumab. |
| Henckel *et al.*, 2004 | Not a cohort study. |
| Kusuda *et al.*, 2006 | Scientific quality – cohort whose indications are different from those of the control group (without palivizumab) |
| Lacaze-Masmonteil *et al.*, 2002 | Results-safety of palivizumab |
| Lacaze-Masmonteil *et al.*, 2003 | Specification – no comparison group |
| Lacaze-Masmonteil *et al.*, 2002 | Results-safety of palivizumab |
| Lagos *et al.*, 2009 | Intervention and results – safety of motavizumab |
| Malkin *et al.*, 2013 | Intervention – vaccine against attenuated RSV |
| Meberg and Bruu, 2006 | Dimension – economic |
| Medrano Lopez and Garcia-Guereta, 2010 | Comparison – inadequate vs adequate prophylaxis |
| Mitchell *et al.*, 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 *et al.*, 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 *et al.*, 2014 | Specification – non-randomized clinical trial in Japan on newborns and immunosuppressed children. N < 30 |
| Naver *et al.*, 2004 | Specification – not a cohort or case-control study. Evaluation of the impact of guidelines |
| Null *et al.*, 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 *et al.*, 2002 | Specification – evaluation of risk factors for RSV-associated hospitalizations<br>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 *et al.*, 2013 | Comparison – both groups are exposed to palivizumab (comparison between data from the Canadian CARESS registry and registries in other territories). |
| Paes *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 2005 | Specification and scientific quality – survey comparing a period before and after palivizumab, but the article does not report any palivizumab exposure data. |
| Parmigiani *et al.*, 2001 | Article cannot be obtained |
| Resch, 2008a | Specification – narrative review |
| Resch, 2008b | Specification – narrative review |
| Resch *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 2012 | Not relevant – analysis of several cases in a Brazil hospital |
| Simoes *et al.*, 1998 | Intervention – effectiveness of intravenous RSV-IG (750 mg/kg) |
| Subramanian *et al.*, 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 *et al.*, 2000a | Dimension – economic projection study |
| Thomas *et al.*, 2000b | Article cannot be obtained, but seems to be a projection study |
| Vogel *et al.*, 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 *et al.*, 2015 | Dimension – economic analysis (4 vs 5 doses of palivizumab) |
| Winchester *et al.*, 2002 | Specification – no comparison group (without prophylaxis), but data on safety of palivizumab |
| Wenzel *et al.*, 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:<br>2009 to 2010<br>2010 to 2011<br>(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<br>(15 mg/kg per intramuscular injection every 30 days; total of five doses) | 41<br>(without placebo) |
| **BLANKEN *ET AL.*, 2013** | Randomized (1:1), double-blind where the control group received a placebo | Two RSV seasons<br>2008 to 2010<br>(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<br>(15 mg/kg per intramuscular injection every 30 days; total of five doses) | 215<br>(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<br>(United States: 40 sites) | Children with cystic fibrosis aged 24 months or less | Unreported | 92<br>(15 mg/kg per intramuscular injection every 30 days; total of five doses) | 94<br>(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<br>1998 to 2002<br>(United States: 47 sites<br>Canada: 6 sites<br>Switzerland: 3 sites<br>Germany: 4 sites<br>Poland: 6 sites<br>France: 4 sites<br>United Kingdom: 6 sites) | Children with congenital heart disease, with:<br>- aged 24 months or less at the start of the RSV season (time of the random allocation);<br>- hemodynamically significant congenital heart disease;<br>- un-operated or partially corrected congenital heart disease | Test to detect an antigen in respiratory secretions | 639<br>(15 mg/kg per intramuscular injection every 30 days; total of five doses) | 648<br>(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) |

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) |
| **SIMOES *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) | | RSV infection diagnosis must be confirmed by a laboratory test, but tests used are not specified. | After the 1999-2002 immunoprophylaxis program | Before the 1995-1998 immunoprophylaxis program |
| | | | - 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 | | 411 | 496 |
| | | | - 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 | | 842 | 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 *et al.*, 2014 | | Wegzyn *et al.*, 2014 † | | Homaira *et al.*, 2014‡ | | Andabaka *et al.*, 2013 | | Checchia *et al.*, 2011 | | Pons *et al.*, 2011 | | Morris *et al.*, 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 *et al.*, 2014 | | Blanken *et al.*, 2013 | | Feltes *et al.*, 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 *et al.*, 2014 | | Yi *et al.*, 2014 | | Winterstein *et al.*, 2013a | | Winterstein *et al.*, 2013b | | Harris *et al.*, 2011 | | Giebels *et al.*, 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? Didauthors 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 *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 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 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 *et al.*, 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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